Analysis of causes that led to subdural bleeding, skull and rib fractures, and death in the case of baby Averial Buie

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Abstract

A female infant from Texas stopped breathing and her mother took her to the hospital. Blood analysis revealed the baby suffered from severe metabolic and respiratory acidosis, hyperglycemia, hyperkalemia, and lymphocytosis. A chest X-ray showed evidence of pneumonitis. Physical examination revealed no evidence of injury caused by trauma. She was treated with epinephrine, sodium bicarbonate, antibiotic, and other medications. She developed bleeding outside the skull and intracranially. No skull or rib fractures were noted on the CT scans and X-rays taken during the fist four days following admission. However, skull and rib fractures were observed on the CT scan and X-rays taken at a later date.

Resuscitation efforts failed and the baby died at 11 days following admission. At autopsy, the medical examiner (ME) found healed skull and rib fractures, bleeding of various ages outside the skull and intracranially, and brain edema and necrosis. His microscopic examination of the H & E stained sections of the lung revealed evidence of bronchopneumonia, hyaline membranes in the alveoli, and bleeding. The ME alleged that the baby's injuries were caused by trauma and her father was accused of killing her.

My investigation reveals that the infant suffered from acute bronchopneumonia and respiratory distress syndrome on August 6, 2004, which led to hypoxemia, severe metabolic and respiratory acidosis, hyperkalemia, loss of consciousness, respiratory failure, and cardiac arrest. Her bleeding, brain edema and necrosis, and skull and rib fractures occurred in the hospital. These injures were caused by infection and medications.

Keywords: anemia; atelectasis; autopsy; bleeding; brain edema; bronchopneumonia; head CT scan; hyaline membrane; epinephrine; hematoma; infarction; metabolic acidosis; necrosis; protein deficiency; respiratory acidosis; respiratory distress syndrome; rib fracture; skull fracture; sodium bicarbonate**,** subdural bleeding; subarachnoid bleeding; subretinal bleeding; thrombocytosis; thymic atrophy; trauma; chest X-ray.

1. Summary of the case and findings

Averial Buie is a white female infant from Texas. She suffered from respiratory failure and cardiac arrest on August 6, 2004 while she was with her parents at home. Her mother took her by car to the nearest hospital. Blood analysis revealed that she suffered from severe metabolic and respiratory acidosis, hyperglycemia, hyperkalemia, and lymphocytosis. Physical examination revealed no evidence of injury caused by trauma on Averial's head and the rest of her body. Averial was treated with epinephrine, sodium bicarbonate, antibiotic and other medications. Her health declined over time until her death on August 17, 2004.

The medical examiner (ME) performed an autopsy on Averial's body on August 18. He found a healed skull fracture; six healed fractured ribs; bleeding in the subgaleal region; bleeding of various ages in the subdural and subarachnoid spaces; brain edema and necrosis. In addition, his microscopical examination of the H & E stained sections of all lobes of the right and the left lungs revealed that Averial was suffering from bronchopneumonia, respiratory distress syndrome, and pulmonary bleeding.

The ME alleged that Averial's injuries and death were caused by trauma and child abuse. Averial's father was accused of causing his daughter's injuries and death. Matthew Watson, who is 27 years old, was arrested, imprisoned, and awaits trial in Texas. He is facing a sentence of either life in prison or possibly the death penalty if convicted.

Matthew and his family requested that I review the medical data in Averial's case and provide an opinion concerning the cause(s) of her injuries and death. I am a pathologist and toxicologist with over twenty years experience in these fields. I have also evaluated many cases of children similar to Averial's case and I have served as an expert witness in these cases.

I reviewed the following documents pertinent to this case: (1) Averial's medical record from birth to the time of her hospitalization on August 6, 2004 (Section 2); (2) Averial's medical record during her hospitalization from August 6-17, 2004 (Sections 3 and 4); (3) autopsy report (Section 5); and (4) published medical literature pertinent to Averial's case (Sections 6-12). Additionally, I examined the H & E stained sections of tissues listed in the autopsy reports microscopically.

I spent about 200 hours evaluating the documents and the materials cited above and writing a detailed report in this case. I used differential diagnosis to identify the likely causes that led to Averial's injuries and death (Sections 6-12). The clinical data and studies described in this report reveal the following:

1) Averial was examined in the hospital on August 6 by a physician who did not find any evidence of injury caused by trauma in the head or in the rest of her body. Furthermore, the CT scans of the head and the chest X-rays taken on August 6 and 7 did not show any evidence of skull and rib fractures.

2) Averial suffered from acute bronchopneumonia and respiratory distress syndrome on August 6, 2004 that led to hypoxemia, severe metabolic and respiratory acidosis, hyperkalemia, loss of consciousness, respiratory failure, and cardiac arrest.

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Blood analysis performed following Averial's admission to the hospital on August 6 showed critically low blood pH of 6.882, high PCO_2 of 70.1 mmol/L, low HCO_3 of 12.9 mmol/L, and high Anion Gap of 27.4 mmol/L. In addition, Averial had a high serum potassium level of 5.83 mmol/L and a blood glucose level of 347 mg/dL.

Averial's chest X-ray exam performed at 0251 on August 6 revealed that she had evidence of pneumonitis. Her blood analysis performed at 0300 on August 6 showed elevated white blood cell and lymphocyte counts and her counts returned to normal following treatment with antibiotic. In addition, the microscopic examination of the H & E stained sections from all lobes of the right and left lungs showed that Averial suffered from bronchopneumonia, hyaline membrane disease, atelectasis, interstitial fibrosis, and pulmonary bleeding (Figures 1-4).

3) The medical examiner (ME) knew that Averial suffered from bronchopneumonia hyaline membrane disease, atelectasis, and pulmonary bleeding. However, he did not consider the impact of these serious and fatal lesions in his evaluation of this case. He examined five H & E stained sections from all lobes of Averial's right and left lungs microscopically and described these lesions in his autopsy report (Section 5).

4) Averial's intracranial bleeding, pulmonary bleeding, and bleeding in other locations occurred during her stay in the hospital. These injuries were caused by the use of epinephrine and sodium carbonate, and hypoxia. The first evidence of bleeding was observed on Averial's CT scan taken at about 90 minutes following the administration of two doses of epinephrine and one hour following the treatment with sodium bicarbonate. Intracranial bleeding has been reported in some individuals treated with epinephrine. The treatment with high therapeutic doses of sodium bicarbonate causes hypoxia and brain edema. Averial was given excessive doses of sodium bicarbonate and her blood pH reached a high critical level of 7.59.

5) Averial's brain edema and necrosis were caused by hypoxia, the use of sodium bicarbonate, bleeding, and infarction. Averial's head circumference was 37 cm on August 6 and it became 38.25 cm on August 9 due to bleeding and brain edema. In addition, the MRI of the brain taken on August 12 revealed the presence of subacute infarction. The likely causes of the infarction were the development of thrombocytosis and the injuries to the blood vessels caused by hypoxia. Averial's platelet count on August 7 was 409,000 cells/μL of blood and it increased by 82% to 745,000/μL on August 14 in response to bleeding.

6) Averial's skull fracture occurred in the hospital due to the increase in the intracranial pressure caused by bleeding and brain edema. The first evidence of skull fracture was noted on Averial's X-ray exam of the head performed on August 10th which was 4 days following her admission to the hospital. Averial's head circumference was 37 cm on August 6 and it was increased by 1.25 cm on August 9 due to bleeding and brain edema.

7) The observation at autopsy of Averial's subretinal bleeding in both eyes occurred during her stay in the hospital. It was caused by hypoxia, anemia, thrombocytosis, and increased intracranial pressure. A physician examined Averial's eyes on August 9 using a fundoscope and no subretinal bleeding was observed in the right eye. This indicates that the subretinal bleeding in the right eye occurred between August 9 and August 18. The bleeding in the left eye was first reported on August 9, which was three days following her admission and treatment with epinephrine and sodium bicarbonate.

8) Averial's rib fractures occurred in the hospital due to acidosis, protein deficiency, illness, and handling. No evidence of rib fracture was observed on Averial's three chest X-rays taken on August 6 and 7. Acute rib fractures (right 6th and 7th) without evidence of healing were noted on Averial's chest X-ray performed on August 10. They were associated with extra-pleural hematoma, which indicates that these fractures occurred within a few hours prior to taking this X-ray. The two healed fractures (right 3rd and 4th) noted on the chest X-ray of August 10 were not observed by the three chest X-rays taken on August 6 and 7th. In addition, the ME found three additional healed rib fractures (right 5th and left 4th and 5th) that were not seen on Averial's four chest X-rays taken on August 6, 7, and 10.

9) The ME did not take into consideration the overwhelming clinical data described in this report that show Averial's bleeding and skull and rib fractures occurred in the hospital. These injuries were caused by infection, acidosis, medications, and hypoxia.

10) There is no evidence that shows Averial's injuries and death were caused by trauma and child abuse. The allegations against her father are false.

2. Review of Averial's medical record from birth to 45 days of age

2.1 Averial's birth event, clinical tests, and treatment given in the hospital

Averial Buie is a white female infant. She was born at full term on June 21, 2004 via normal vaginal delivery in Northwest Texas hospital. Averial's weight was 3107 g and her height and head circumference were 49.5 cm and 33.0 cm, respectively. Averial's mother was 24 years old at the time of delivery and Averial is her second child [1].

Averial was treated with 1 mg of vitamin K (IM) and erythromycin ointment in both eyes. She was also administered hepatitis B vaccine (GSK lot number ENG5553A2) on June 22nd. Averial was released from the hospital on June 22, 2004 and she was fed formula milk. Averial's newborn's screen tests were performed on June 23, 2004 and appeared normal (Table 1).

