Analysis of causes that led to baby Ryan's hemorrhagic pneumonia, cardiac arrest, intracranial bleeding, and retinal bleeding

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Abstract

Ryan George was two months old when he suffered from cardiac arrest 9 days after receiving his second injection of Hepatitis B vaccine (HBV). He was successfully resuscitated at Coney Island Hospital in New York. His chest X-ray and CT scan showed evidence of pulmonary edema, bleeding, and pneumonia. A CT exam of his head showed brain edema. He had a blood pH of 6.83 and a potassium level of 6.0 mEq/L. He was stabilized and transferred to Maimonides Medical Center (MMC).

Blood tests performed at MMC revealed that Ryan had an elevated band neutrophil count, hyperglycemia, hyperkalemia, hyperammonimia, hemolytic anemia, liver damage, hyperphosphatemia, and hypermagnesiumia. In addition, his PT, PTT, and INR were elevated. Ryan was treated with four types of antibiotics and other medications.

Ryan had an MRI head exam and an eye exam performed at 8 days and 9 days after admission, respectively. His MRI showed intracranial bleeding and his eye exam revealed retinal bleeding. Ryan's father was accused of causing his son's injuries by shaking him vigorously (Shaken Baby Syndrome).

My investigation indicates that infection with Streptococcus pneumoniae caused Ryan's illness and led to the development of hemorrhagic pneumonia, hemolytic uremic syndrome, kidney and liver problems, hepatic encephalopathy, seizure, coma, and cardiac arrest. The likely causes of Ryan's intracranial and retinal bleeding are liver damage, infections, vitamin K deficiency, and severe anemia. Hepatitis B vaccine increased Ryan susceptibility to infection. The allegation of child abuse in this case is false.

Keywords: brain edema; hemolytic anemia; hemorrhagic pneumonia; Hepatitis B vaccine; hyperammonimia; hyperkalemia; hypermagnesiumia hyperphosphatemia; hepatic encephalopathy; intracranial bleeding; retinal bleeding; Shaken Baby Syndrome; Streptococcus pneumoniae; vitamin K deficiency

1. Summary of the case and findings

Ryan George was two months old when he suffered from cardiac arrest on June 13, 2007 in New York. Prior to his cardiac arrest, Ryan was at home sleeping in a bouncy chair and his father was with him in the room. At about 1700, the father went to the bathroom for a brief time and when he returned, he found Ryan's chair on the floor and the baby was crying. The baby had blood coming from his nose, but was alert.

The parents took Ryan by car to the emergency room at Coney Island Hospital and arrived at about 1715. Upon arrival, Ryan was blue and pulseless. He was successfully resuscitated with cardiopulmonary resuscitation and without the use of medications.

Ryan's chest X-ray and CT scan exams showed evidence of pulmonary edema, bleeding, and pneumonia. A CT exam of his head showed brain edema and no intracranial bleeding was observed. His CT scan exams of the abdominal region and the cervical spine were normal. No bone fracture or injury caused by trauma was observed at the hospital.

Blood analysis performed at 1756 showed that Ryan was suffering from a severe acidosis and hyperkalemia. He had blood pH of 6.83, pCO_2 of 43 mm Hg, pO_2 of 92 mm Hg, and potassium level of 6.0 (mEq/L). Ryan was intubated and given sodium bicarbonate 1 mEq/kg IV.

Ryan was transferred from Coney Island Hospital on June 13th to Maimonides Medical Center (MMC) and arrived at 2148. He had agonal breathing with blood coming from the endotracheal tube. Ryan's chest X-ray showed fluffy infiltrates in both lungs.

Blood analysis performed on June 14th showed that Ryan had a high band neutrophil count of 28% of the total white blood cell count (WBC). His band count increased to 42% of the WBC by June 15th. Ryan also had hyperglycemia, hyperkalemia, and an elevated serum ammonia level of 84 µmol/L (normal range: 10-47 µmol/L).

In addition, he developed hemolytic anemia, liver damage, hyperphosphatemia and hypermagnesiumia following admission to the hospital. Furthermore, Ryan's blood analysis performed during the 24 hours following admission showed that his prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR) were highly elevated.

Ryan was treated with four types of antibiotics (ceftriaxone, clindamycin, vancomycin, Co-Trimoxazole) during the 11 days following admission to fight bacterial infections. He was also treated with fentanyl citrate, phenobarbital, lorazepam, vecuronium bromide, Tylenol, Zantac, furosemide (diuretic), corticosteroids, and other medications.

Ryan had a Magnetic Resonance Imaging (MRI) head exam performed at 8 days after admission to the hospital. It showed bilateral extra-axial fluid collections in the occipital parietal areas and posterior interhemispheric fissure that suggest subacute hematomas and acute infarcts. In addition, Ryan's eye exam performed at 9 days following admission revealed bilateral retinal bleeding. Ryan was discharged from the hospital on July 19th.

It has been alleged that Ryan's intracranial and retinal bleeding were caused by vigorous shaking (Shaken Baby Syndrome). Ryan's father was accused of causing his son's injuries. Ryan's parents requested that I evaluate the medical evidence in their

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son's case to find the likely causes that led to his serious illnesses and bleeding.

I am a toxicologist and pathologist with over 20 years experience in these fields. I have evaluated many cases of children who died suddenly from unexplained causes and cases of children and adults who suffered from acute and/or chronic illnesses. I was able to explain the causes of illnesses and death in these cases using differential diagnosis. I have served as an expert witness in many medical-legal cases involving children and adults and published over 45 articles in medical and scientific journals.

I evaluated Ryan's medical records and the articles cited in this report using differential diagnosis. Approximately 220 hours were required to evaluate the medical evidence, perform an analysis, and write this report. My investigation in this case reveals the following:

1) Ryan's acute illness was caused by Streptococcus pneumonia infection. His chest X-ray and CT scan exams performed on June 13th showed evidence of pulmonary edema, bleeding, and pneumonia. The lungs were the likely source of Ryan's nose bleed observed on June 13th. He also had blood coming from the endotracheal tube.

In addition, a blood analysis performed on June 14th revealed that Ryan had a high band neutrophil count of 28% of the total white blood cell count (WBC). His band count increased to 42% of the WBC by June 15th. Ryan was treated with antibiotics (ceftriaxone, clindamycin, vancomycin, Co-Trimoxazole) and his band count decreased to 6% (Sections 3, 4).

2) Ryan suffered from an acute hepatic injury, which led to the development of encephalopathy, seizure, and coma as indicated by the clinical tests and biomarkers cited below. Seizure is the likely cause of Ryan's fall from the bouncy chair onto the floor on June 13, 2007.

a) Ryan had elevated levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) on June 14th. His serum ALT and AST levels on June 14th were increased by 28 and 34 times their levels measured on June 13th, respectively.

b) He developed hypoalbuminemia and hypoprotenemia. His serum albumin and protein levels were reduced by 30% and 25% within 6 hours following admission, respectively. They reached their lowest levels at two days following admission.

c) He had an elevated serum ammonia level of 84 μmol/L on June 14th (normal range: 10-47 μmol/L).

3) Ryan developed hyperglycemia. His serum glucose level on June 13th was 227 mg/dL. The likely cause of Ryan's hyperglycemia was the high levels of ammonia in his blood. Ammonia inhibits the use of glucose by the peripheral tissues.

4) Ryan suffered from severe metabolic and respiratory acidosis as a result of renal and pulmonary problems. His initial blood pH was 6.96. His lactic acid level at the time of admission was 5.45 times higher than the upper normal limit. He developed hyperkalemia as a result of metabolic acidosis. He had a serum potassium level of 6.0 mmol/L.

5) Ryan's blood and urine analyses performed following admission showed that he suffered from hemolytic anemia. His urine analysis performed on June 14th revealed a significant amount of hemoglobin in the urine.

6) Ryan had acute kidney damage as indicated by the following clinical data:

a) He developed subcutaneous edema as indicated by the significant increases in his weight, head circumference (HC), abdominal girth (ABG), and length. After Ryan was treated with furosemide (diuretic), his HC and ABG were reduced by 4 cm and 6.5 cm, respectively. His body weight was reduced by 15%.

b) Ryan developed hyperphosphatemia and hypermagnesiumia following admission as a result of kidney failure. His blood phosphate level was about twice the upper normal level. His magnesium level reached 126% of the upper normal level. He also developed hypocalcemia as a result of calcium binding with the phosphorous. His serum calcium level was reduced by 21% of those measured at the time of admission.

7) Ryan suffered from hemolytic uremic syndrome (HUS) induced by the Streptococcus pneumoniae infection. HUS has been observed in some children infected with S. pneumoniae. For example, Waters *et al.* evaluated the medical records of 43 cases of children who developed pneumococcal-associated hemolytic uremic syndrome (P-HUS). The median age at presentation was 13 months (range, 5-39 months).

These children had microangiopathic hemolytic anemia (Hb <10 g/dL with fragmented RBCs), thrombocytopenia (platelet count < 130 x 10(9)/L), acute renal impairment with oliguria and elevated plasma creatinine levels. These symptoms were also observed in Ryan's case (Sections 4, 5).

8) The clinical studies described in this report indicate that Ryan's intracranial bleeding developed after his admission in the hospital on June 13, 2007. A CT scan of his brain performed on June 13th did not show intracranial bleeding. Bleeding and necrosis in the brain were first observed on June 21st by MRI head exam. The likely causes of Ryan's intracranial bleeding are liver damage, infections, and vitamin K deficiency.

A blood analysis performed during the 24 hours following admission showed that his prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) were highly elevated as a result of liver damage. His PT and PTT were 26.4 seconds (normal range: 10.5-14.5) and 53.9 seconds (normal range: 22.7-36), respectively.

In addition, Ryan was treated with four types of antibiotics for 11 days following admission and the treatment of ill children with antibiotics for a significant period of time has caused vitamin K deficiency and intracranial bleeding. For example, Choo *et al.* conducted a retrospective study of 42 infants who were admitted to the hospital for spontaneous bleeding and prolonged prothrombin and partial thromboplastin times. Subdural

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hemorrhage was the most common form of intracranial hemorrhage, followed by subarachnoid hemorrhage [Section 6].

9) The likely causes of Ryan's retinal bleeding observed on June 22nd are liver damage, infections, severe anemia, and vitamin K deficiency. Ryan was suffering from a severe anemia. His blood analysis performed on June 13th at 2317 showed that he had a hemoglobin level of 6.7 g/dL and a hematocrit value of 20.3%. His platelet count was reduced by 70% following admission.

Individuals with severe anemia have developed retinopathy and bleeding in the retina. For example, Carraro *et al.* conducted a cross-sectional study involving 226 individuals with anemia and/or thrombocytopenia. Retinopathy was observed in 28.3% of the anemic individuals.

The presence of fundus lesions was closely associated with severe anemia (Hb<8 g/dL) and severe thrombocytopenia ($PLT<50x10^3/\mu L$). Among the individuals with concomitant anemia and thrombocytopenia, the incidence of retinopathy was 38%. Retinal hemorrhages were found in all of the individuals with concomitant severe anemia and thrombocytopenia [Section 7].