Table 1. The results of Averial's newborn screening tests

Test type	Results	Reference range
Thyroid hormone (T4)	Normal	Normal
PKU	Normal	Normal
Galactosemia	Normal	Normal
HGP Type	Normal	Normal
CAH	Normal	Normal

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2.2 Averial's health condition between June 23 and August 5, 2004

Averial was fed formula milk after her release from the hospital on June 22, 2004. She was examined three times by her pediatrician between July 1 and 23 and her vitals appeared normal (Table 2). However, her mother reported that Averial was fussy and did not sleep well. She was awakened with minimal stimulation or even by soft sounds. Averial's pediatrician reported on July 7 that the baby appeared fussy due to having intestinal gas [2]. During her fist thirty-three days of life, Averial gained 775 g (24 g/day) in weight and 5 cm in height (Table 2).

Table 2. Averial's growth and vitals measurements[1]

Measurements	Exam on 7/01/04	Exam on 7/07/04	Exam on 7/23/04
Age days	10	16	32
Weight (g) and percentile	3145 (25%)	3380	3882 (50%)
Height (cm) and percentile	52.0 (75%)	-	54.5 (75%)
Head circumference (cm) and percentile	34.3 (25%)	-	36.3 (25%)
Temperature (^oF)	98.9	99.3	99.5
Respiratory (rate/minute)	62	42	41
Pulse (rate/minute)	134	136	155

[1]Averial was born on June 21, 2004. Her birth weight, height, and head circumference were 3107 g, 49.5 cm, and 33.0 cm, respectively.

2.3 Averials's health condition prior to her hospitalization on August 6, 2004

Averial was fed formula milk around 2230 on August 5, 2004 and then put to bed. She slept and woke up at about 0030 on August 6 and began to cry. Her mother tried to pacify her but she did not settle down. Her father tried to comfort her. Averial's mother reported hearing a raspy cry at approximately 15 minutes following leaving the infant with her father. At that time, the father called for help stating that the baby had turned limp [3].

Averial's mother immediately rushed to the living room where the baby was and found her limp, unresponsive, and not breathing. She also noticed that pinkish fluid was coming from her nose. She administered mouth-to-mouth breathing to the baby almost 7 times. She also administered chest compressions over the left side of the chest with two fingers with a ratio of 5 compressions to two breaths. The infant's condition did not improve and the mother transferred the baby to her car and drove straight to Baptist St. Anthony's Heath System (BSA). She arrived at the emergency room in approximately five minutes.

The mother reported that the baby turned blue when she put her into the car. She did not see any evidence of formula milk present in the baby's mouth. However, she did state that whenever she tried to administer mouth breaths to the baby, she felt that the baby's lungs were filled with fluid. The mother also reported that two days prior to this episode where the baby's breathing stopped, Averial had diarrhea.

3. Averial's clinical tests and treatments given on August 6th in the hospital

Averial's mother brought her infant to Baptist St. Anthony's Heath System (BSA), arriving at the emergency room approximately at 0220 on August 6. At the emergency room, the infant was placed on cardiopulmonary resuscitation. This included the establishment of interosseus access and the administration of endotracheal epinephrine 1x followed by IV epinephrine 1x [1x=0.01 ml/kg (1/1000)] as shown in Table 3. Averial's weight and head circumference at the time of admission were 4.29 kg and 37 cm, respectively. Her length was 54 cm [3].

Blood analysis performed at 0249 revealed critically low blood pH (6.882), high PCO_2 (70.1 mmol/L), low HCO_3 (12.9 mmol/L), and high Anion Gap (27.4 mmol/L) levels. Averial suffered from mixed respiratory and metabolic acidosis (Table 4). Additionally, Averial had a high serum potassium level of 5.83 mmol/L and suffered from hyperkalemia. Also, she had a high blood glucose level of 347 mg/dL and low serum protein and albumin levels (Table 5). Averial was administered fluid bolus of 60 ml of normal saline and sodium bicarbonate (1 mEq per kg IV) that increased her blood pH and lowered her blood potassium level (Tables 3 and 4).

Averial's hemoglobin level (10.7 g/dL), red blood cell count ($2.97 \times 10^6/\mu L$), and hematocrit value (31.5) measured at 0250 and 0255 were lower than the normal range. Averial was suffering from moderate anemia (Table 4). Averials's low levels of serum albumin and total protein indicate that she suffered from health problems (Table 5).

Furthermore, Averial's hemoglobin and the hematocrit values were reduced by 21% at 0530 as compared to the values recorded at 0250. The red blood cell count was also reduced by 22% at 2030 as compared to the earlier measured value (Table 4). These data indicate that a significant bleeding occurred following Averial's treatment with epinephrine and sodium bicarbonate.

Table 3. Treatments given to Averial in the ER on August 6th

Treatments	Time	Doses and routes
Epinephrine	0220-0240	1 x[1] (endotracheal) 1 x (IV)
Sodium bicarbonate	0250-5	1 mEq per kg Twice (IV)
N-saline	0250-5	60 mL (IV)
Ceftriaxon (Rocephin)	0300	200 mg each 12 hours (IV)

[1] 1 x= 0.01 mL/kg (1/1000).

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Table 4. Averial's hematology and blood gas analyses performed on August 6, 2004

Time	Blood pH	PCO_2 (mmHg)	HCO_3 mmol/L	BEVT mmol/L	HB (g/dL)	RBC x 10^6/µL	HCT %
0249	6.882	70.1	12.9	-20.2	10.6		31
0255	7.212	31.3	12.3	-14.3	10.8	2.97	32
0350	7.417	20.5	12.9	-12.9	-[1]	-	-
0454	7.436	24.7	16.3	-5.9	-	-	-
0530	7.419	29.7	18.8	-5.0	8.4	-	25
0810	7.422	34.4	31.9	-1.8	-	-	-
1807	7.424	30.7	19.6	-3.5	-	-	-
2030	-	-	-	-	-	2.30	-
Reference range	**7.350-7.450**	**35.0-44.0**	**21-28**		**12-18**	**3.4-4.6**	**37-50**

[1] (-): Not measured

Table 5. Averial's serum analyses performed on August 6, 2004

Measurements	Values at 0249	Values at 0300	Values at 2030	Reference range
Na (mmol/L	136	139	146	135-148
K+ (mmol/L)	5.83	4.1	3.8	3.6-5.0
Ca++ (mmol/L	1.30	-	-	1.13-1.32
Cl- (mmol/L	102	107	118	98-106
Anion Gap (mmol/L)	27.4	22	10	6-16
Glucose (mg/dL)	-[1]	347	101	70-105
T. Protein (g/dL)	-	3.9	-	4.2-7.4
Albumin (g/dL)	-	2.5		2.8-5.0
Creatinine (mg/dL)	-	0.6	-	
Alk. Phospohotase (IU/L)	-	235	-	50-260
SGOT (IU/L)	-	40	-	13-64
SGPT (IU/L)	-	21	-	3-37
T. Bilirubine (mg/dL)	-	0.7	-	0.2-1.0

[1] (-). Not measured

Averial's chest X-ray performed at 0251 revealed evidence of pneumonitis in the right lower lobe. No rib fracture was noted on this X-ray. Her blood analysis performed at 0300 showed her white blood cell and lymphocyte counts were elevated and she suffered from lymphocytosis (Table 6). She was treated with ceftriaxon (Rocephin) IV (Table 3) and her white blood cell count and lymphocyte count returned to normal levels by 2030 on August 6 (Table 6). These data indicate that Averial suffered from bacterial infection.

Table 6. Averial's white blood cell counts on August 6, 2004

Measurements	Values at 0300	Values at 2030	Reference range
WBC x 1000/µL	17.8	9.30	6.8-16.0
Lymphocyte x 1000/µL	9.0	4.46	0.9-5.2
Neutrophil x 1000/µL	8.0	4.47	1.9-8.0
Monocyte x 1000/µL	0.60	0.37	0.1-1.0
Basophil x 1000/µL	0.00	-	0.0-0.8
Eosinophil x 1000/µL	0.10	-	0.0-0.2

Dr. Nandkishore Reghuram examined Averial at the emergency room on August 6. Averial was on a cardiorespiratory monitor with assisted ventilation including manual bagging with 100% oxygen. Her blood oxygen saturation was 100% on 100% oxygen. She demonstrated intermittent agonal respirations. She had tachycardia with a heart rate ranging from the 160s to 170s. The cardiac monitor demonstrated a sinus rhythm with no appreciable murmur**.** Her blood pressure was 85/36 mm Hg and her body temperature was 92.8°F.

Averial's anterior fontanelle appeared full but flat and her head circumference was 37 cm. She had a small area of erythema over the occipital region. Dr. Reghuram neither appreciated any crepitus on palpation of the cranial vault and the skull, nor on any depressed regions in the skull bone. Moreover, no evidence of any surface bruising, petechia, ecchymosis or purpura was observed over the skin in the head region or the rest of the body.

Averial's left pupil measured approximately 4 mm while her right pupil was 2 mm and not reactive. There was also transient deviation of the left pupil superiorly and laterally. Her oropharynx appeared moist. Examination of Averial's extremities revealed peripheral pulses of 1+ with cap refill of approximately 3 seconds and she had mild to moderate generalized pallor. Averial's genitalia was normal and there was no evidence of any discharge from her vagina.

Averial's first CT scan of the head was taken at 0350. It showed a small scalp hematoma, small subdural hemorrhage, and brain edema (Table 7). No skull fractures were observed on this CT scan. It was taken at about 90 minutes following the administration of two doses of epinephrine and one hour following the treatment with sodium bicarbonate. Epinephrine and sodium bicarbonate given at therapeutic doses have been reported to cause intracranial bleeding and brain edema in some individuals [4-9].

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Table 7. Findings of the X-ray and CT scan exams performed within 90 minutes following Averial's admission to the hospital

Time	Hours following admission[1]	Events	Findings
0251	0.5	Chest-X rays	• Pneumonitis in the right lower lobe. • No rib fracture.
0350	1.5	CT scan-Brain	• No skull fracture. • Scalp hematoma over the right posterior temporal to right zone. • Small amount of right frontal epidural or subdural hematoma. • Suggestion of diffuse cerebral edema.