10) Ryan was enjoying good health prior to receiving his second injection of hepatitis B vaccine (HBV) on June 4, 2007, Lot # 1245 F. The clinical data indicate that HBV was the primary cause that led to Ryan's infection with Streptococcus pneumoniae. Infections and autoimmune disorders have been reported in some children who received HBV (Section 8).

11) There is no clinical evidence that shows Ryan was suffering from any injury caused by trauma and the allegation of child abuse in this case is false.

2. Ryan's health condition during the first two months following birth and vaccine given

Ryan George was born at 40 weeks gestation on April 13, 2007. His Apgar scores at 1 and 5 minutes were 9 and 9, respectively. His weight and length were 3850 g and 54.5 cm, respectively. His head circumference was 37 cm. He had a heart rate of 156/minutes and a body temperature of 98.9 ^oF. He was born at Richmond University Medical Center, New York.

He developed mild jaundice. A blood analysis performed on April 15th showed that he had a total biliribun of 11.2 mg/dL (normal rang: 6.0-7.0) and a direct bilirubin level of 1.10 mg/dL (normal rang: 0.0-0.3). He passed his hearing test on April 14th. Ryan was vaccinated with hepatitis B and discharged from the hospital on April 16th [1].

Ryan was examined on April 24th and his pediatrician reported that Ryan had an umbilical hernia. The rest of his exam was normal. Ryan's weight gain rate during the first 11 days after birth was 28.3 g/day (Table 1).

Ryan was also examined on June 4th and his exam was normal. Ryan's gained weight at the rate of 31.0 g/day during the 53 days after birth. His length and head circumference increased at the rate of 4.32 cm/month and 2.26 cm/month, respectively (Table 1).

Ryan received his second injection of hepatitis B (Lot # 1245F) on June 4th. He developed a fever and was treated with Tylenol at a dose of 80 mg every 4 hours starting on June 4th and ending on June 5th. Additionally, Ryan was given two doses of Tylenol (80 mg/dose) between June 6th and the 13th.

Ryan appeared sick during the week of the 4th. He was throwing up, lethargic and seemed very tired, especially towards the end of the week. Ryan suffered from cardiac arrest on June 13th. The clinical tests performed in the hospital showed that he had pneumonia and hemolytic anemia.

During the 9 days following his second injection of hepatitis B vaccine (HBV), Ryan gained weight at the rate of 47.7 g/day and his length increased by 6.37 cm. However, during the period between birth and June 4th, Ryan gained weight at the rate of 31.0 g/day and his length increased at the rate of 4.32 cm/month (Table 1). These clinical data indicate that Ryan developed fluid retention problems following vaccination with HBV.

Table 1. Ryan's weight, length, and head circumference measured during the 53 days following birth

Date	Age (days)	Weight (g)	Length (cm)	Head circumf. (cm)
4/13/07	Birth	3850	54.5 cm	37
4/24/07	11	4139	55.63	38
6/04/07	53	5471	60.63	41
6/13/07	66	5900	67.0	---[1]

[1]Not measured

3. Ryan's hospitalization at Coney Island Hospital on June 13, 2007, clinical tests, diagnosis, and treatments given

On June 13, 2007, baby Ryan was at home sleeping in a bouncy chair and his father was with him in the room. At about 1700, the father went to the bathroom for a brief time and when he returned, he found Ryan's chair on the floor and the baby was crying. The baby had blood coming from his nose, but was alert.

The parents took Ryan by car to the emergency room (ER) at Coney Island Hospital (CIH) and arrived at about 1715. Upon arrival, Ryan was blue and pulseless. He was successfully resuscitated with two minutes of cardiopulmonary resuscitation (CPR) and without the need for medications.

Ryan's mother reported that Ryan was not acting well during the 2-3 days prior to his admission to the hospital. He appeared sometime irritable, lethargic, and pale. Ryan received his second injection of hepatitis B on June 4th and he developed a fever. He was treated with Tylenol for about 3 days.

Blood analysis performed at 1756 showed that Ryan was suffering from severe acidosis and hyperkalemia. He had a blood pH of 6.83, pCO_2 of 43 mm Hg, pO_2 of 92 mm Hg, and potassium level of 6.0 (mEq/L). Ryan was intubated and given sodium bicarbonate 1 mEq/kg IV [2, 3].

Furthermore, Ryan was suffering from severe anemia. His hemoglobin and hematocrit levels were 8.3 g/dL and 23.8%, respectively. A red blood cell morphology study showed that he had macrocytic anemia. His platelet count was higher than the normal range and he had thrombocytosis (Table 2).

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Ryan's chest X-ray and CT scan exams showed evidence of pulmonary edema, bleeding, and pneumonia; no evidence of rib fracture or injury caused by trauma was observed (Table 3). His CT head exam showed brain edema. The CT scan exams of the abdominal region and the cervical spine were normal (Table 4).

Ryan's blood analysis showed that his serum electrolytes levels were normal at 1756, except for a high potassium level. He also had a high blood glucose level. Ryan's serum protein level was lower than normal (Table 5). His white blood cell count and differential count were within the normal range (Table 6).

A urine analysis performed at 1828 showed a trace amount of blood and protein (Table 7). Ryan's blood was tested for ethanol, acetaminophen, and salicylic acid and the results were with the normal limit. Ryan was transferred to Maimonides Medical Center and arrived at 2148 on June 13th [2, 3].

Table 2. Ryan's hematology values measured at 1756 on June 13th

Measurements	Values	Reference Range
RBC x $10^6/\mu L$[1]	2.40	4.0-5.3
Hemoglobin (g/dL)	8.3	11.5-14.5
Hematocrit %	23.8	33-43
MCV (fL)	99.4	76-90
MCH (pg)	34.5	26.6-33.5
RDW%	13.8	11.0-15.5
Platelet x $10^3/\mu L$	472	130-400

[1]RBC morphology: anisocytosis (1+), macrocytosis (2+), rouleaux (1+)

Table 3. Ryan's chest X-ray and CT scan performed on June 13th at CIH

Test Type	Findings
X-ray	• X-ray taken at 1800 correlates clinically for interstitial and air space infilterates. The right lung was affected more than left. • No evidence of pneumothorax. • No definite acute bony abnormalities
X-ray	• There was interval increased confluent opacity in the right upper and lower lung fields as compared with the previous X-ray of 1800. The changes were distributed centrally at both hilar regions and suggest worsening of air space infiltrates, edema, and hemorrhage.
CT scan	• Diffuse bilateral pulmonary consolidations and extensive pulmonary hemorrhage. • No rib fracture was identified.

Table 4. Ryan's CT scans of the head, abdomen, and the cervical spine performed following admission at CIH

Region	Findings
Brain	• No evidence of acute intracranial hemorrhage • No evidence of midline shift or hydrocephalus. Cortical and white matter distinction not clearly delineated and clinical correlation for edema was suggested. • No definite acute bony abnormality.
Abdomen	• No definite intra-abdominal organ injury. • No evidence of obstruction or intraperitoneal free air. • No acute bony abnormalities
Cervical spine	• Normal bony alignment without evidence of acute fracture, subluxation or dislocation. • No definite soft tissue abnormality

Table 5. Ryan's serum analysis performed at 1756 on June 13th

Measurements	Values	Reference Range
Na (mEq/L)	135	136-145
K (mEq/L)	6.0	3.5-5.0
Cl (mEq/L)	105	98-111
CO_2 (mEq/L)	12	24-32
BUN (mg/dL)	6	8-22
Glucose (mg/dL)	227	60-110
Creatinine (mg/dL)	0.3	0.5-1.3
Ca (mg/dL)	9.9	8.0-10.5
Total protein (g/dL)	5.2	6.0-8.0
Albumin (g/dL)	3.7	3.5-5.0
Total Bilirubin (mg/dL)	0.3	0.1-1.2
Alkaline phosp. (U/L)	257	56-350
AST (U/L)	27	5-50
ALT (U/L)	19	10-55
Amylase (U/L)	7	36-128
Anion GAP (mEq/L)	18	7.0-16.0

Table 6. Ryan's white blood cell and differential counts measured at 1756

Measurements	Values	Reference Range
White blood cell x $10^3/\mu L$	10.5	5.0-19.5
Segmented neutrophil %	20	15.0-50.0
Bands neutrophil %	2	0.0-3.0
Lymphocyte %	72	40.0-80.0
Monocyte %	4	0.0-12.0
Eosinophil %	2	1.0-3.0

Table 7. Ryan's urine analysis performed at 1828 on June 13th

Measurements	06/13/07	Reference Range
Color	Yellow	Yellow
Appearance	Clear	Clear
Spec. grav (g/mL)	<1.005	1.010-1.020
PH	7.0	4.6-8.0
Protein	Trace	Negative
Glucose	Negative	Negative
Ketone bodies	Negative	Negative
Blood	Trace	Negative
Bill	Negative	Negative
Urob (mg/dL)	0.1	0.2-1.0
Nitrite	Negative	Negative
Leuko esterase	Negative	Negative
WBC	None seen	<5
RBC	0-2	0

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4. Ryan's hospitalization at Maimonides Medical Center on June 13-19, 2007, clinical tests, diagnosis, and treatments given

Ryan was transferred from Coney Island Hospital to Maimonides Medical Center (MMC) on June 13th and arrived at 2148. He had agonal breathing with blood coming from the endotracheal tube (ETT). Ryan's chest X-ray showed fluffy infiltrates in both lungs.

His systolic blood pressure and body temperature were 70-80 mm Hg and 91°F, respectively. He required 100% oxygen. Physical exam revealed no sign of injury caused by trauma [3].

Ryan's blood analysis performed at 2317 showed that he was suffering from a severe metabolic and respiratory acidosis. He had a blood pH of 6.99, PCO_2 of 66 mm Hg, bicarbonate level of 15 mmol/L, and a lactic level acid of 12.0 mmol/L. He was treated with sodium bicarbonate IV and his blood pH was raised to a normal level of 7.37 on June 16th (Table 8). The excessive treatment with sodium bicarbonate IV raised Ryan's blood pH to 7.50 on June 22nd (Table 9).

Ryan also suffered from hyperkalemia resulting from metabolic acidosis. He had a serum potassium level of 6.0 mmol/L. Treatment with sodium bicarbonate lowered his blood potassium level to 4.2 mmol/L at 11 hours following admission (Table 10). Ryan also suffered from hyperammonemia and hyperglycemia.

Ryan had a serum ammonia level of 84 μmol/L (normal range: 10-47 μmol/L), which indicates that he had a liver problem. His blood glucose level was 227 mg/dL and he was suffering from hyperglycemia (Table 11). Ryan was treated with ceftriaxone (Rocephin) antibiotic to fight bacterial infections and given IV fluid (0.9% NaCL).

Ryan developed hyperphosphatemia and hypermagnesiumia as a result of kidney failure. His blood phosphate level was about twice the upper normal level and his magnesium level reached 126% of the upper normal level. He also developed hypocalcemia as a result the calcium binding with the phosphorous. His serum calcium level was reduced by 21% of those measured at the time of admission on June 13th (Table 12).