[1] Averial was admitted to the hospital at 0220 on August 6, 2004

Averial's blood analysis performed at 0300 showed normal platelet count of 535,000/μL. Her blood analysis performed at 0548 showed that her prothrombin time (PT) and paritial prothrombin time (PTT) were within the normal range. However, her fibrinogen level was lower than normal (Table 8). Urine analysis performed at 0559 revealed that Averial had a high glucose level (Table 9).

Table 8. Averial's clotting parameters on August 6, 2004

Measurements	Time	Values	Reference range
Prothrombin time (PT) seconds	0548	15.4	11.5-14.0
INR	0548	1.31	
PTT (seconds)	0548	26	23-24
Fibrinogen (mg/dL)	0548	148	180-490
Platelet x 1000/μL	0300	535	288-598
	2030	512	

Table 9. Results of Averial's urine test performed on August 6 at 0559

Measurements	Values	Reference range
Color	Yellow	Yellow
Appearance	Clear	Clear
Specific gravity (g/mL)	1.023	1.005-1.030
PH	5.5	5.0-8.0
Protein (mg/dL)	Negative	Negative
Glucose (mg/dL)	>1000	Negative
Clinitest (%)	2	Negative
Ketones (mg/dL)	Negative	Negative
Bilirubin	Negative	Negative
Blood	Trace	Negative
Nitrite	Negative	Negative
Urobilinogene (EU/dL)	0.2	0.2-1.0
Leuk. Esterase	Negative	Negative
RBC/HPF	4	0-4
WBC/HPF	3	0-4

Averial was treated with phenobarbital, zantac, Tylenol and other medications listed in Table 10. The CT scan taken for Averial's head region at 1611 indicated that her subdural bleeding and brain edema became worse as compared with the CT scan taken at 0350 (Table 11). The CT scan of 1611 also did not show any skull fracture.

Table 10. Treatments given to Averial after 0300 on August 6th

Treatments	Time	Doses and routes
N-saline	0400	60 mL (IV)
Phenobarbitol	0410	80 mg (IV)
Albutrol	0502	1 puffs inh; Q3 hr
Lasix	0545	4 mg (IV)
Acetaminophen	0640	60 mg Q4-6 hrs (oral)
Reglan	0710	0.4 mg (IV)
Zantac	0900	4 mg Q12 (IV)
Versed	1240	0.4 mg IV
Fantanyl	1345	5 μg IV
D5 ½ NS	2200	
Dextrose	2200	5%-0.45% NaCl(IV) + Potas-
Lanolin ointment		Application on lips

Table 11. Findings on CT scan exam performed at 1611 on August 6, 2004

Regions	Findings
Soft tissues	• Soft tissue swelling noted over the right parietotemporal region consistent with scalp hematoma.
Skull	• No skull fracture.
Subdural space	• Blood identified in right subdural space extending over right frontal convexity and paralleling flax at the level of vertex.
Brain	• Generalized cerebral edema. The lateral ventricles were compressed by the edematous cortex. The expected sulcal markings were also affected.

4. Clinical tests and treatments given on August 7-17, 2004

Averial's health condition became worse after August 6 and she died at 1435 on August 17, 2004. Her CT scans and the MRI exams of the head region taken on August 8, 12, and 13 (Table 12) indicated that the subdural bleeding and brain edema had become worse as compared with the CT scans of August 6 (Tables 7 and 11). No skull fracture was observed on the CT scans of August 6 and 8. However, a skull fracture was noted on the X-ray and the CT scan exams of the head performed on August 10 and 13, respectively (Table 12).

Furthermore, no evidence of rib fractures was observed on the Averial's chest X-rays taken on August 6 at 0251 and August 7 at 0538 and 0653. However, evidence of rib fractures was noted on the chest X-ray performed on August 10 at 0920. The August 10 chest X-ray showed fractures without evidence of healing in the right lateral 6th and 7th ribs associated with extra-pleural hematoma. It also showed healing fractures of the right costovertebral junctions of 3rd and 4th ribs.

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Dr. Michael Ryan examined Averial on August 9 and stated that she was not responsive; she did not open her eyes with stimulation. Her blood pressure and pulse were 138/82 mmHg and 197 beats/minute, respectively. Her temperature was 100.3°F. She had a respiratory rate of 39 per minute on the vent. Her head circumference was 38.25 cm and had increased by 1.25 cm since August 6 [3].

Fundoscopic exam of Averial's eyes performed on August 9 showed extensive hemorrhage through the left fundus obscuring the disk. The hemorrhage seemed to some extent to be multifocal. Dr. Ryan saw no hemorrhage in the right fundus and the disk was flat.

Table 12. Findings on CT scans and MRI of the head

Date & time	Exam type	Findings
08/08/04 at 0653	CT	• No skull fracture. • The diffuse cerebral edema worsened since the August 6 exam.
8/10/04 at 0920	X-ray	• A linear skull fracture present in right parietal bone and extends from coronal to lamboid.
8/12/04 at 1227	MRI	• Gyral enhancement indicating subacute infarction. • Diffuse cerebral edema appeared to be improving allowing better visualization of the lateral ventricles compared to recent CT. • Right subdural hemorrhage. • T1 shortening in the right fronto-temporo-pariatal region indicating some hemorrhage within the gray matter.
08/13/04 at 0514	CT	• Right parietal skull fracture seen • 5 mm right parietotemporal subduralhematoma with a more focal rounded appearance seen in the right frontal region. • The grey-white matter was better seen, may be due to gyriform petechial hemorrhage and/or subacute ischemia. • Cerebral edema possibly improved.

Blood analyses showed Averial developed severe anemia on August 8 and this indicates she suffered from bleeding between 1900 on August 7 and 0500 on August 8. Her hemoglobin level and hematocrit value were reduced by 25% and 27%, respectively (Table 13). Averial's platelet count was also reduced by 24% of baseline by August 7. The bleeding resulted in the development of thrombocytosis on August 12 (Table 14). Additionally, Averial was given excessive doses of sodium bicarbonate on August 9-11, 2004. Her blood pH reached a high critical level of 7.59 (Table 13).

Averial's white blood cell counts performed on August 7-14 indicate that the treatment with antibiotic kept her infection under control (Table 15). Her serum analysis indicates that she suffered from albuminemia (Table 16). Her urine analysis indicates that her urine was negative for glucose (Table 17). Averial was treated with antibiotic, sodium bicarbonate, Tylenol, and other medications. Table 18 contains a list of some of the medications given to Averial on August 7 until her death on August 17.

Averial died at 1435 on August 17, 2004 in Potter County, Texas after spending 11 days in BSA. She was 57 days old. Five days prior to Averial's death, a blood sample was collected and the serum was analyzed for the presence of alcohols and other chemical agents listed in Table 19. Only a trace level of barbiturates was found. Phenobarbital was given to the baby in the hospital as therapy.

Table 13. Averial's blood gases and hematology data measured on August 7-17, 2004

Date	Time	Blood pH	PCO_2 (mmHg)	HCO_3 (mmol/L)	BEVT (mmol/L)	HB (g/dL)	RBC	HCT %
08/07/04	0415	7.273	53.6	24.2	-2.9	10	-	29
	0506	7.362	55.3	30.7	4.3	10.7	-	31
	0920	7.431	36.5	23.7	-0.3	11.2	3.48	33
	1815	7.283	57.6	26.6	-0.7	10.6	-	31
	1900	7.385	46.4	27.1	1.7	10.1	-	30
	2125	7.398	42.5	25.5	0.5	-	-	-
08/08/04	0500	7.430	41.0	26.6	2.1	7.6	3.41	22
	1220	7.449	39.2	26.6	2.5	-	-	-
	1645	7.484	32.5	23.9	1.2	-	-	-
	2345	7.473	34.5	24.7	1.6	-	-	-
08/09/04	0530	7.590	29.8	64.4	6.9	-	-	-
	1205	7.454	43.2	29.6	5.1	12.8	-	38
08/10/04	0515	7.509	32.9	25.6	3.0	13.2	3.83	39
	1925	7.537	30.9	25.7	3.5	11.6	-	34

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Date	Time	Blood pH	PCO_2 (mmHg)	HCO_3 (mmol/L)	BEVT (mmol/L)	HB (g/dL)	RBC	HCT %
08/11/04	0525	7.523	30.8	24.8	2.8	-	-	-
08/12/04	0530	7.442	33.8	22.5	-1.0	12.5	-	37
08/13/04	0449	7.449	27.9	18.9	-3.5	-	-	-
	1200	7.451	27.2	18.5	-3.8	-	-	-
	1810	7.423	29.3	18.7	-4.3	-	-	-
08/14/04	0520	7.472	21.1	15.1	-6.0	-	-	-
	1300					10.5	3.41	31.5
	1705	7.445	31.7	21.3	-1.7	-	-	-
08/15/04	0448	7.478	27.1	19.6	-2.3	-	-	-
	1155	7.450	28.7	19.5	-3.0	-	-	-
	1436	7.487	29.7	19.8	-2.0	-	-	-
	1736	7.488	29.1	20.6	-1.8	14.9	-	44
	2040	7.463	27.5	19.3	-2.9	-	-	-
	2340	7.453	23.2	19.9	-5.8	-	-	-
08/16/04	0520	7.510	23.0	17.9	-2.9	-	-	-
	0701	7.460	27.4	19.1	-3.2	-	-	-
	0847	7.469	29.5	20.9	-1.5	-	-	-
	1143	7.485	30.4	22.4	0.1	-	-	-
	1515	7.474	30.4	21.8	-0.9	12.3	-	36
08/17/04	0020	7.373	35.2	20.0	-4.9	11.3	-	33
	0445	7.406	35.6	21.9	-2.2	-	-	-
Reference range		**7.350-7.450**	**35.0-44.0**	**21-28**		**12-18**		**37-50**

Table 14. Platelet count

Date	Time	Cells x 1000/µL	% of base-line
8/06/04	0300	535	100
8/06/04	2030	512	96
8/07/04	1000	409	76
8/08/04	0610	469	88
8/10/04	0515	541	101
8/14/04	1300	745	139
Reference Range		**288-598**	