A blood analysis performed on June 13th showed that Ryan was suffering from hypoalbuminemia, and hypoprotenemia. His serum albumin and protein levels were reduced by 30% and 25% within 6 hours following admission, respectively. They reached their lowest levels at two days following admission (Table 13). In addition, Ryan's serum creatinine and urea nitrogen levels were lower than the lower normal limit on June 13th (Table 14).

Ryan's red blood cell count, hemoglobin level, and hematocrit values were about 53-58% of the average normal values (Table 15). His urine showed a high level of hemoglobin on June 14th (Table 16). He was suffering from hemolytic anemia. He was given red blood cell transfusions.

Ryan had normal levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) on June 13th. However, on June 14th, his ALT and AST levels in serum were increased by 28 and 34 times their levels measured on June 13th, respectively (Table 17). These data indicate that Ryan developed liver damage during the 24 hours following admission due to infections and/or the precipitation of calcium phosphate in the liver.

A blood analysis performed during the 24 hours following admission showed that Ryan prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR) were highly elevated as a result of liver damage. His serum levels of fibrinogen (FIB) and D-dimer fragments were also elevated (Table 19). His platelet count was reduced by 70% following admission (Table 15). These data indicate that Ryan was suffering from Disseminated Intravascular Coagulation (DIC).

Ryan's body weight, length, head circumference (HC), and abdominal girth (ABG) measurements indicate that he had subcutaneous edema prior to his admission and his edema became worse during the first week following admission. His weight and length at the time of admission on June 13th were 5900 g and 67 cm, respectively. His weight and length were 5471 g and 60.6 cm on June 4th.

During the 9 days prior to admission, Ryan gained weight at the rate of 47.7 g/day and his length increased by 6.37 cm. However, during the period between birth and June 4th, Ryan gained weight at the rate of 31.0 g/day and his length increased at the rate of 4.32 cm/month. In addition, during the first week following admission, his HC, ABG, and weight increased by 4.5 cm and 6.5 cm, and 1965 g, respectively. His weight gain rate was 281 g/day (Table 20).

Ryan's treatment with furosemide (diuretic) started on June 16th and his head circumference and abdominal girth were reduced by 4 cm and 6.5 cm, respectively. His body weight was reduced by 15%. These data indicate that Ryan's body was not eliminating fluid as it should and he had a severe kidney problem.

Blood analysis performed on June 14th showed that Ryan had a high band neutrophil count of 28% of the total white blood cell count (WBC). His band count increased to 42% of the WBC by June 15th (Table 21). Ryan was treated with antibiotics (ceftriaxone, clindamycin, vancomycin, Co-Trimoxazole) and his band count was reduced to 6%. These data indicate that Ryan was suffering from bacterial infections.

Ryan was treated with four types of antibiotics (ceftriaxone, clindamycin, vancomycin, Co-Trimoxazole) during the 11 days following admission to fight infection. He was also treated with fentanyl citrate, phenobarbital, lorazepam, vecuronium bromide, Tylenol, Zantac, furosemide (diuretic), corticosteroids, and other medications (Tables 22, 23).

A CT scan of the brain performed on June 13th did not show intracranial bleeding or necrosis. Bleeding and necrosis in the brain were first observed on June 21st by a Magnetic Resonance Imaging (MRI) head exam. It showed bilateral extra-axial fluids collections in the occipital parietal areas and posterior interhemispheric fissure suggestive of subacute hematomas and acute infarcts.

Ryan's eye exam was performed on June 22nd and it showed bilateral retinal bleeding. Ryan was discharged from the hospital on July 19th. The clinical data described in Section 4 (1-12) indicate that Ryan's acute illness was caused by Streptococcus pneumonia infection, which led to hemolytic uremic syndrome (HUS) and multiorgan failure.

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The likely causes of the bleeding in the brain and retina in Ryan's case were liver damage, infections, and vitamin K deficiency. Infections caused blood clotting problems and Disseminated Intravascular Coagulation (DIC). Vitamin K deficiency resulted from the use of antibiotics. The likely causes of Ryan's brain ischemia were the high blood ammonia levels, metabolic acidosis, brain edema, anoxia, and DIC.

4.1 Metabolic and respiratory acidosis

Ryan suffered from severe metabolic and respiratory acidosis as a result of renal and pulmonary problems. His initial blood pH was 6.96. He was treated with sodium bicarbonate that raised his blood pH to 7.37 at three days following admission. His lactic acid level at the time of admission was 5.45 times higher than the upper normal limit (Table 8). The excessive treatment with sodium bicarbonate IV raised his blood pH to 7.50 (Table 9).

4.2 Hyperkalemia and hypokalemia

Ryan suffered from hyperkalemia as a result of metabolic acidosis. He had a serum potassium level of 6.0 mmol/L. He was treated with sodium bicarbonate and his potassium level was reduced to 4.2 mmol/L at 11 hours following admission. Ryan developed hypokalemia on June 18th and he was treated with potassium chloride. Ryan had normal serum sodium and chloride levels at the time of admission (Table 10).

Table 8. Ryan's blood gases measured during the first 4 days following admission at MMC

Date	Time	PH	PCO_2 (mmHg)	PO_2 (mm Hg)	HCO_3 (mmol/L)	Lactic Acid (mmol/L)
06/13/07	2317	6.96	66	261	15	12.0
06/14/07	0111	7.02	55	278	15	10.3
06/14/07	0405	7.27	38	282	17	6.1
06/14/07	0654	7.31	40	398	20	2.0
06/14/07	0949	7.21	58	100	23	1.8
06/14/07	1105	7.24	50	93	21	1.4
06/14/07	1352	7.26	48	131	22	2.3
06/14/07	1553	7.28	48	128	23	2.8
06/14/07	1958	7.30	39	92	19	2.8
06/15/07	0050	7.16	50	90	18	4.5
06/15/07	0442	7.04	58	86	16	5.8
06/15/07	0622	7.12	49	71	16	4.6
06/15/07	0712	7.05	66	49	18	3.9
06/15/07	0855	6.96	82	57	19	3.7
06/15/07	0957	7.10	71	55	23	6.1
06/15/07	1035	7.10	89	159	28	4.3
06/15/07	1206	7.23	64	141	27	3.2
06/15/07	1545	7.23	66	158	28	2.7
06/15/07	1735	7.25	57	115	25	2.5
06/15/07	1956	7.26	56	82	25	1.7
06/16/07	0007	7.27	53	85	25	2.3
06/16/07	0341	7.31	50	73	26	1.9
06/16/07	0824	7.29	49	81	24	1.9
06/16/07	1206	7.22	61	84	25	4.1
06/16/07	1428	7.29	48	100	23	1.8
06/16/07	1849	7.24	56	96	24	1.5
06/16/07	2354	7.37	41	147	24	2.7
Reference Range		7.34-7.45	35-45	60-70	17-25	0.2-2.2

Table 9. Ryan's blood gases measured on June 17-24, 2007 at MMC

Date	Time	PH	PCO_2 mm Hg	PO_2 mm Hg	HCO_3 mmol/L	Lactic Acid mmol/L
06/17/07	0452	7.45	37	80	26	3.0
06/17/07	1243	7.40	40	84	25	2.2
06/17/07	1954	7.44	36	69	25	1.7
06/18/07	0359	7.38	53	69	32	1.1
06/18/07	1312	7.46	40	84	29	1.6
06/18/07	2126	7.44	46	86	32	1.5
06/19/07	0411	7.48	40	84	29	1.6
06/19/07	1227	7.43	46	86	32	1.5
06/19/07	1730	7.38	39	67	30	1.5
06/19/07	2229	7.44	44	155	30	0.9
06/20/07	0504	7.45	36	98	25	1.4
06/20/07	1138	7.44	38	133	26	1.1
06/20/07	1515	7.49	33	127	25	1.2
06/20/07	1823	7.45	27	117	19	0.7
06/21/07	0458	7.45	29	115	21	0.8
06/22/07	0514	7.47	32	69	23	---[1]
06/22/07	1130	7.50	29	86	22	1.2
06/23/07	0555	7.39	40	94	24	0.9
06/24/07	0454	7.45	32	122	22	1.0
Refer. Range		7.34-7.45	35-45	60-70	17-25	0.2-2.2

[1]Not measured

Table 10. Ryan's serum potassium, sodium, and chloride levels

Date	Time	Potassium (mmol/L)	Sodium (mmol/L)	Chloride (mmol/L)
06/13/07	1756	6.0	135	105
06/13/07	2317	5.3	144	115
06/14/07	0900	4.2	142	114
06/15/07	0400	5.3	133	113
06/15/07	1209	4.7	135	108
06/15/07	1735	4.2	133	108
06/16/07	0400	4.9	131	105
06/16/07	0500	3.5	134	98
06/18/07	0400	2.6	141	98
06/18/07	0834	2.5	139	97
06/18/07	1718	3.1	141	102
06/19/07	0400	3.3	141	99
06/20/07	0400	3.8	142	106
06/21/07	0500	5.0	134	103
06/22/07	0500	4.5	134	105
06/24/07	0400	4.5	139	113
07/02/07	1237	4.8	137	106
Reference Range		3.8-4.8	136-143	100-108

4.3 Hyperammonemia and hyperglycemia

A blood analysis performed following admission on June 13th showed that Ryan suffered from hyperammonemia and hyperglycemia. He had a serum ammonia level of 84 µmol/L (normal range: 10-47 µmol/L). He had a high serum glucose level of 227 mg/dL and his blood glucose level reached a normal level at two days following admission (Table 11).

Hyperglycemia resulted from the inhibition of glucose use by the peripheral tissues due to the high levels of ammonia in Ryan's blood. An increase in the glucagon blood level due to

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stress and infections and/or reduction in the in the level of insulin can also lead to hyperglycemia.

4.4 Hyperphosphatemia, hypermagnesiumia, and hypocalcemia

Ryan developed hyperphosphatemia and hypermagnesiumia as a result of kidney failure. His blood phosphate level was about 2 times the upper normal level. His magnesium level reached 126% of the upper normal level. He also developed hypocalcemia as a result of calcium binding with the phosphorous. His serum calcium level was reduced by 21% of those measured at the time of admission on June 13th (Table 12).