Table 15. White blood cell counts performed on August 6-14, 2004

Date	WBC x 1000/µL	Neutrophil x 1000/µL	Lymphocyte x 1000/µL
8/6/04 at 0300	17.8	8.0	9.0
8/6/04 at 2030	9.30	4.47	4.46
8/7/04	9.59	5.18	3.36
8/8/04	13.41	7.24	5.36
8/10/04	13.71	6.17	6.71
8/14/04	10.10	6.26	2.73
Reference range	**6.8-16.0**	**1.9-8.0**	**0.9-5.2**

Table 16. Results of serum analyses performed on August 16, 2004

Measurements	8/7	8/8	8/9	8/10	8/12	8/14	8/16	Reference range
Na (mmol/L	146	143	136	134	139	140	144	135-148
K+ (mmol/L	4.6	5.3	4.6	4.2	4.5	4.7	5.4	3.6-5.0
Ca (mg/dL)	8.2	9.2	9.2	9.2	9	9.4	10.1	7.3-12.0
Cl- (mmol/L	115	107	99	99	109	114	111	98-106
Anion Gap (mmol/L)	13	14			10	11	13	6-16
Glucose (mg/dL)	124	136	123	103	105	83	100	70-105
T. Protein (g/dL)	3.9	4.6	4.3	4.2	4.2	4.4	-	4.2-7.4
Albumin (g/dL)	2.2	2.3	2.3	2.2	2.4	2.5	-	2.8-5.0
Creatinine (mg/dL)	0.3	0.3	0.3	0.2	-	-	-	<0.7
BUN (mg/dL)		8	15	9	11	19	9	5-15
Alk. Phospohotase	151	148	166	150	-	-	-	50-260
SGOT (IU/L)	21	30	61	61	70	67	-	13-64
SGPT (IU/L)	20	20	32	32	32	31	-	3-37
T. Bilirubin (mg/dL)	1.0	-	-	-	0.3	0.4		0.2-1.0

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Table 17. Results of urine test performed on August 14 at 2103

Measurements	Values 08/14 at 2103	Reference range
Color	Yellow	Yellow
Appearance	Clear	Clear
Specific gravity (g/mL)	1.018	1.005-1.030
PH	6.5-7.0	5.0-8.0
Protein (mg/dL)	Negative	Negative
Glucose (mg/dL)	Negative	Negative
Clinitest (%)	Negative	Negative
Ketones (mg/dL)	Negative	Negative
Bilirubin	Negative	Negative
Blood	Trace	Negative
Nitrite	Negative	Negative
Urobilinogene (EU/dL)	0.2	0.2-1.0
Leuk. Esterase	Negative	Negative
WBC/HPF	3	0-4
Seqamous epi	<1	0-4

Table 18. List of medications given August 6-17, 2004

Treatments	Starting date
Ceftriaxon (Rocephin) 200 mg each 12 hours	08/06/04
Albutrol 1 puffs inh Q3 hr	08/06/04
Acetaminophen oral 60 mg Q4-6 hrs	08/06/04
Dextrose	08/06/04
Phenobarbital 11 mg IV/Q12 hours	08/06/04
Fentanyl 5µg/IV	08/06/04
Midazolam	08/06/04
Dextrose 5%-0.45% NaCl(IV) + Potassium phosphate 10 MEQ	08/06/04
Lanolin ointment Application on lips	08/06/04
Metoclopramide (reglan) 0.4 mg each 6 hours	08/07/04
Furosemide 4 mg/IV	08/07/04
Lanolin/Mineral oil/Petrolatum drop, both eyes	08/07/04
Ibuprofen oral 40 mg Q6 hrs	08/08/04
Ranitidine syrup (Zantac) 8 mg/12 hours	08/10/04
Dexamethasone (IV)	08/15/04

Table 19. Blood toxicology screen performed on August 12 at 0600

Agents	Results
Ethyl Alcohol	Negative
Methanol	Negative
Isopropylalcohol	Negative
Acetone	Negative
Salicylate	Negative
Tricyclic antidepressant	Negative
Acetaminophen	Negative
Barbuturates[1]	Positive

[1]Quantity was not sufficient for GC/MS confirmation

5. Autopsy findings in case of Averial Buie

Sridhar Natarajan, M.D. performed an autopsy on Averial's body at 1000 on August 18, 2004 in the Texas Tech University Health Sciences Center (Autopsy No: FA04-0631) [10]. Dr. Natarajan described Averial's body as that of a normally developed, adequately nourished, 7.5-week-old female, white infant. Her weight and length were 4160 grams and 56 cm, respectively. Averial had a head circumference of 37 cm, a chest circumference of 35.2 cm, an abdominal circumference of 36 cm, a crown to rump length 39.5 cm, and a heel to toe length of 7.8 cm bilaterally.

Dr. Natarajan examined Averial's body and observed three minor areas of erythema (redness) on her face and two areas of erythema on her shaved head as described in Table 20. The physicians who had examined Averial in the emergency room on August 6 did not see these red areas or any evidence of injury caused by trauma.

Table 20. External marks observed on the skin of Averial's head region.

Region	Findings
Face	• A 16x18 mm area of patchy erythema observed on the right cheek. • There was a 3 mm area of erythema along the anterior right distal nostril. • There was a 21x11 mm cluster of patchy erythema involving the body of the right mandible.
Head	• Along the occipital aspect both right and left of the mid line was a 16x2 mm band-like area of light purple discoloration. • On the right side of the parieto-temporal scalp was a 23x18 mm area of light purple ovale shapped erythema.

Furthermore, Dr. Natarajan reported the following gross and microscopic lesions in Averial's organs and tissues:

5.1 Lesions observed outside the skull

Reflection of the scalp showed a right parieto-temporal 6 x 3 cm subgaleal hemorrhage. The underlying temporal bone had a 56 cm linear fracture with slight displacement (1 mm). The left temporal scalp had a 2 x 1.5 cm superficial subgaleal area of hemorrhage.

Microscopic examination of the H & E stained tissue section from the right temporal scalp in the area of grossly identified contusions (Slide #4) showed hemorrhage with deep extension into the underlying subcutaneous tissue.

5.2 Examination of the skull fracture

The microscopic examination of the H & E stained sections of skull fracture (Slides #19 and #20) revealed healing bone fracture with fibrovascular response, mild areas of hemorrhage, and esteoblastic activity. No evidence of significant acute or chronic inflammation was observed. Adjacent skull bone showed no significant pathological changes.

5.3 Lesions observed intracranially

5.3.1 Gross and microscopic examination of the dura and suubdural region

The calvarial skull was removed and 13 cc of subdural hemorrhage was collected. The hemorrhagic fluid was dull brown-red and patchy adherence to the dura was noted. The majority

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of the hemorrhage overlied the right parietal region adjacent to the mid line.

A 2cc measured subdural hemorrhage was identified within the right middle cranial fossa with focal areas of clot adherence. There was patchy subarachnoid hemorrhage overlying the right parietal hemisphere and patchy involving the mid brain and pons.

Microscopic examination of the H & E stained section of dura with attached subdural clot (Slide #10) showed an organized clot with multiple layers of fibroblastic proliferation (ranging from 10 to 15 layers in thickness). Pigment laden macrophages and areas of vascular sinusoids were present with the clot. Along the arachnoid, a patchy area of a fibroblastic membrane was also seen.

5.3.2 Gross examination of the brain

The brain weight was 483 grams. The surface was edematous and light tan gray with areas of translucent gelatinous appearance. Subarachnoid hemorrhages were seen overlying the convexities of the frontal and parietal lobes. Patchy subarachnoid hemorrhages were seen over the lateral and inferior temporal lobes. After fixation cortical contusions were noted involving the right temporal and frontal lobes, with the cortical rim showing a yellow brown color. Softening and friability of these injured areas were noted—the largest involving the medial right temporal lobe (2.5 x 2.0 x 1.3 cm).

5.3.3 Microscopic examination of H & E stained sections of the brain

Sections of cerebellum with subarachnoid hemorrhages (Slide #11) and the right temporal lobe of the brain (Slides #12 and #13) revealed the presence of necrosis, focal acute inflammatory cells, edema, and abundant macrophage. Sections of the right frontal cortex of the brain (Slides #14 and #15) also revealed the presence of necrosis, focal acute inflammatory cells, edema, and abundant macrophages. Sections of corpus callosum, brain stem, and basal ganglia (Slides #16-18) showed the presence of edema, reactive astrocytes, areas of macrophages, and subarachnoid hemorrhage.

5.4 Lesion observed in the eyes

Microscopical examination of the H & E stained sections of the right globe (Slide #6) and the left globe (Slide #8) showed subretinal hemorrhage.

5.5 Lesions observed in ribs

Autopsy of the chest showed the presence of tan white raised notched areas involving right anterolateral rib numbers 5, 6, and 7. The right posterior rib numbers 3 and 5 and the left lateral ribs showed thickened and raised areas. The microscopic examination of the H & E stained sections of the right anterolateral ribs 5, 6 and 7 (Slides #21 and #22) and the posterior right rib number 3 (Slide #23) showed bone marrow; fibrostastic proliferation with neovascularization and osteoblastic activity; and bony spicules overlying callus formation of periosteum (healing fractures). The posterior right rib number 3 (Slide #23) and left lateral ribs, number 4 and 5 (Slide #4), also showed healing fractures.

5.6 Lesions observed in lungs

The weights of the right and left lungs were 81 and 69 grams, respectively. The microscopic examination of the H & E sections from all lobes of the right and left lungs showed areas of atelectasis; congestion; focal areas of alveolar hemorrhage; alveolar macrophage; and alveolar spaces containing a neutrophilic response (broncho pneumonia). Some of the alveolar spaces had septal walls which showed a proteinaceous pink thickening (hyaline membrane); and some of the alveolar spaces showed proteinaceous debris lying freely (Slide #1).

5.7 Abnormal changes in spleen and thymus

The spleen weighed 11 grams and had a glistening brown-red capsular surface. On section, the parenchyma was dark and soft. The weight of thymus gland was 12 grams. Microscopic examination of the H & E section of the thymus (Slide #2) showed areas of focal lymphocyte drop-out without significant evidence of fatty change.