Table 11. Ryan's glucose levels

Date	Time	Glucose (mg/dL)
6/13/07	1756	227
6/13/07	2317	174
6/14/07	0900	166
6/15/07	0400	154
6/15/07	1735	90
6/16/07	0400	58
6/17/07	0500	112
06/18/07	0400	87
06/19/07	0400	88
06/21/07	0500	78
06/24/07	0400	91
07/02/07	1237	91
07/10/07	1344	79
Reference Range		60-110

Table 12. Ryan's serum electrolyte levels

Date	Time	Phosphorous (mg/dL)	Calcium (mg/dL)	Magnesium (mg/dL)
06/13/07	1756	---[1]	9.9	-
06/13/07	2317	**9.5**	8.9	2.9
06/14/07	0900	---	8.2	---
06/15/07	0400	9.4	8.8	2.4
06/15/07	1209	6.9	8.1	2.1
06/15/07	1735	---	8.0	-
06/16/07	0400	5.6	8.3	2.0
06/16/07	0500	5.3	8.4	1.8
06/18/07	0400	---	8.6	---
06/18/07	0834	---	7.8	---
06/18/07	1718	---	7.8	---
06/19/07	0400	3.2	9.1	1.9
06/20/07	0400	3.1	9.2	2.0
06/21/07	0500	3.1	9.8	2.0
06/22/07	0500	---	9.5	---
06/24/07	0400	5.5	9.6	2.0
07/02/07	1237	5.9	10.3	2.2
Ref. Range		2.5-4.8	9.1-10.5	1.5-2.3

[1]Not measured

4.5 Hypoalbuminemia and hypoprotenemia

A blood analysis performed on June 13th showed that Ryan suffered from hypoalbuminemia, and hypoprotenemia. His serum albumin and protein levels were reduced by 30% and 25% within 6 hours following admission, respectively. They reached their lowest levels at two days following admission (Table 13). In addition, on June 13th, Ryan's serum creatinine and urea nitrogen levels were lower than the normal lower limit (Table 14).

Table 13. Ryan's serum albumin and protein levels

Date	Time	Albumin (g/dL)	T. Protein (g/dL)
6/13/07	1756	3.7	5.2
6/13/07	2317	2.6	3.9
6/14/07	1200	2.8	4.0
6/15/07	0400	2.5	4.0
6/15/07	1700	2.3	3.7
6/16/07	0400	2.3	3.8
6/19/07	0400	2.2	3.7
6/21/07	050	2.7	4.6
7/02/07	1237	3.9	6.2
7/10/07	1344	3.8	5.6
Reference range		4.1-5.1	6.8-8.6

Table 14. Ryan's serum creatinine and urea levels

Date	Time	Creatin. (mg/dL)	BUN (mg/dL)
6/13/07	1756	0.3	6
6/13/07	2317	0.4	12
6/14/07	0900	0.3	12
6/15/07	0400	0.6	19
6/15/07	1735	---[1]	22
6/16/07	0400	0.7	26
6/17/07	0500	---	26
06/18/07	0400	---	22
06/19/07	0400	0.5	19
06/21/07	050	0.3	17
06/24/07	0400	0.2	12
07/02/07	1237	0.3	12
07/10/07	1344	-	11
Reference Range		0.4-1.0	7-23

[1]Not measured

4.6 Evidence of hemolytic anemia

A blood analysis performed following admission on June 13th showed that Ryan was suffering from anemia (Table 15). A urine analysis performed on June 14th showed a significant amount of hemoglobin in the urine (Table 16). These data indicate that he was suffering from hemolytic anemia.

4.7 Evidence of liver damage

Ryan had normal levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (ASAT) on June 13th. However, on June 14th, his serum ALT and AST levels were increased by 28 and 34 times their levels measured on June 13th, respectively (Table 17). These data indicate that Ryan developed liver damage during the 24 hours following admission due to infection and/or precipitation of calcium phosphate in the liver. His serum bilirubin level was within the normal range (Table 17).

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Table 15. Ryan's hematology values

Date	Time	RBC x10^6/µL	HGB (g/dL)	HCT%	PLT x10^3/µL
06/13/07	1756	2.40	8.3	23.8	472
06/13/07	2317	2.02	6.7	20.3	459
06/14/07	1200	3.64	11.3	33.0	142
06/14/07	1554	3.72	11.3	33.6	155
06/15/07	0400	3.87	12.0	35.4	264
06/15/07	1209	3.56	11.0	32.5	196
06/15/07	1735	3.38	10.5	30.7	195
06/16/07	0400	3.30	10.2	30.2	191
06/17/07	0500	2.78	8.70	24.9	167
06/17/07	1600	3.36	10.3	29.9	120
06/18/07	0400	3.64	10.9	32.7	117
06/19/07	0400	3.75	11.7	33.6	122
06/19/07	1833	3.05	9.40	27.3	119
06/20/07	0400	4.23	13.0	38.3	126
06/21/07	0500	4.76	14.5	43.0	172
06/22/07	0500	4.66	14.5	42.5	201
06/24/07	0400	4.74	15.2	43.2	249
07/02/07	1237	4.15	12.4	37.5	565
Ref. Range		3.1-4.5	9.5-13.5	29.0-41.0	150-500

Table 16. Urine analyses performed during the 24 hours following admission

Measurements	06/13/07	06/14/07	Reference Range
Color	Yellow	Yellow	Yellow
Appearance	Clear	Cloudy	Clear
Spec. gravity (g/mL)	<1.005	1.018	1.010-1.020
PH	7.0	5.5	4.6-8.0
Protein	Trace	Trace	Negative
Glucose	Negative	Negative	Negative
Ketone bodies	Negative	Negative	Negative
Hemoglobin	---[1]	3+	Negative
Bill	Negative	Negative	Negative
Urob (mg/dL)	0.1	0.2	0.2-1.0
Nitrite	Negative	Negative	Negative
Leuko esterase	Negative	Negative	Negative
WBC	None seen	0-2	<5
RBC	0-2	0-2	0

[1]Not measured

Table 17. Ryan' serum enzymes levels

Date	Time	Alk phospho (IU/L)	LDH (IU/L)	ALT (IU/L)	AST (IU/L)
06/13/07	1756	257	---[1]	19	27
06/13/07	2317	235	-	26	63
06/14/07	1200	171	-	533	934
06/15/07	0400	150	-	444	746
06/15/07	1230	-	172	-	-
06/15/07	1700	113	-	364	695
06/16/07	0400	108	-	370	556
06/19/07	0400	104	-	221	140
06/21/07	0500	135	-	176	102
06/22/07	1130	-	1173	-	-
07/02/07	1237	202	457	50	53
07/10/07	1344	261	-	50	46
Ref. Range		56-350	110-227	10-40	15-37

[1]Not measured

Table 18. Ryan's serum bilirubin levels

Date	Time	Total Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)
06/13/07	2317	0.3	0.1
06/15/07	0400	0.2	0.1
06/15/07	1700	0.2	0.1
06/16/07	0400	0.2	0.1
06/19/07	0400	0.1	0.0
06/21/07	0500	0.3	0.1
07/02/07	1237	0.2	0.1
07/10/07	1344	0.1	0.1
Ref. range		0.2-0.9	0.1-0.5

Table 19. Ryan's blood clotting and DIC indicators

Date	Time	PT (Sec.)	PTT (Sec.)	INR	FIB (mg/dL)	DDIM (ng/mL)	DDIMH (ng/mL)
6/14/07	0400	---[1]	53.9	---	1591	>1050	>5250
6/14/07	1200	19.7	---	1.6	---	---	---
6/15/07	0400	26.4	40.4	2.1	514	1050	3489
6/15/07	1235	19.0	35.7	1.5	---	1050	2658
6/15/07	1700	18.5	32.3	1.5	---	---	---
6/16/07	0400	17.3	31.8	1.4	---	435	---
6/17/07	0500	12.8	28.8	1.0	---	---	---
Reference Range		10.5-14.5	22.7-36.0	0.8-1.2	239-531	<318	<318

[1]Not measured

4.8 Evidence of blood clotting problems

Blood analyses performed during the 24 hours following admission showed that Ryan's prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR) were highly elevated as a result of liver damage. His serum levels of fibrinogen (FIB) and D-dimer fragments (DDIM) were also elevated (Table 19). His platelet count was reduced by 70% following admission (Table 15). These data indicate that Ryan was suffering from Disseminated intravascular Coagulation (DIC).

4.9 Evidence of edema

Ryan's body weight, length, head circumference (HC), and abdominal girth (ABG) measurements indicate that he suffered from subcutaneous edema prior to his admission as a result of kidney problems. His edema became worse during the first week following admission. His weight and length at the time of admission on June 13th were 5900 g and 67 cm, respectively. His weight and length were 5471 g and 60.6 cm on June 4th.

During the 9 days prior to admission, Ryan gained weight at the rate of 47.7 g/day and his length increased by 6.37 cm. However, during the period between birth and June 4th, Ryan gained weight at the rate of 31.0 g/day and his length increased at the rate of 4.32 cm/month.

In addition, during the first week following admission, his head circumference, abdominal girth, and weight increased by 4.5 cm and 6.5 cm, and 1965 g, respectively. His weight gain rate was 281 g/day (Table 20).

Ryan's treatment with furosemide (diuretic) started on June 16th and his head circumference and abdominal girth were reduced by 4 cm and 6.5 cm, respectively. His body weight was reduced by 15%. These data indicate that Ryan's body was not eliminating fluid as it should and he had severe kidney problems.

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Table 20. Ryan's weight, length, head circumference, and abdominal girth

Date	Weight (g)	Length (cm)	HC (cm)	ABG (cm)
June 13	5900	67	---[1]	---
June 14	---	---	42.5	---
June 15	---	---	43.5	48.5
June 16	---	67	44.5	---
June 17	---	---	45.5	48.5
June 18	---	---	47	---
June 19	---	---	45	47
June21	---	---	---	48
June 22	7865	---	---	48
June 25	7000	---	---	43
June 26	---	---	---	43
June 28	6668	---	---	---
June 29	6649	---	---	42
July 2	6741	---	---	---
July 4	6780	---	---	---
July 6	6809	---	---	---
July 10	---	---	43.5	---
July 11	7092	---	---	---
July 13	7165	---	---	---

[1]Not measured

4.10 Evidence of infections

Blood analysis performed on June 14th showed that Ryan had a high band neutrophil count of 28% of the total white blood cell count (WBC). His band count was increased to 42% of the WBC by June 15th (Table 21). Ryan was treated with antibiotics (ceftriaxone, clindamycin, vancomycin, Co-Trimoxazole) and his band count decreased to 6%. These data indicate that Ryan was suffering from bacterial infections.

4.11 Treatments given

The lists of medications given to Ryan in the hospital are presented in Tables 22 and 23. Ryan was treated with four types of antibiotics (ceftriaxone, clindamycin, vancomycin, Co-Trimoxazole) during the 11 days following admission to fight bacterial infections. He was also treated with fentanyl citrate, phenobarbital, lorazepam, vecuronium bromide, Tylenol, zantac, corticosteroids, and other medications.

Ryan's treatment with furosemide (diuretic) started on June 16th and his head circumference and abdominal girth were reduced by 4 cm and 6.5 cm, respectively. His body weight was reduced by 15%.