6. Averial suffered from bronchopneumonia and respiratory distress syndrome

The clinical data in Averial's case indicate that she suffered from acute bronchopneumonia and respiratory distress syndrome that led to hypoxemia, severe acidosis, respiratory failure, cardiac arrest, and death. These clinical data include:

1) Blood analysis performed at 0249 on August 6, 2004 revealed critically low blood pH (6.882), high PCO_2 (70.1 mmol/L), low HCO_3 (12.9 mmol/L), and high Anion Gap (27.4 mmol/L) levels. Averial suffered from mixed respiratory and metabolic acidosis (Table 4). Additionally, Averial had a high serum potassium level of 5.83 mmol/L and suffered from hyperkalemia. Also, she had a high blood glucose level of 347 mg/dL and low serum protein and albumin levels (Table 5).

2) Averial's chest X-ray exam performed at 0251 on August 6 revealed evidence of pneumonitis in the right lower lobe.

3) Averial's blood analysis performed at 0300 on August 6 showed that her white blood cell and lymphocyte counts were elevated. She suffered from lymphocytosis. She was treated with ceftriaxon (Rocephin) IV and her white blood cell and lymphocyte counts returned to normal levels by 2030 on August 6 (Tables 3 and 6). These data indicate that Averial was suffering from bacterial infection.

4) The microscopic examination of the H & E stained sections from all lobes of the right and left lungs showed that Averial suffered from bronchopneumonia, hyaline membrane disease, interstitial fibrosis, and pulmonary bleeding (Figures 1-4).

5) Averial had atrophy of the thymus and spleen that indicates she was sick for a few days prior to her cardiac arrest on August 6, 2004. Her spleen and thymus's weights were 11 and 12 grams, respectively. The expected average spleen and thymus's

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weight for a child of Averial's age is 19 and 20 grams, respectively [11].

Below are detailed descriptions of the following: (1) gross and microscopic lesions observed in Averial's lungs; (2) the likely causes of Averial's respiratory failure; and (3) biomarkers and published medical studies that show Averial died as a result of respiratory failure.

6.1 Description of abnormal changes observed in Averial's lung and their significance

The weights of the right and left lungs were 81 and 69 g, respectively. The expected average weights for the right and left lungs for a child in Averial's age are 67 and 58 g, respectively [11]. These data indicate that the weight of the lung was increased by 20% of normal as a result of inflammation, accumulation of fluid, and/or bleeding.

The medical examiner (ME) examined five H & E stained sections of Averial's right and left lungs microscopically and observed evidence of bronchopneumonia, hyaline membrane, and bleeding as described in Section 5 of this report. I also examined these five H & E stained sections of the lungs microscopically and observed the following lesions:

1) Averial had a severe form of bronchopneumonia that affected significant portions of her right and left lung, which led to the collapse of the alveoli (atelectasis) as show in Figures 1 and 2. The lumens of the bronchioles were filled with inflammatory cells (mostly macrophages) and red blood cells. The walls of the bronchioles were also thickened (Figure 3). Furthermore, the alveolar walls were thickened and some of the alveoli contain hyaline membrane (Figure 4). Figures 5 and 6 represent the H & E stained sections of a lung of a child (Eliza Jane) without evidence of broncopneumonia and bleeding. They show the normal structure of the lung. Eliza Jane died as a result of adverse reaction to antibiotic [12-14].

2) Congestion and bleeding (Figures 1-4).

Rubin *et al.* stated that bronchopneumonia remains a common cause of death in humans. The lesions consist of scattered irregular foci of pneumonia centered on terminal bronchioles and respiratory bronchioles. Bronchiolitis is present, with exudation of polymorphonuclear leukocytes into the adjacent alveoli. Large continuous areas of alveolar involvement do not occur in bronchopneumonia [15].

Averial died 11 days following her admission to the hospital and the majority of the inflammatory cells present in the lumen of the bronchioles are macrophages (Figure 3). Obstruction of the airways usually lead to the collapse of the alveoli (atelectasis) and a significant portion of Averial's lung showed areas of atelectasis (Figures 1 and 2). Atelectasis causes hypoxemia.

Hyaline membranes were also observed in some alveoli in Averial's case, which resulted from injury to the lung. Injury to endothelial cells allows the leakage of protein-rich fluid from the alveolar capillaries into the interstitial space. The destruction of type I pneumocytes permits the exudation of fluid into the alveolar spaces, where the deposition of plasma proteins result in the formation of fibrin-containing precipitates (hyaline membranes) on the injured alveolar wall [15].

Diffuse alveolar damage (DAD) usually leads to acute respiratory distress syndrome (ARDS). Individuals who suffer from ARDS usually develop rapidly progressive respiratory failure. This condition reflects decreased lung compliance and hypoxemia. The overall mortality of ARDS is more than 50%. DAD can be caused by Gram-negative septicemia and other bacterial infections and viral infections [15]. The clinical evidence showed that Averial had bacterial infection.

Averial died at 11 days following her admission to the hospital. It is likely that most of the hyaline membranes that were present on the day of Averial's admission to the hospital (August 6) were cleared by macrophages.

Rubin *et al.* stated that the exudative phase of DAD develops during the first week after the pulmonary insult and features edema, exudation of plasma proteins, accumulation of inflammatory cells, and hyaline membranes. The earlier manifestation of alveolar injury is evidenced by electron microscopy, which reveals degenerative changes in both endothelial cells and type I pneumocytes. It is followed by the sloughing of type I cells and the appearance of denuded basement membranes. Interstitial and alveolar edema is prominent by the first day but soon recedes [15].

Hyaline membranes begin to appear by the second day and the most conspicuous morphological feature of the exudative phase occurs after 4 to 5 days. These eosinophilic, glassy membranes consist of precipitated plasma proteins and the cytoplasmic and nuclear debris of sloughed epithelial cells.

Interstitial inflammation consisting of lymphocytes, plasma cells, and macrophages, is apparent early and reaches its maximum in about a week. Toward the end of the first week and persisting during the subsequent organizing stages, regularly spaced cubodial type II pneumocytes become arrayed along the denuded alveolar septa. In fatal cases of DAD, the lungs are heavy, edematous, and virtually airless [15]. These features were observed in Averial's right and left lung.

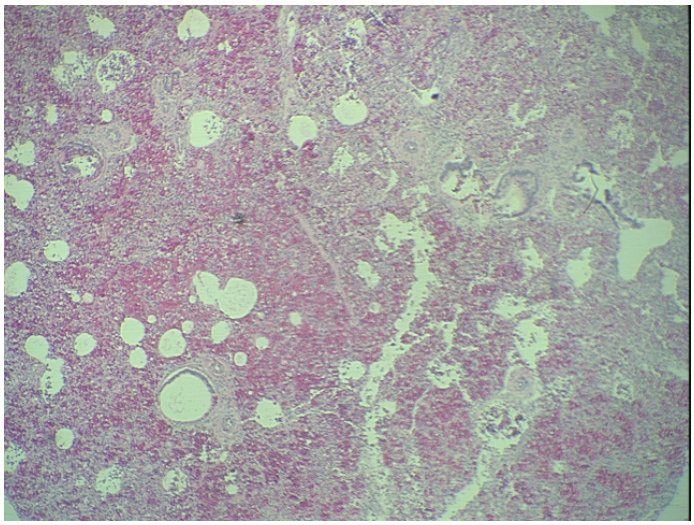

Figure 1. Section of Averial's lung (H & E, x5) showing collapsed aleveoli (atelectasis), bleeding, and dilated bronchioles.

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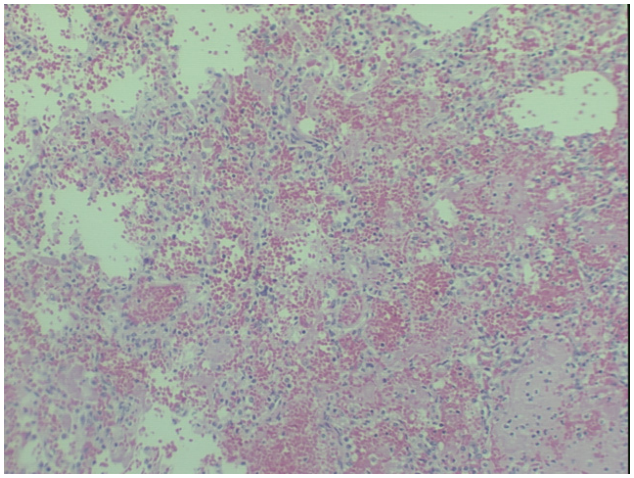

Figure 2. Section of Averial's lung (H & E, x20) showing collapsed aleveoli (atelectasis), bleeding in the alveoli and the interstitial tissue, and exudate and blood in the lumen of the bronchioles.

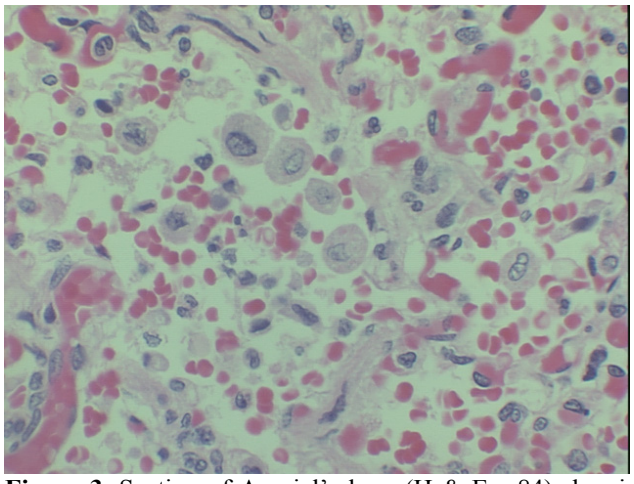

Figure 3. Section of Averial's lung (H & E, x84) showing inflammatory cells (macrophage and neutrophill) and red blood cells in the lumen of the bronchioles.