Table 21. Ryan's white blood cell and differential counts

Date	Time	WBC	Neutro-phil %	Neutro. Band %	Lympho-cyte %	Mono-cyte %	Esono-phil %
6/13/07	2317	9.4	36.7	---[1]	61.0	0.8	1.3
6/14/07	1200	3.8	58	28	8	5	1
6/14/07	1554	4.8	88.3	-	7.6	3.8	0.2
6/15/07	0400	15.0	29	42	22	3	1
6/15/07	1209	12	89	2	8	1	---
6/16/07	0400	12.5	71	8	15	6	---
6/17/07	0500	12.7	87.5	---	5.2	6.1	---
6/17/07	1600	14.2	92.6	---	6.3	0.6	---
6/18/07	0400	11.3	63	7	19	8	3
6/19/07	0400	7.3	42	6	37	8	7
6/19/07	1833	8.3	45.2	---	31.1	17.3	6.2
6/20/07	0400	9.1	40.7	---	30.8	20.5	7.3
6/21/07	0500	10.2	46.7	---	27.3	18.8	6.8
6/22/07	0500	9	47.1	---	29.5	17.0	5.7
6/24/07	0400	8.7	59	8	27	5	---
7/02/07	1237	7.5	45.8	---	41.1	8.4	3.8
Reference range		7-19	30-40	0-8	45-60	1-5	1-5

[1]Not measured

Table 22. Medications given to Ryan on June 13-21, 2007

Date	Treatments Given
June 13	0.9% NaCl, Ceftriaxone (Rocephin)
June 14	Sodium bicarbonate, Fentanyl citrate, RBC transfusion, Vecuronium bromide, Zantac, Lorazepam, Phenobarbital, Clindamycin, Phenobarbital, and Ceftriaxone (Rocephin).
June 15	Dopamine, Tromethamine, Dopamine, Vancomycin, Hydrocortisone INJ, Zantac, RBC transfusion, fresh frozen plasma transfusion, Phenobarbital, Zantac, Norepinephrine, Sodium bicarbonate, Ceftriaxone (Rocephin), Co-Trimoxazole, Clindamycin, Vecuronium bromide, and Phenobarbital.
June 16	Dopamine, Vecuronium bromide, Heparin 500 unit in 500 mL D5, Norepinephrine, Hydrocortisone INJ, Fentanyl citrate, Furosemide, Vancomycin, Phenobarbital, and Phytonadione (vitamin K), 1 mg/day.
June 17	Dextrose, Fentanyl citrate, Heparin 500 unit in 500 mL NS, Co-Trimoxazole, RBC transfusion, Vecuronium bromide, Hydrocortisone INJ, Midzolam (versed), Lorazepam, and Phytonadione (vitamin K), 1 mg/day.
June 18	Dextrose, potassium chloride, Vancomycin, Zantac, Furosemide, Fentanyl citrate, Phenobarbital, Vecuronium bromide, Lorazepam, Phytonadione (vitamin K), 1 mg/day.
June 19	Hydrocortisone INJ, Co-Trimoxazole, Fentanyl citrate Vecuronium bromide, and Phytonadione (vitamin K), 1 mg/day.
June 20	Dextrose, Heparin 500 unit in 500 mL NS, Vecuronium bromide, Phenobarbital, Co-Trimoxazole, Fentanyl citrate, and Phytonadione (vitamin K), 1 mg/day.
June 21	Dextrose, Vancomycin,Vecuronium bromide, Furosemide, Phenobarbital, Fentanyl citrate, and Phytonadione (vitamin K), 1 mg/day.

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Table 23. Medications given to Ryan on June 22-July 16, 2007

Date	Treatments Given
June 22	Fentanyl citrate, Lorazepam, Vecuronium bromide, Heparin 500 unit in 500 mL NS, Zantac, and Phenobarbital.
June 23	Vecuronium bromide, and Phenobarbital.
June 24	Vancomycin, Phenobarbital, Lorazepam, Zantac
June 25	Lorazepam, Fentanyl citrate, Vecuronium bromide, and Zantac
June 28	Tylenol
June 30	Lorazepam
July 2	Lorazepam and Phenobarbital
July 3	Albuterol, Lorazepam, and Tylenol
July 4	Tylenol and Lorazepam
July 5	Phenobarbital
July 6	Tylenol, Zantac, Lorazepam, Phenobarbital, and Dexamethasone.
July 10	Tetracaine HCL 0.5% (ophthalmic solution), and Neo-Synephrine (ophthalmic solution).
July 11	Phenobarbital, Lorazepam, and D5-1/2 NS.
July 12	Cefazolin, Tylenol, D5-1/2 Ns, D5/0.33% NaCl, Pedialyte, Morphine, and Phenobarbital.
July 13	Phenobarbital, Lorazepam, Pedialyte, and Benadryl.
July 14	D5/0.33% NaCl, and Benadryl.
July 16	Tylenol, Morphine, Neo-Synephrine (ophthalmic solution) Pontocaine, and Benadryl.

4.12 Development of brain and retinal bleeding following admission to the hospital

A CT scan of Ryan's brain performed following admission on June 13th did not show intracranial bleeding or necrosis. brain. Bleeding and necrosis in the brain were first observed on June 21st by the Magnetic Resonance Imaging (MRI) head exam. Ryan's MRI exam showed bilateral extra-axial fluids collections in the occipital parietal areas and posterior interhemispheric fissure suggestive of subacute hematomas. It also showed areas of acute infarcts in the temporoccipital perital lobes and frontal lobes.

Ryan's eye exam performed on June 22nd showed bilateral retinal bleeding. The bleeding in the brain and retina in Ryan's case was caused by liver damage, infections, and vitamin K deficiency. The infections caused blood clotting problem and Disseminated Intravascular Coagulation (DIC). Vitamin K deficiency resulted from the use of antibiotics. The brain ischemia was caused by the high levels of ammonia and other toxicants in the blood, brain edema, and DIC resulted from the infections.

5. The likely causes of Ryan's acute illness, seizure, nose bleeding, coma, and cardiac arrest

The clinical data described in Sections 3 and 4 of this report indicate that Ryan's acute illness was caused by Streptococcus pneumonia infection. It led to the development of hemorrhagic pneumonia, hemolytic uremic syndrome (HUS), kidney and liver problems, hepatic encephalopathy, metabolic and respiratory acidosis, seizure, coma, and cardiac arrest. The following is a detailed description of the clinical events that led to Ryan's acute illness and cardiac arrest on June 13, 2007.

1) Ryan suffered from seizure, coma, and cardiac arrest on June 13, 2007 due to the development of hepatic encephalopathy which resulted from high levels of ammonia and other metabolic toxins in his blood. His serum ammonia level on June 14th was 84 µmol/L (normal range: 10-47 µmol/L). Ryan's serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) on June 14th were highly elevated (Table 17). Seizure is the likely cause of Ryan's fall from the bouncy chair onto the floor on June 13, 2007.

2) Ryan suffered from hemorrhagic pneumonia on June 13th. His chest X-ray and CT scan exams performed on June 13th showed evidence of pulmonary edema, bleeding, and pneumonia. He had agonal breathing with blood coming from the endotracheal tube (ETT). The lungs were the likely source of Ryan's nose bleed observed on June 13th.

Blood analysis performed on June 14th showed Ryan had a high band neutrophil count of 28% of the total white blood cell count (WBC). His band count increased to 42% of the WBC by June 15th (Table 21). Ryan was treated with antibiotics (ceftriaxone, clindamycin, vancomycin, Co-Trimoxazole) and his band count was reduced to 6%. These data indicate that Ryan was suffering from bacterial infections.

3) Ryan suffered from severe metabolic and respiratory acidosis as a result of renal and pulmonary problems. His initial blood pH was 6.96. His lactic acid level at the time of admission was 5.45 times higher than the upper normal limit (Table 8). He developed hyperkalemia as a result of metabolic acidosis. He had a serum potassium level of 6.0 mmol/L (Table 10).

4) Ryan developed hyperglycemia. His serum glucose level on June 13th was 227 mg/dL. The likely cause of Ryan's hyperglycemia was the high levels of ammonia in his blood. Ammonia inhibits the use of glucose by the peripheral tissues.

5) A blood analysis performed following admission on June 13th showed that Ryan suffered from anemia (Table 15). His urine analysis performed on June 14th showed a significant amount of hemoglobin present in the urine (Table 16). These data indicate that he was suffering from hemolytic anemia.

6) Ryan developed subcutaneous edema as a result of kidney problems. His weight and length at the time of admission on June 13th were 5900 g and 67 cm, respectively. His weight and length were 5471 g and 60.6 cm on June 4th. During the 9 days prior admission, Ryan gained weight at a rate of 47.7 g/day and his length increased by 6.37 cm. However, during the period between birth and June 4th, Ryan gained weight at a rate of 31.0 g/day and his length increased at a rate of 4.32 cm/month.

In addition, during the first week following admission, Ryan's head circumference, abdominal girth, and weight increased by 4.5 cm and 6.5 cm, and 1965 g, respectively. His weight gain rate was 281 g/day (Table 20). Ryan's treatment with furosemide (diuretic) started on June 16th and his head cir-

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cumference and abdominal girth decreased by 4 cm and 6.5 cm, respectively. His body weight decreased by 15%.

7) Ryan developed hyperphosphatemia and hypermagnesiumia following admission as a result of kidney failure. His blood phosphate level was about twice the upper normal level. His magnesium level reached 126% of the upper normal level. He also developed hypocalcemia as a result of calcium binding with phosphorous. His serum calcium level was reduced by 21% of those measured at the time of admission (Table 12).

5.1 Streptococcus pneumoniae infection in children and hemolytic uremic syndrome

Ryan suffered from hemorrhagic pneumonia, hemolytic anemia, and kidney problems. The likely cause of Ryan's health problems was infection with Streptococcus pneumoniae. Constantinescu *et al.* reviewed the medical records of 247 children with HUS and found 27 of them (11%) had non-enteropathic hemolytic uremic syndrome (HUS). Infection caused by S pneumoniae was diagnosed in 9 children (38%). The mean age of these children at the onset of illness was 4.2 +/- 0.9 (SE) years.

Dialysis was performed in 17 children (71%) for 40 +/- 27 days. Median length of hospitalization was 22 days (range, 2 to 71 days). Children with S. pneumoniae-related HUS had a longer hospital stay than those with other causes of non-enteropathic HUS, but all children with S. pneumoniae-related HUS recovered kidney function [4].

In addition, Waters *et al.* evaluated the medical records of 43 cases of children who developed pneumococcal-associated hemolytic uremic syndrome (P-HUS). The median age at presentation was 13 months (range, 5-39 months). These children had microangiopathic hemolytic anemia (Hb <10 g/dL with fragmented RBCs), thrombocytopenia (platelet count < 130 x 10(9)/L), acute renal impairment with oliguria and elevated plasma creatinine levels.

Pneumococcus was identified in 34 of 43 cases; T-activation was identified in 36 of 37 cases. The mortality rate was 11%, comprising 3 cases of meningitis, 1 case of sepsis and 1 case of pulmonary embolism at 8 months follow up while on dialysis [5].

Streptococcus pneumoniae-related hemolytic uremic syndrome (HUS) represents a heterogeneous group of disorders [4]. Malla *et al.* reviewed the clinical presentations of hemolytic uremic syndrome (HUS) in 25 children less than 5 years of age. HUS was confirmed after laboratory investigations showing features of hemolytic anemia, thrombocytopenia and renal insufficiency.

The symptoms in these children were fever 88%, respiratory distress and convulsion 52%, oliguria 40%, anuria 60%, reluctant to feed 40% and cough 28%. The main physical findings noted were irritability 40%, pallor 100%, dehydration 28%, puffy face with edema 32%, high blood pressure 16%, hepatomegaly 28%, jaundice, sclerema and petechial rashes 8%, lethargic 16%, acidotic breathing 48% and rectal prolapse 12% [6].

In addition, Mencía Bartolomé *et al.* studied 43 cases of children (mean age 3.2 years) who developed hemolytic uremic syndrome (HUS). All children had acute renal failure, 32 of them (74%) required peritoneal dialysis. Anuria was found in 22 case (51%) and the mean duration was 10.3 days. The most frequent complications were: Hypertension in 21 cases (48%), peritonitis in 9 cases (20%), seizures in 8 children (16%) and 3 deaths (6%). The mean hospital stay was 14.5 days [7].

Furthermore, Krysan and Flynn reviewed the literature and found 37 cases of children who developed hemolytic uremic syndrome (HUS) resulting from infection with Streptococcus pneumoniae. They developed oligoanuria and 2 of them progressed to end-stage renal disease [8]. Mizusawa *et al.* also evaluated 55 children (aged 2 months to 13 years) who developed hemolytic uremic syndrome. They found HUS in 10 children was caused by pneumococcal pneumonia [9].

In addition, Nathanson *et al.* described 11 cases of Streptococcus pneumoniae-induced HUS associated with meningitis and pneumonia. The mean duration of dialysis was 32 days in the individuals with acute renal failure who survived the acute infectious period. Cortical necrosis was documented in 5 of 6 kidney specimens [10].

Furthermore, Tinaztepe *et al.* described the symptoms and kidney lesions in 15 cases of children (age 10 months-15 years) who developed hemolytic uremic syndrome (HUS). Ten children (67%) presented with gastrointestinal symptoms, 4 (27%) had neurological symptoms, and three children (20%) had upper respiratory infections. All children had anemia (Hb 3.4-10 g/dl) and acute renal failure. Light microscopy revealed microangiopathic type involvement of the glomeruli in all cases [11].

Pan *et al.* stated that the production of neuraminidase by S. pneumoniae results in exposure of red blood cell T-antigen, resulting in hemolysis, thrombocytopenia, and acute renal failure. They reported three cases of children who had S. pneumoniae-associated HUS. These children also developed liver failure. The increases in asparagine transaminase ranged from 11 to 46 times normal values and an increase in alanine transaminase ranged from 1.6 to 8 times normal. The hepatic injury in all three cases resolved within 9, 5, and 10 days [12].

In addition, Chen *et al.* reported a 10-month-old female infant with Streptococcus pneumoniae-associated hemolytic uremic syndrome (HUS) who had severely elevated conjugated bilirubin and hepatic transaminases. Screening for viral hepatitis was negative. Evidence of biliary obstruction and hepatotoxic drug exposure was also absent [13].

5.2 Hepatic encephalopathy, seizure, and coma

Several biomarkers indicate that Ryan was suffering from acute hepatic injury, which led to the development of encephalopathy, seizure, and coma. These biomarkers include:

1) Highly elevated levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) on June 14th. Ryan's serum ALT and AST levels on June 14th were increased by 28 and 34 times of their levels measured on June 13th, respectively (Table 17).
2) Ryan's blood analysis performed on June 13th showed that he had hypoalbuminemia, and hypoprotenemia. His serum albumin and protein levels were reduced by 30% and 25% within 6

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hours following admission, respectively. They reached their lowest levels at two days following admission (Table 13).

3) Ryan had an elevated serum ammonia level of 84 µmol/L on June 14th (normal range: 10-47 µmol/L).

Individuals with acute or chronic hepatic failure usually develop hepatic encephalopathy (HE). It is characterized by neuropsychiatric manifestations that can range in severity from a mild alteration in mental state to a coma. Some neuromuscular symptoms may also develop. The complications of either acute or chronic hepatic disease are the result of a diminished hepatic reservoir and inability of the liver to detoxify some toxins that originate in the bowel or a product of the body metabolism [14-19].

Individuals suffering from acute liver failure usually develop cerebral edema. The increased intracranial pressure as a result of cell swelling may cause brain herniation [20, 21]. Overall incidence of seizures in hepatic encephalopathy varies between 2% and 33%. Non-convulsive status epilepticus may be particularly common in these individuals [22].

Ryan had an elevated serum ammonia level of 84 µmol/L on June 14th (normal range: 10-47 µmol/L). Clinical studies suggest that the rapid accumulation of ammonia by the brain is the major cause of the central nervous system complications of acute liver failure. Increased brain ammonia may cause cell swelling via the osmotic effects of an increase in astrocytic glutamine concentrations or by inhibition of glutamate removal from brain extracellular space [20, 23, 24].

Individuals experiencing acute elevations of ammonia usually present to the hospital with encephalopathy, which may progress quickly to cerebral herniation [25]. The following clinical studies show that there is a strong correlation between blood ammonia levels and the severity of HE in individuals suffering from acute or chronic hepatic failure:

1) Ong *et al.* conducted prospective a study to evaluate the correlation between ammonia levels in the blood and the severity of hepatic encephalopathy in 121 individuals with cirrhosis. Of the 121 individuals, 30 (25%) had grade 0 encephalopathy (no signs or symptoms), 27 (22%) had grade 1, 23 (19%) had grade 2, 28 (23%) had grade 3, and 13 (11%) had grade 4 (the most severe signs and symptoms).

Four types of ammonia measurements were analyzed: arterial and venous total ammonia, and arterial and venous partial pressure of ammonia. Spearman rank correlations (r(s)) were calculated. They found that each of the four measures of ammonia increased with the severity of hepatic encephalopathy: arterial total ammonia (r(s) = 0.61, $P \leq 0.001$), venous total ammonia (r(s) = 0.56, $P \leq 0.001$), arterial partial pressure of ammonia (r(s) = 0.55, $P \leq 0.001$), and venous partial pressure of ammonia (r(s) = 0.52, $P \leq 0.001$) [26].

2) Bernal *et al.* evaluated the relation of the admission arterial ammonia concentrations and other clinical variables with the development of encephalopathy (HE) and intracranial hypertension (ICH) in individuals with acute liver failure (ALF). Arterial ammonia was measured on admission to the intensive care unit in 257 individuals; 165 had ALF and severe HE, and there were 3 control groups: acute hepatic dysfunction without severe HE (n = 50), chronic liver disease (n = 33), and elective surgery (n = 9).

They found that ammonia was higher in the blood of ALF individuals than in controls. High blood levels of ammonia were associated with hepatic encephalopathy (HE) and intracranial hypertension (ICH). Ammonia level greater than 100 umol/L predicted the onset of severe HE with 70% accuracy [27].

3) Bhatia *et al.* conducted a prospective study to evaluate the relationship of arterial ammonia levels at admission to complications and survival among individuals with acute liver failure (ALF). Eighty consecutive ALF individuals were followed up until death or complete recovery. All had arterial ammonia estimation at admission. Logistic regression analysis was performed to identify independent predictors of mortality.

Forty-two individuals (52.5%) died within 32 months. Non-survivors had significantly higher median ammonia levels than survivors (174.7 v 105.0 µmol/L; $p<0.001$). An arterial ammonia level of $\geq$ 124 µmol/L was found to predict mortality with 78.6% sensitivity and 76.3% specificity, and had 77.5% diagnostic accuracy. Individuals with higher ammonia levels also developed more complications, including deeper encephalopathy ($p = 0.055$), cerebral edema ($p = 0.020$), need for ventilation ($p<0.001$), and seizures ($p = 0.006$) [24].

4) Clemmesen *et al.* conducted prospective and retrospective studies involving 44 individuals with acute liver failure (ALF) who developed hepatic encephalopathy (HE). Fourteen of these individuals also developed cerebral herniation (CH). They found that the individuals who developed CH (n = 14) had higher arterial plasma ammonia than the non-CH (n = 30) individuals (230 +/- 58 vs. 118 +/- 48 µmol/L; P <. 001) [28].

5) Kundra *et al.* designed a study to (a) evaluate and compare plasma ammonia levels (PAL) in 20 individuals with acute liver failure (ALF) and 12 individuals with chronic liver disease (CLD) and without hepatic encephalopathy (HE) and 8 individuals with CLD who developed HE; (b) correlate the severity of HE with PAL; and (c) correlate PAL with clinical features of raised intracranial tension in ALF.

They found that all individuals with ALF showed PAL more than the upper limit of the normal range, and there was strong correlation between the severity of HE and PAL [$r = 0.91$ at $P < 0.05$]. The mean PAL (µmol/L) +/- SD was 172.1 +/- 52.55 (normal levels = 10-47 µmol/L). In addition, their study showed that high PAL in ALF individuals correlate with clinical features of cerebral edema and raised intracranial tension [29].

6) Nicolao *et al.* compared venous, arterial and partial pressure of ammonia (pNH(3)) in 27 cirrhotics individuals with hepatic encephalopathy, 15 cirrhotics without hepatic encephalopathy, and a controls. In individuals with encephalopathy, each form of ammonia was higher than in both controls and individuals without encephalopathy. The correlation with the severity of hepatic encephalopathy was similar for venous (r=0.72), arterial ammonia (r=0.76) and pNH(3) (r=0.75) [30].

7) Tofteng *et al.* used in vivo brain microdialysis technique together with intracranial pressure (ICP) monitoring in 17 indi-

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viduals with fulminant hepatic failure (FHF). They found that individuals (n=8) who had a persisting high arterial ammonia concentration (above 200 μmol/L) developed high ICP (n=8) while individuals who did not experience surges of increased ICP (n=9) had a decline in the ammonia level (P<0.05) [31].

It has been reported that direct interference of ammonia at several points in cerebral energy metabolism, including glycolysis, TCA cycle, and the electron transport chain, could lead to energy depletion. Additionally, ammonia and glutamine may induce the mitochondrial permeability transition in astrocytes, a process capable of causing mitochondrial dysfunction. Altered mitochondrial metabolism appears to be an important mechanism responsible for the cerebral abnormalities associated with HE and other hyperammonemic states [32].

One effect of ammonia is the inhibition of the rate limiting TCA cycle enzyme alpha-ketoglutarate dehydrogenase (alphaKGDH). Inhibition of alphaKGDH both enhances the detoxification of ammonia by formation of glutamine from alpha-ketoglutarate and reduces the rate of NADH and oxidative ATP production in astrocytic mitochondria.

In the astrocytic cytosol, this will lead to formation of lactate even in the presence of sufficient oxygen supply. Since the aspartate-malate shuttle is compromised, there is a risk of depletion of mitochondrial NADH and ATP unless compensatory mechanisms are recruited [33-35].