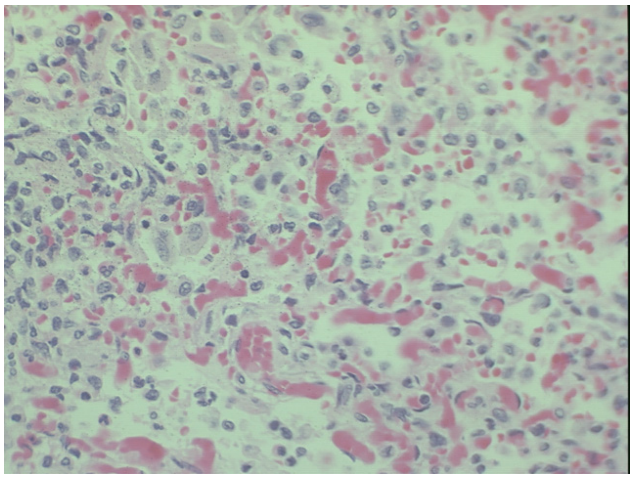

Figure 4. Section of Averial's lung (H & E, x52) showing hyaline membranes in some alveoli, inflammatory cells in the alveoli and bronchioles, evidence of interstitial fibrosis and congested blood vessels.

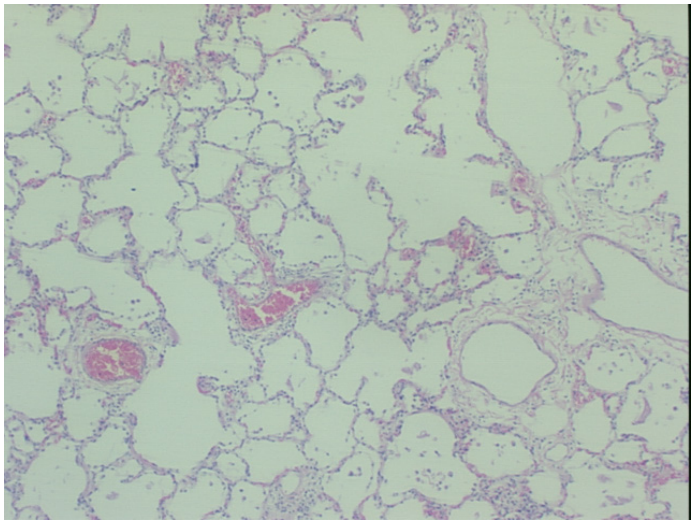

Figure 5. Section of Eliza Jane's lung (H & E, x52) showing normal structure of a child's lung [12].

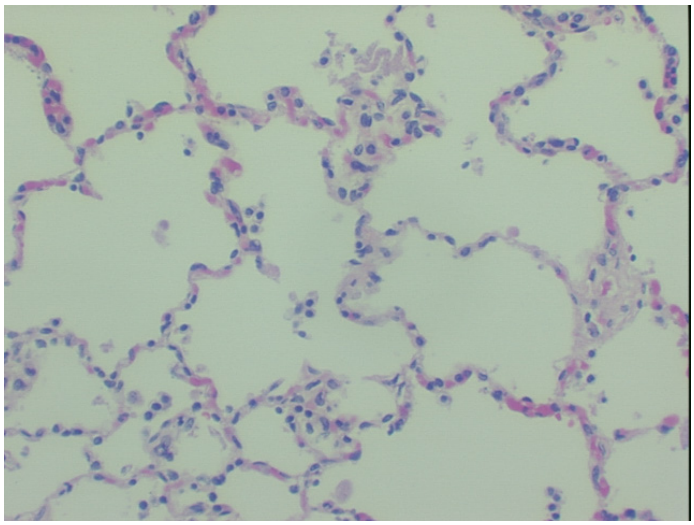

Figure 6. Section of Eliza Jane's lung (H & E, x84) showing the normal thickening of the alveolar walls.

6.2 Bronchopneumonia and acute respiratory distress syndrome (ARDS) cause acidosis

Blood analysis performed shortly after Averial's admission to the hospital on August 6, 2004 revealed that she had critically low blood pH (6.882), high PCO_2 (70.1 mmol/L), low HCO_3 (12.9 mmol/L), and high Anion Gap (27.4 mmol/L) levels. Averial suffered from mixed respiratory and metabolic acidosis (Table 4). Averial's acidosis was caused by her lung injury that led to respiratory failure.

Bhushan and Gupta evaluated forty cases of children (29 males and 11 females) who suffered from bronchopneumonia (n=32), bronchiolits (n=4), and pneumonia (n=3). They found uncompensated acidosis in 75% of the cases at admission. $PaCO_2$ was elevated in 65% of cases and hypoxemia was an almost universal finding. $PaCO_2$ above 65 mm Hg was associated with bad prognosis [16].

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Furthermore, Simpson *et al.* evaluated 11 infants who suffered from respiratory failure due to severe lower respiratory tract infections. Progressive respiratory difficulties leading to exhaustion, peripheral circulatory collapse, recurrent apnoeic attacks or generalized convulsions were the main clinical presentations resulting in severe ventilatory failure. In nine infants preventilation $PaCO_2$ exceeded 65 mm Hg [17].

In addition, Simpson and Flenley studied the arterial blood-gas and pH changes in 32 children under three years of age with acute lower-respiratory tract infections. Hypoxia was common, the PO_2 being below 80 mm Hg in 14 (67%) of the 21 cases in which it was measured and below 50 mm Hg in 5 of these (24%). Carbon-dioxide retention, with a PCO_2 over 50 mm Hg was present in 16 cases (50%). There were 8 cases in which the pH was less than 7.20 or the PCO_2 greater than 65 mm Hg. In the three deaths that occurred during the study, the blood pH values on admission were 7.14, 7.19, and 7.25. The respective PCO_2 levels were 52, 110, and 68 mm Hg [18].

6.3 The likely cause of Averial's respiratory infection

Averial's blood analysis performed at 0300 on August 6 showed that her white blood cell and lymphocyte counts were elevated and she suffered from lymphocytosis (Table 6). She was treated with ceftriaxon (Rocephin) IV and her white blood cell and lymphocyte counts returned to normal levels by 2030 on August 6 (Tables 3 and 6). These data indicate that she had a bacterial infection.

Lymphocytosis is one of the features associated with the Bordetella pertusis respiratory infection in children. Typically, the total white blood cell count ranges from 10,000 to 30,000 cells/μL with 50 to 70% lymphocytes. Fauci *et al.* reported that a dramatic inspiratory whoop following a paroxysmal cough is a hallmark of severe pertusis in children, but is frequently lacking in infants. In addition, fever is absent or low except in cases of superinfection. Therefore, an absolute lymphocytosis may provide an additional clue to the diagnosis [19]. Averial's white blood cell count at the time of admission was 17,800 cells/μL with 51% lymphocytes.

Greenberg *et al.* stated that infants with pertussis experience the highest rates of hospitalization, complications, and death. Severe complications include pneumonia, encephalopathy, and meningoencephalitis. In addition, infants may experience weight loss, bronchitis, otitis media, apnea, cyanosis, inguinal hernia and rectal prolapse [20]. The standard diagnostic test is the isolation of B. pertussis from nasopharyngeal swab culture. B pertussis is a small, nonmotile, gram-negative coccobacillus [19]. This test was not performed in Averial's case.

6.4 Reduction in thymus and spleen weight and its indication

Averial had atrophy of the thymus and spleen. Her spleen and thymus weights were 11 and 12 grams, respectively. The expected average spleen and thymus weights for a child of Averial's age are 19 and 20 grams, respectively [11]. These data indicate that the weights of the spleen and the thymus in Averial's case were reduced by 42 and 40%, respectively. This indicates that Averial was sick for a few days prior to her cardiac arrest on August 6, 2004.

A significant reduction in the thymus and lymphoid organ's weight has been reported in individuals suffering from a variety of illnesses. The degree of atrophy is dependent on the type and the duration of illness. Below are the results of four clinical studies that show thymus and spleen atrophy caused by stress due to illnesses.

1) Kitonyi reviewed one hundred anteroposterior chest radiographs of children under the age of five years suspected of having chest infection. Thymocardiac ratio was determined. It was concluded that in children under five years, the thymus generally decreases in size with age and that often the thymus will undergo atrophy as a primary response to infection [21].

2) Liang *et al.* studied 70 thymuses obtained at autopsy from children who died of various diseases using histological, immunohistochemical and ultrastructural methods. In the immunohistochemical study, antibodies against 8 lymphocyte differentiation antigens, including CD4, CD8, CD3, CD1, CD2, CD25, CD22 and T9 as well as those against keration and S-100 protein were used. The findings suggested that thymus involution can occur in different diseases [22].

3) Zhang reviewed thymuses, spleens, lymph nodes, tonsils and appendices from 621 autopsy cases. He found that more than 130 different illnesses cause atrophy of the thymus. For example, cases of infection with a course less than 5 days showed mild atrophy of the thymus and those cases with a longer course might show moderate or severe degree of atrophy. In 81% of the cases, the degree of thymus atrophy was in accordance with those of the other immune organs [23].

4) The characteristics of the normal adult thymus in both sexes were determined in 50 cases of accidental death by a simplified quantitative histologic technique. A table of normal values derived from these findings was used for making comparisons with the thymuses from autopsies of 50 additional individuals suffering from terminal illness. Changes ascribed to disease included accelerated involution of the thymus accompanied by loss of septae, smaller lobules, increased adipose tissue and fusiform cells, a reduced number of lymphocytes and Hassall's corpuscles and a relative increase in the number of cystic corpuscles [24].

7. Acidosis and levels of consciousness

Averial stopped breathing and became unresponsive in the morning of August 6 and her mother took her to Baptist St. Anthony's Health (BSA). Averial was examined by physicians at the emergency room and no evidence of injury caused by trauma was observed (Section 3). Blood analysis performed at 0249 revealed critically low blood pH (6.882), high PCO_2 (70.1 mmol/L), low HCO_3 (12.9 mmol/L), and high Anion Gap (27.4 mmol/L) levels. Averial suffered from mixed respiratory and metabolic acidosis (Table 4). In addition, Averial had high serum potassium level of 5.83 mmol/L and suffered from hyper-

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kalemia. Also, she had a high blood glucose level of 347 mg/dL and low serum protein and albumin levels (Table 5).