Zwingmann evaluated the in vivo and ex vivo (1)H-, (13)C-, and (15)N-nuclear magnetic resonance (NMR) spectroscopy data collected from individuals with hepatic encephalopathy (HE) and experimental models of HE. The in vivo and ex vivo (1)H-NMR investigations revealed several fold increases in brain glutamine and concomitant decreases in myo-inositol, an important osmolyte in astrocytes. An osmotic disturbance in these cells has long been suggested to be responsible for astrocyte swelling and brain edema. The (15)N-NMR investigations have demonstrated that glutamine fluxes between neurons and astrocytes are affected by ammonia [36].

Additional factors such as systemic inflammation, alterations of the brain extracellular concentration of amino acids and neurotransmitters, and others have been identified and may contribute to the cerebral alterations of ALF [37].

Cerebral blood flow (CBF) is also altered in ALF and strongly influences the development of brain edema and intracranial pressure. For example, Jalan *et al.* conducted study in 21 individuals with acute liver failure (ALF) to determine the role of inflammation in the pathogenesis of increased intracranial pressure (ICP) in these individuals and its interplay with cerebral blood flow (CBF) and ammonia. These individuals were divided into two groups depend upon ICP. Group 1 (n=8) required specific treatment (ICP>20 mmHg) and group 2 (n=13) did not (ICP< or =20 mmHg).

They found that inflammatory markers, arterial ammonia and CBF were significantly higher in the individuals in group 1 than those in group 2. Their findings also suggest that inflammation plays an important synergistic role in the pathogenesis of increased ICP possibly through its effects on CBF [38].

Arias *et al.* described changes in the brain of individuals that are associated with the development of acute and chronic hepatic encephalopathy (HE) as follows: 1) An immediate or nervous phase with ischemia-reperfusion, which is associated with reperfusion injury, edema, and oxidative stress. 2) An intermediate or immune phase with microglia hyperactivity, which produces cytotoxic cytokines and chemokines and is involved in enzyme hyperproduction and phagocytosis. 3) A late or endocrine phase, in which neuroglial remodeling, with an alteration of angiogenesis and neurogenesis, occurs [39].

Furthermore, several abnormalities of cerebral blood flow (CBF), namely loss of cerebral autoregulation, altered reactivity to carbon dioxide, and development of cerebral hyperemia, have been described in individuals as well as experimental models of acute liver failure (ALF) and/or hyperammonemia. The development of cerebral hyperemia seems particularly relevant to the pathogenesis of brain edema in ALF. In addition to the potential increase of brain blood volume causing a rise in intracranial pressure, an increase of CBF could facilitate the movement of water across the blood brain barrier in an osmotically altered brain [40].

5.3 Acidosis induces brain edema

A CT scan of Ryan's brain taken following admission to the hospital on June 13th showed that he had a brain edema. Ryan suffered from severe acidosis and hyperglycemia. He had blood pH of 6.83, pCO_2 of 43 mm Hg, and blood glucose level of 227 mg/dL. Metabolic acidosis causes brain edema as shown by the clinical studies cited below.

1) Hanas *et al.* reviewed the records of 292 cases of diabetic ketoacidosis (pH < 7.30), aged 0.8-19.9 years. They found two children (11 years old) had overt symptoms of cerebral edema and one developed neurological sequelae. In addition, symptoms of subclinical cerebral edema after admission (headache, vomiting, lethargy) were recorded in an additional 16 cases. In two of these cases mannitol was given, and both recovered within 1-2 h [41].

2) Glaser *et al.* measured the intercaudate width of the frontal horns of the lateral ventricles using magnetic resonance imaging (MRI) in 41 children with diabetic ketoacidosis (DKA) during treatment and after recovery from the DKA episode. They found that narrowing of the lateral ventricles is evident in just over half of children being treated for DKA. They concluded that clinical evidence of cerebral edema in children with DKA is more common than previously reported [42].

3) Marcin *et al.* evaluated the medical records of 61 children with diabetic ketoacidosis who developed cerebral edema. They found 17 (28%) children died or survived in a vegetative state; 8 (13%) survived with mild to moderate neurologic disabilities; and 36 (59%) survived without sequelae. Factors associated with poor outcomes included greater neurologic depression at the time of diagnosis of cerebral edema, a high initial serum urea nitrogen concentration, and intubation with hyperventilation to a PCO2 <22 mm Hg [43].

Furthermore, Ryan was treated with high doses of sodium bicarbonate that raised his blood pH from 6.83 to 7.50. The treatment with high doses of sodium bicarbonate causes anoxia and brain edema [44-46].

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6. The likely causes of Ryan's intracrainal bleeding

The clinical evidence indicates that the intracranial bleeding observed in Ryan's case developed after his admission in the hospital on June 13, 2007. The CT scan of his brain performed on June 13th did not show intracranial bleeding. Bleeding and necrosis in the brain were first observed on June 21st by Magnetic Resonance Imaging (MRI) head exam. It showed bilateral extra-axial fluids collections in the occipital parietal areas and posterior interhemispheric fissure suggestive of subacute hematomas and acute infarcts.

The likely causes of Ryan's intracranial bleeding were liver damage, infections, and vitamin K deficiency. He developed liver damage due to infection and/or precipitation of calcium phosphate in the liver. Ryan was suffering from S. Pneumonia infection, which caused blood clotting problems and Disseminated Intravascular Coagulation (DIC). Vitamin K deficiency resulted from the treatment with high doses of four antibiotics for a significant time.

6.1 Liver damage leads to reduction in the synthesis of clotting factors and bleeding

Ryan developed liver damage as result of infection and/or the precipitation of calcium phosphate in the liver. The following clinical studies indicate that his liver damage was severe:

1) His levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were highly elevated on June 14th. His serum ALT and AST levels on June 14th were increased by 28 and 34 times of their levels measured on June 13th, respectively (Table 17).

2) Ryan had an elevated serum ammonia level of 84 μmol/L on June 14th (normal range: 10-47 μmol/L). His liver was not able to convert the ammonia generated as a result of metabolic product to urea.

3) Ryan's blood analysis performed on June 13th showed that he had hypoalbuminemia, and hypoprotenemia. His serum albumin and protein levels were reduced by 30% and 25% within 6 hours following admission, respectively. They reached their lowest levels at two days following admission (Table 13). His liver was not able to make protein.

A blood analysis performed during the 24 hours following Ryan's admission showed that his prothrombin time (PT), partial thromboplastin time (PTT) and international normalized ratio (INR) were highly elevated as a result of liver damage. His PTT on June 14th was 53.9 seconds (normal range: 22.7-36), which indicates problems with the *intrinsic pathway* of coagulation.

His PT and INR on June 15th were 26.4 seconds (normal range: 10.5-14.5) and 2.1 (normal range: 0.8-1.2), respectively and these measure the integrity of the *extrinsic pathway* of coagulation. PT measures factors II, V, VII, X and fibrinogen. These data indicate that Ryan's liver was unable to make clotting factors.

The liver plays a central role in the clotting process. Injuries and diseases of the liver are usually associated with coagulation disorders due to multiple processes. These include reducing the synthesis of clotting and inhibitor factors, decreasing the clearance of activated factors, and producing quantitative and qualitative platelet defects. Some of these abnormalities may lead to hyperfibrinolysis and the acceleration of the intravascular coagulation process [47-53].

6.2 Sepsis causes clotting problems and bleeding

Chest X-ray and CT scan exams performed following Ryan's admission on June 13th showed evidence of pulmonary edema, bleeding, and pneumonia. His blood analysis performed on June 14th showed that he had a high band neutrophil count of 28% of the total white blood cell count (WBC). His band count increased to 42% of the WBC by June 15th (Table 21). Ryan was treated with antibiotics (ceftriaxone, clindamycin, vancomycin, Co-Trimoxazole) and his band count was reduced to 6%. These clinical studies and others indicate that Ryan's illness was caused by Streptococcus pneumonia.

Septicemia is frequently accompanied by changes in the plasmatic as well as cellular coagulation systems and by microclot formation. The activation of coagulation by endotoxin is mediated by synthesis of tissue factor by monocytes and endothelial cells.

Some microorganisms have specific properties, which affect individual components of hemostasis and thus increase their virulence. Furthermore, thrombocytopenia, thrombocytopathy and endothelial cell damage caused by a direct effect of the toxic agents contribute to the bleeding diathesis [54, 55].

The occurrence of a hemorrhagic diathesis and microthrombosis is best explained by the syndrome Disseminated Intravascular Coagulation (DIC). Widespread intravascular coagulation and hemostatic defect are common in individuals with sepsis. The main cause of hypercoagulation state during sepsis seems to be the inhibition of fibrinolysis as a result of overproduction of plasminogen activator inhibitor-1 in later stages of the disease [54-58].

Levi *et al.* reviewed articles and published peer-reviewed abstracts on the mechanism of the initiation of disseminated intravascular coagulation (DIC) in sepsis. They found that significant coagulation activation was detected after the appearance of endotoxin in the circulation. This activation is preceded by an increase in the serum levels of various cytokines, such as tumor necrosis factor and interleukins. The activation of coagulation seems to be amplified by impaired function of the protein C-protein S inhibitory pathway [59].

Ryan's serum levels of fibrinogen (FIB) and D-dimer fragments were highly elevated (Table 19). His platelet count was reduced by 70% following admission (Table 15). These data indicate that Ryan suffered from DIC.

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6.3 Vitamin K deficiency causes intracranial bleeding in children

Vitamin K controls the formation of coagulation factors II (prothrombin), VII (proconvertin), IX (Christmas factor), and X (Stuart factor) in the liver. Other coagulation factors that depend on vitamin K are proteins C, S, and Z. Furthermore; two bone matrix proteins necessary for normal bone metabolism are vitamin K-dependent.

These vitamin K-dependent proteins contain the amino acid γ-carboxyglutamic acid and the carboxyl groups of the glutamic acid residues that provide the vitamin-K-dependent proteins with characteristic calcium and phospholipid binding properties. Vitamin K deficiency leads to the production of abnormal vitamin K-dependent factors, which lack gamma-carboxy glutamic acid residues in the NH2-terminal part of their molecules [49, 60-64].

In humans, the body does not synthesize the 1, 4 naphthoquinone nucleus of vitamin K and gets it from food. In addition, bacteria in the intestinal tract synthesize vitamin K and can supply part of the vitamin K requirement. Signification reduction of food intake that occurres in serious illness and the treatment with high therapeutic doses of antibiotics for a significant time can lead to vitamin K deficiency and intracranial bleeding in children [60, 61, 65-68].

Ryan was treated with four types of antibiotics (ceftriaxone, clindamycin, vancomycin, Co-Trimoxazole) for 11 days following admission. The following clinical studies show that the treatment of ill children with antibiotics for a significant period of time has caused vitamin K deficiency and bleeding:

1) Bhat and Deshmukh conducted a prospective non-randomized study on children receiving antibiotic therapy. Coagulation abnormalities were seen in children with malnutrition, receiving prolonged course of antibiotics, and in children who were critically ill in intensive care. Inhibition of intestinal microorganisms by antibiotics was thought to be a likely explanation of this phenomenon. They suggested Vitamin K prophylaxis in severely ill individuals, on extended periods of antibiotics and inadequate diet to prevent morbidity and mortality [66].