Review of the medical literature on the impact of acidosis on the levels of consciousness indicates that Averial became unconscious because she had critically low blood pH. For example, Edge *et al.* evaluated 225 episodes of diabetic ketoacidosis (DKA) in children without evidence of cerebral edema and examined the relationship between conscious level and initial biochemical variables. These findings were contrasted with those in 42 children who later developed cerebral edema. The study found that in children with DKA, initial conscious level is closely related to pH. Thus cerebral function in DKA is related to severity of acidosis even when there is no evidence of cerebral edema [25].

On admission in the hospital, 42/225 (19%) of the children had mild (pH 7.26-7.35); 96 (44%) moderate (pH 7.11-7.25); and 80 (37%) severe DKA (pH $\leq$ 7.10). Conscious level: alert and oriented (group 1, n=123), drowsy but oriented when woken (group 2, n=62), semi-conscious or confused/agitated (group 3, n=9), comatose (group 4, n=4).

Glasgow Coma Score (GCS) was available in 65. The pH varied significantly with conscious level: group 1, 7.20± 0.11(mean+/- SD); group 2, 7.10±0.16; group 3, 6.96±0.11; group 4, 6.88±0.09 (anova, $p<0.001$). Using multivariate analysis comparing groups 1 with groups 2-4, lower pH and younger age were the only independent determinants of impaired conscious level ($p<0.001$, $p=0.036$). Conscious level in the children with cerebral edema was also closely related to pH and not to other biochemical variables. The pH was lower at each conscious level in the children with later cerebral edema [25].

Furthermore, Averial had a high serum potassium level of 5.83 mmol/L and suffered from hyperkalemia. In metabolic acidosis, potassium usually leaves the intracellular environment because the intracellular proteins bind with hydrogen, which leads to cardiac arrest and paralysis of the respiratory muscles [19]. Her potassium returned to the normal level of 4.1 mmol/L following treatment with sodium bicarbonate.

8. The likely causes of bleeding in the subdural and subarchanoid spaces and in other tissues

Averial died in the hospital on August 17, 2004, which is 11 days following her admission and the medical examiner (ME) performed the autopsy on August 18. He described bleeding of various ages grossly and microscopically in the subgaleal areas, the subdural and the subarachnoid spaces, and the lungs (Section 5). In addition, he removed 13 mL of hemorrhagic fluid from the subdural space.

The ME alleged that the bleeding in this case was caused by trauma. My review of the clinical medical data indicates that the bleeding in these regions occurred in the hospital and was caused by medications and hypoxia. Below is a list of clinical events and medical studies that support my conclusions.

1) Dr. Reghuram examined Averial in the emergency room on August 6 and did not observe any injury caused by trauma in the head, neck, or the rest of her body. Reghuram did not appreciate any crepitus on palpation of the cranial vault and the skull. Neither did he appreciate any depressed regions in the skull bone. In addition, no evidence of any surface bruising, petechia, ecchymosis or purpura was observed over the skin in the head region or the rest of the body (Section 3).

2) The first evidence of bleeding in Averial's case was reported at about 90 minutes following her admission to the hospital on August 6. A small scalp hematoma, small subdural hemorrhage, and brain edema were observed on CT scan of the head taken at 0350 (Table 7). This CT scan was taken at about 90 minutes following the administration of two doses of epinephrine and one hour following the treatment with sodium bicarbonate.

Intracranial bleeding has been reported in some individuals treated with epinephrine given at therapeutic doses [4-9]. For example, bleeding (intracerebral, subdural and/or subarachnoid hemorrhage) was reported as one of the serious adverse reactions of epinephrine, even when given to individuals at a low dosage level of 0.05 mg subcutaneously, which is 25% of the dosage of epinephrine given to Averial in the emergency room [4]. Horowitz *et al.* also reported the development of acute cardiac arrest and fatal subarachnoid hemorrhage in an individual who suffered from allergic reaction and treated with epinephrine subcutaneously [5].

Furthermore, the treatment with sodium bicarbonate caused brain edema in children and adults [8, 9]. Averial's hemoglobin level (10.7 g/dL), red blood cell count (2.97 x 10^6/μL), and hematocrit value (31.5) measured at 0250-5 were reduced by 21-22% at 0530 and 2030 (Table 4). These data indicate that a significant bleeding occurred following Averial's treatment with epinephrine and sodium bicarbonate.

3) The head CT scan taken at 1611 on August 6 indicated that Averial's subdural bleeding and brain edema became worse in comparison to the CT scan taken at 0350 on August 6 (Table 11). Furthermore, the CT scans and the MRI exams of the head region taken on August 8, 12, and 13 indicated that Averial's subdural bleeding and brain edema become worse (Table 12) in comparison to the CT scans of August 6 (Tables 7, 11). Averial's head circumference was 38.25 cm on August 9 and 37 cm on August 6.

4) Blood analyses showed Averial developed severe anemia on August 8, indicating that she suffered from bleeding between 1900 on August 7 and 0500 on August 8. Her hemoglobin level and hematocrit value were reduced by 25% and 27%, respectively (Table 13). Averial's platelet count was also reduced by 24% of baseline by August 7. The bleeding resulted in the development of thrombocytosis on August 12 (Table 14). Averial was given excessive doses of sodium bicarbonate on August 9-11, 2004. Her blood pH reached a high critical level of 7.59 (Table 13).

5) The Medical examiner (ME) collected 13 mL of hemorrhagic fluid from Averial's subdural space, indicating that the bleeding likely occurred within 48 hours prior to autopsy. Additionally, the ME examined the H & E stained section of dura with attached subdural clot (Slide #10) microscopically and reported the presence of an organized clot with multiple layers of fibroblastic proliferation, pigment laden macrophages, and areas of vascular sinusoids within the clot.

I also examined this section microscopically and observed fibroblastic proliferation and pigment laden macrophages

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within the clot. In addition, I observed an area of fresh bleeding (Figure 7). These data indicate that the bleeding occurred at various intervals within hours to days prior to autopsy.

6) The ME examined five H & E stained sections of Averial's right and left lungs microscopically and observed evidence of bleeding in the lungs. I also examined these five H & E stained sections of Averial's lungs and observed bleeding in significant areas of the lungs. The red blood cells were intact, indicating that the bleeding occurred within 24 hours prior to autopsy (Figures 1-4). These data also indicate that the bleeding in Averial's case was not limited to the head region.

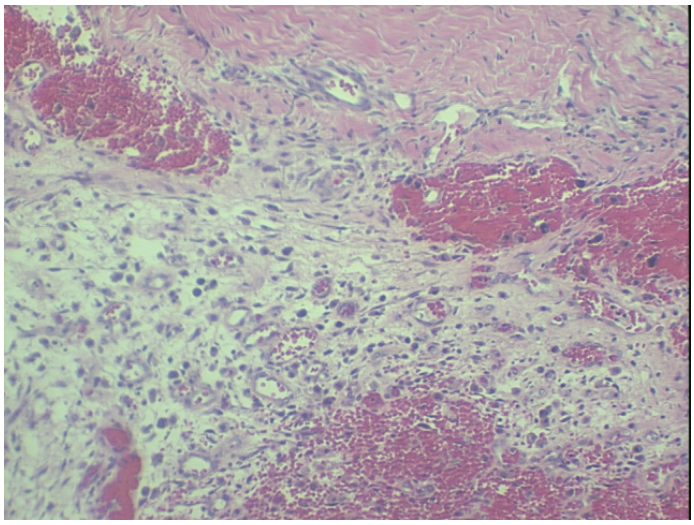

Figure 7. Averial's dura with attached subdural clot (H & E, x20) showing fibrosed clot and areas with recent bleeding.

9. The likely causes of brain damage reported in Averial's case

The Medical examiner (ME) stated that he observed cortical contusions in Averial's formalin-fixed brain involving the right temporal and frontal lobes. In addition, he examined the H & E stained sections of the brain (frontal cortex, corpus callosum, brain stem, and basal ganglia) and reported the presence of necrosis, focal acute inflammatory cells, edema, abundant macrophages, and reactive astrocytes (Section 5). He alleged that these lesions in the brain were caused by trauma.

I also examined these sections of the brain and observed areas of necrosis and non-specific inflammatory response. My review of the medical data and published medical studies pertinent to the type of lesions observed in the brain indicate that these lesions developed during Averial's stay in the hospital. These lesions were caused by hypoxia, medications, bleeding, and infarction. Below are clinical data and medical studies that describe the sequence of events that led to the formation of the brain's lesions observed in Averial's case.

1) The medical staff that examined Averial after her admission on August 6 did not observe any injury caused by trauma in the head region as described in Section 3 of this report.

2) The first evidence of intracranial bleeding and brain edema in Averial's case was observed on the head CT scan taken at about 90 minutes following the administration of epinephrine and sodium bicarbonate. The CT scans of the head taken on August 6, 8, and 12 showed that the bleeding and edema became worse with time. Averial's head circumference was 37 cm on August 6, increasing to 38.25 cm on August 9.

The use of sodium bicarbonate at high therapeutic levels causes hypoxia and brain edema. Fauci *et al.* reported that alkalinization of the blood with sodium bicarbonate increases the avidity of hemoglobin to bind oxygen, thus impairing the release of oxygen in peripheral tissues. Averial's blood pH reached levels higher than 7.5 on August 9, 10, and 11 (Table 13) and the elevation in pH resulted from the treatment with sodium bicarbonate [19].

Hypoxia, edema, and bleeding cause necrosis and inflammation in the brain similar to that observed in Averial's brain [26-28]. For example, Mayer *et al.* performed paired consecutive CT and 99mTc-hexamethylpropylenamine oxime single-photon emission computed tomography (SPECT) scans during the acute (mean, 18 hours) and subacute (mean, 72 hours) phase of intracerebral hemorrhage (ICH) in 23 individuals. Hematoma and edema volumes were traced and calculated from CT images. They found that the ICH volume (18 mL) did not change but the mean edema volume increased by 36% (from 19 to 25 mL, $P<0.0001$). Perilesional edema on CT always corresponded topographically with perfusion deficits on SPECT [27].