2) Sunakawa *et al.* found that the incidences of diarrhea after administering oral antibiotics in children were high for amoxicillin and amoxicillin + clavulanic acid. In some individuals with depressed immunity, decreases in intestinal bacteria after doses of antibiotics led to increases in pathogenic bacteria. They invaded the circulating blood, leading to septicemia.

Septicemia originating in the intestinal tract was frequently associated with the development of vitamin K deficiency. Besides changes in the intestinal flora, a reduction in oral food intake and the presence of a methylthiotetrazole group in the structure of the administered antibiotics were also found to play a crucial role in causing vitamin K deficiency [67].

3) de Montalembert evaluated the medical records of 43 cytic fibrosis individuals and found a significant correlation between PIVKA-II concentrations and the administration of antibiotics in these individuals [68].

Infants who develop vitamin K deficiency usually suffer from intracranial hemorrhage and bleeding in other locations. For example, Choo *et al.* conducted a retrospective study of 42 infants who were admitted to the hospital for spontaneous bleeding and prolonged prothrombin and partial thromboplastin times. None of the infants had bleeding due to inherited coagulopathy or disseminated intravascular coagulation. Subdural hemorrhage was the most common form of intracranial haemorrhage, followed by subarachnoid hemorrhage [69].

In addition, Chaou *et al.* reported late-onset intracranial hemorrhage related to vitamin K deficiency in 32 breast-fed infants (1/2 to 6 months of age). Computerized tomography showed mild to severe intracranial hemorrhage. Most (90.6%) had subarachnoid hemorrhage, either alone or in combination with subdural hemorrhage (37.5%), parenchymal hemorrhage (31.3%), or intraventricular hemorrhage (12.5) [70]

Further more**,** Aydinli *et al.* conducted a retrospective study that included 11 babies between 30 and 119 days of age, who developed bleeding due to vitamin K deficiency. The presenting complaints were seizures (91%), drowsiness (82%), poor sucking (64%), vomiting (46%), fever (46%), pallor (46%), acute diarrhea (27%), irritability and high-pitched cry (18%). On examination, tense or bulging fontanelle (73%), anisocoria (36%), weak neonatal reflexes (18%), cyanoses (18%) were the most frequent findings. The localizations of the intracranial haemorrhage were as follows: intracerebral (91%), subarachnoid (46%), subdural (27%), and intraventricular (27%) [71].

7. The likely causes of Ryan's retinal bleeding

Ryan was admitted to the hospital with cardiac arrest on June 13, 2007 and an eye exam was performed on June 22nd. It showed retinal bleeding in both eyes. Ryan had the following risk factors that led to bleeding in the retina and these factors should be considered in the differential diagnosis in this case:

1) Acute liver injury that led to a significant reduction in the synthesis of clotting factors. His prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR) were highly elevated (Section 6.1).

2) Bacterial infections and hemolytic uremic syndrome, which led to blood clotting problem and Disseminated intravascular coagulation. His serum levels of fibrinogen and D-dimer fragments were highly elevated. His platelet count was reduced by 70% following admission (Section 6.2).

3) Treatment with four types of antibiotics (ceftriaxone, clindamycin, vancomycin, Co-Trimoxazole) for 11 days following admission. The treatment of ill children with high doses of antibiotics for significant period of time has caused vitamin K deficiency and bleeding (Section 6.3)

4) Ryan was suffering from a severe anemia and individuals with severe anemia have developed retinopathy and bleeding in the retina as shown by the clinical studies described below. A blood analysis performed on June 13th at 2317 showed that Ryan had a hemoglobin level of 6.7 g/dL and a hematocrit value of 20.3% (Table 15). His platelet count was reduced by 70%

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following admission (Section 6.2). Thrombocytopenia also enhances retinal bleeding in individuals with severe anemia.

Carraro *et al.* conducted a cross-sectional study involving 226 individuals with anemia and/or thrombocytopenia to evaluate the incident of retinopathy among these individuals. A group of 47 healthy age-matched individuals were used as a control. Retinopathy was observed in 28.3% of the anemic individuals as a whole.

The presence of fundus lesions was closely associated with severe anemia (Hb < 8 g/dL) and severe thrombocytopenia (PLT < 50 x 10^3/μL). Among the individuals with concomitant anemia and thrombocytopenia, the incidence of retinopathy was 38%. Retinal hemorrhages were found in all of the individuals with concomitant severe anemia and thrombocytopenia [72].

Furthermore, Asien *et al.* evaluated the occurrence of clinically apparent retinal changes in 35 anemic individuals and 35 age-and sex-matched healthy control individuals. Retinal photographs of all subjects were obtained and all vascular and extra vascular retinal lesions were recorded. No retinal abnormalities were observed in the control subjects.

Seven (20%) of the anemic patients exhibited extra vascular lesions (flame-shaped hemorrhages, hard exudates, and cotton-wool spots). Within the group of anemic individuals, the mean hematocrit reading for those with extravascular lesions (N=7) was 24.7%. A significant negative correlation was determined between venous length and the level of hematocrit, thereby implying that retinal venous tortuosity is directly related to severity of anemia [73].

In addition, I evaluated the medical records of two infants who developed retinal bleeding as a result of severe anemia and vitamin K deficiency. The first infant had a hemoglobin level of 7.01 g/dL and a hematocrit value of 20.4% [74]. The hemoglobin level and the hematocrit value of the second infant were 6.8 g/dL and 19.4%, respectively [75].

8. Predisposing factor for Ryan's acute illness

Ryan was born on April 13, 2007 and he was discharged from the hospital on April 16th without significant health problems. In addition, he had physical exams on April 24th and June 4th and both exams revealed that he did not have health problems. Ryan gained weight at the rate of 31.0 g/day during the 53 days after birth. His length and head circumference increased at the rate of 4.32 cm/month and 2.26 cm/month, respectively (Table 1).

Ryan developed a fever after receiving his second injection of Hepatitis B vaccine (HBV) on June 4, 2007. He was treated with Tylenol at a dose of 80 mg every 4 hours starting on June 4th and ending late on June 5th. Furthermore, he was given two doses of Tylenol (80 mg/dose) between June 6th and the 13th.

During the 9 days following receiving his second injection of HBV, Ryan gained weight at the rate of 47.7 g/day and his length increased by 6.37 cm. However, during the period between birth and June 4th, Ryan gained weight at the rate of 31.0 g/day and his length increased at the rate of 4.32 cm/month (Table 1). These observations indicate that Ryan developed fluid retention problems following vaccination with HBV.

Ryan appeared sick during the week of the 4th. He was throwing up, lethargic and he seemed very tired especially towards the end of the week. Ryan suffered from cardiac arrest on June 13th and the clinical tests performed in the hospital showed that he had severe acidosis, pneumonia and hemolytic anemia.

The clinical evidence indicates that HBV predisposed Ryan to developing pulmonary infections. Infections and autoimmune disorders have been reported in some children who received HBV. For example, the database from the 1994 National Health Interview Survey (NHIS) in the USA was analyzed to evaluate vaccine related adverse reactions. It included 6,515 children less than six years of age who received the hepatitis vaccine.

HBV was found to be associated with prevalent arthritis [odds ratio (OR) = 5.91, 95% confidence interval (CI) = 1.05-33.14], incident acute ear infections (OR = 1.60, 95% CI = 1.00-2.58), and incident pharyngitis/nasopharyngitis (OR = 1.41, 95% CI = 0.95-2.09). The authors of this study concluded that there is enough evidence to suggest that hepatitis B vaccine is positively associated with adverse health outcomes in the general population of US children [76].

In addition, Niu *et al.* evaluated reports of neonatal deaths (aged 0-28 days) after hepatitis B (HepB) immunization reported to the National Vaccine Adverse Event Reporting System (VAERS) between January 1, 1991, through October 5, 1998. They identified 18 deaths and the mean age at vaccination for these 18 cases was 12 days.

The median time from vaccination to onset of symptoms was 2 days and the median time from symptoms to death was 0 days (range, 0-15 days). The mean birth weight of the neonates (n = 15) was 3034 g (range, 1828-4678 g). The causes of death for the 15 autopsied cases were sudden infant death syndrome for 12 and infection for 3 [77].

Furthermore, hepatitis B vaccine induced autoimmune disorders in some individuals. These include erythema nodosum; thrombocytopenia; myasthenia gravis; uveitis; Reiter's syndrome; arthritis; systemic lupus erthematosus; and central nervous system demyelination [78-82].

For example, Geier and Geier examined the adverse events and positive re-challenge of symptoms reported in the scientific literature and to the National Vaccine Adverse Event Reporting System (VAERS) following hepatitis B vaccination (HBV). The VAERS and PubMed (1966-2003) were searched for autoimmune conditions in individuals who received HBV. These include arthritis, rheumatoid arthritis, myelitis, optic neuritis, multiple sclerosis (MS), Guillain Barre syndrome (GBS), glomerulonephritis, pancytopenia/thrombocytopenia, fatigue, and chronic fatigue, and Systemic Lupus Erythematous (SLE).

They found that HBV was associated with serious illnesses. There were 415 cases of arthritis, 166 rheumatoid arthritis, 130 myelitis, 4 SLE, 100 optic neuritis, 101 GBS, 29 glomerulonephritis, 283 pancytopenia/thrombocytopenia, and 183 MS events reported in individuals received HBV. In addition, a total of 465 positive re-challenge adverse events were observed following adult HBV that occurred sooner and with more severity than initial adverse event reports. A case-report of arthritis occurring in identical twins was also identified [81].

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9. Conclusions

The clinical data and medical studies described in this report clearly show the following:

1) Ryan's acute illness that occurred on June 13, 2007 was caused by Streptococcus pneumoniae infection. It led to the development of hemorrhagic pneumonia, hemolytic uremic syndrome (HUS), kidney and liver problems, hepatic encephalopathy, metabolic and respiratory acidosis, seizure, coma, and cardiac arrest.

2) Ryan suffered from seizure, coma, and cardiac arrest on June 13, 2007 due to the development of hepatic encephalopathy resulting from high levels of ammonia and other metabolic toxins in his blood. Seizure is the likely cause of Ryan's fall from the bouncy chair on the floor on June 13, 2007.

3) Ryan suffered from hemorrhagic pneumonia and the lungs were the likely source of Ryan's nose bleed observed on June 13th. Blood was also coming from the endotracheal tube.

4) The intracranial bleeding observed in Ryan's case developed after his admission in the hospital on June 13, 2007. The likely causes of his bleeding are liver damage, infections, and vitamin K deficiency.

5) The likely causes of Ryan's bilateral retinal bleeding are liver damage, severe anemia, vitamin K deficiency and systemic infections that led to blood clotting problems and Disseminated Intravascular Coagulation.

6. There is no clinical evidence that shows Ryan suffered from an injury caused by trauma and the allegation of child abuse in this case is false.

7) Ryan was enjoying good health prior to receiving his second injection of hepatitis B vaccine (HBV) on June 4, 2007 and HBV was the primary cause that led to Ryan's infection with Streptococcus pneumoniae.

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