Furthermore**,** Gong *et al.* conducted a study in rats to evaluate the development of brain edema following the induction of intracerebral hemorrhage (ICH). Immunocytochemistry for polymorphonuclear leukocyte marker (myeloperoxidase, MPO), microglia marker (OX42) and intracellular adhesion molecule-1 (ICAM-1) was performed in control, and 1, 3, 7, and 10 days after the injection of 100 μL autologous blood in the right basal ganglia. They observed an inflammatory response in the brain after ICH. Infiltrating leukocytes and activated microglia may release cytotoxic mediators contributing to secondary brain injury and edema formation [28].

Experimental studies also showed that bleeding in the brain induced gliosis. Gliosis is the proliferation of fibrillary astrocytes with the formation of many glial fibers. Gliosis was observed one week following the injection of the blood into the brain and lasted for at least three weeks [26, 29-31].

For example, Kowianski *et al.* and Karwacki and Kowianski found that experimentally induced hemorrhage in the brain of rats caused programmed cell death and acted as a strong stimulus for both microglial and astroglial activations. They produced the intracerebral hematoma by injecting 100 μL of autologous arterial blood into the striatum of a rat. The animals' brains were removed at 1, 3, 7, 14, and 21 days after production of the hematoma.

The terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) method was used to detect DNA fragmentation and TUNEL-positive cells. Microglial-macrophage lineage cells were immunocytochemically stained with antibodies OX42, OX6 and ED1. The astrocytic population was studied by means of anti-GFAP staining [30, 31].

TUNEL-positive cells were found on the first day of observation and were present for three weeks after hematoma pro-

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duction. Changes in cellular morphology and intensity of staining were time-dependent reactions in both microglial and astroglial cells.

Strong activation of microglial-macrophage lineage cells revealed with OX6-and OX42-immunoreactivity started during the first postoperative day. The complete pattern of activation for ED1-immunoreactivity was observed from the third postoperative day. At this stage, numerous phagocytic macrophages started to appear in the perihematoma region.

Morphological changes were most intensive during the second postoperative week. The astroglial (anti-GFAP) reaction was observed after the third postoperative day and proceeded less dynamically. The glial reaction gradually stopped but not completely during the period of observation. The early occurrence of glial activation, pattern of morphological changes, and characteristic sequence of antigen expression indicate a very intense type of glial reaction [29, 30].

Furthermore, Koeppen *et al.* injected 100 μL of autologous whole blood intracerebrally in adult rabbits. They found that the extravasation of blood elicits a cellular reaction in the adjacent surviving tissue where the lesion activates resident microglia and attracts many more phagocytes from the blood stream. The cellular responses to the injections were studied by iron histochemistry and immunocytochemistry for ferritin, the ferritin repressor protein (FRP), the glial fibrillary acidic protein (GFAP), and the complement receptor CR3. Conversion to hemosiderin began at 5 days after the injection of blood. The lesions caused initial destruction of astrocytes in the perifocal zone as judged by GFAP- and FRP-immunoreactivity. However, at 5 days, astrocytic processes reentered the perifocal zone and intermingled with microglia and macrophages [31].

3) The MRI of the brain taken on August 12 revealed the presence of subacute infarction (Table 12). The likely causes of the infarction were the development of thrombocytosis and the injuries to the blood vessels caused by hypoxia.

Averial's platelet count on August 7 was 409,000 cells/μL of blood and it was increased by 82% to 745,000/μL on August 14 in response to bleeding (Table 14). The occlusion of blood vessels with blood clot causes ischemia and necrosis in tissue [15].

10. The likely causes of the subretinal bleeding observed in Averial's case

The ME examined the H & E stained sections of Averial's right and left eyes microscopically and reported the presence of subretinal hemorrhage in both eyes. He alleged that the bleeding was caused by trauma. My review of the clinical data indicate that the bleeding in the eyes occurred during Averial's stay in the hospital. It was caused by medications, hypoxia, anemia, and the elevation in the intracrainal pressure. Below is a list of observations that support my conclusions.

1) A physician examined Averial's eyes on August 9 using fundoscope and no subretinal bleeding was observed in the right eye. It indicates that the subretinal bleeding in the right eye occurred between August 9 and August 18.

2) The bleeding in the left eye was first reported on August 9, which is three days following her admission. A fundoscopic exam showed hemorrhage through fundus obscuring the disk. I believe that this bleeding occurred following Averial's admission to the hospital on August 6 and resulted from the use of epinephrine and sodium biacarbonate, hypoxia, anemia, and the increase in the intracranial pressure. Averial's head circumference of 37 cm on August 6 increased to 38.25 cm by August 9.

On August 6, Averial suffered from bleeding following the treatment with epinephrine and sodium bicarbonate and became anemic. Her hemoglobin level and the hematocrit value were 10.7 g/dL and 32% at 0250, respectively and were reduced to 8.4 g/dL and 25%, respectively at 0530. In addition, her red blood cell count was reduced from 2.97 x 10^6/μL at 0250 to 2.3 x10^6/μL at 2030 (Table 4). Averial also suffered from thrombocytosis. Her platelet count was increased to 745,000 cells/μL in response to bleeding (Table 14).

It has been reported that severe anemia and thrombocytosis cause retinal bleeding and other retinal pathology [32-35]. For example, Asien *et al.* evaluated the occurrence of clinically apparent retinal changes in 35 anemic individuals and 35 age- and sex-matched healthy control subjects. 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 individuals exhibited extra vascular lesions (flame-shaped hemorrhages, hard exudates, and cotton-wool spots). Within the group of anemic patients, 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 [33].

Furthermore, Nobacht *et al.* reported a case of a 24-year-old man who developed acute vitreous hemorrhage of the right eye. Fluorescein angiography of the right eye showed an avascular peripheral retina with marked capillary nonperfusion, arteriovenous anastomosis, and sea fan neovascularization. Blood studies showed thrombocytosis without other associated systemic diseases. They concluded that the avascular retina in this man was associated with thrombocytosis. They also stated that thrombocytosis may cause an avascular peripheral retina with neovascularization and vitreous hemorrhage in otherwise healthy persons [34].

Moreover, Kacer *et al.* reported two cases of individuals with ophthalmologic complications associated with mild iron deficiency anemia. The first case is a 37-year-old female who suffered from blurred vision in her left eye for four days. Ophthalmoscopic and angiographic findings were consistent with the diagnosis of central retinal vein occlusion. Further hematologic investigation into possible causes disclosed mild iron deficiency anemia (Hb 9.4 g/dl, hematocrit 30.5%) [35].

The second case is a 50-year-old female who presented with a 1-week-history of blurred vision and metamorphopsia. Her visual acuity was 20/200. Further examination revealed a nonarteritic ischemic optic neuropathy and an iron deficiency anemia as the underlying disease (Hb 7.3 g/dl, hematocrit 25%). They stated that clinicians involved in the management of chronic iron deficiency anemia should be aware of possible ophthalmic manifestations in this disease [35].

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11. The likely causes of the skull fracture reported in Averial's case

Physicians examined Averial in the emergency room on August 6 and did not see any evidence of injury caused by trauma. Moreover, no evidence of skull fracture was noted on Averial's three head CT scans taken on August 6 and 8. However, Averial's X-ray exam of the CT scan of the head region performed on August 10 and 13 showed evidence of skull fracture (Table 12).

On August 18, the ME reported the presence of linear fracture (56 cm) in the temporal bone of the skull. Microscopic examination of the H & E stained sections of the fractured bone revealed healing bone fracture with fibrovascular response, mild areas of hemorrhage, and esteoblastic activity. The ME alleged that the skull fracture in Averial's case was caused by trauma to the head.

Below are list of clinical observations and descriptions of medical studies that indicate the skull fracture occurred in the hospital. It was caused by increased intracranial pressure resulting from bleeding and brain edema.

1) Dr. Nandkishore Reghuram examined Averial at the emergency room on August 6 and did not see any evidence of injury caused by trauma in the head region. No evidence of any surface bruising, petechia, ecchymosis or purpura was observed over the skin in the head region. Moreover, he did not appreciate any crepitus on palpation of the cranial vault and the skull, and he did not appreciate any depressed regions in the skull bone.

2) There was no evidence of skull fracture observed on Averial's CT scan of the head taken on August 6 at 0350, or about 90 minutes following her admission to the hospital.

3) There was no evidence of skull fracture noted on Averial's CT scan of the head taken on August 6 at 1611, or about 14 hours following her admission to the hospital. However, this scan showed Averial's subdural bleeding and brain edema became worse by comparison to the CT scan taken August 6 at 0350 (Table 11).

4) There was no evidence of skull fracture found on Averial's CT scan of the head taken on August 8 at 0653, or about 52 hours following her admission to the hospital. However, this scan showed that the diffuse cerebral edema became worse by comparison to the prior exam on August 6.

5) The first evidence of skull fracture was noted on Averial's X-ray exam of the head performed on August 10, which was 4 days following her admission to the hospital. Averial's head circumference increased by 1.25 cm, from 37 cm on August 6 to 38.25 cm on August 9, due to bleeding and brain edema.

The clinical observations described above indicate that the skull fracture in Averial's case occurred after the CT scan exam of August 8 because many studies show that CT scan has a high diagnostic value in detecting skull fracture. Paperno *et al.* examined 27 cadavers with cranial computed tomography (CT) prior to autopsy to assess the diagnostic value of postmortem CT in comparison to autopsy. They found that the detection of skull fractures was equal for both methods (n=3) [36].

Moreover, Li *et al.* evaluated a 16-year-old male who sustained closed head injury and skull fracture following a motor vehicle collision. The initial head CT scan was able to detect the bilateral temporal bone fractures [37]. Also, Oshiro *et al.* evaluated a 5-year-old boy who was struck by a pickup truck, and admitted with Glasgow Coma Scale score of 14. Initial computed tomography (CT) showed no evidence of intracerebral lesions except for a skull fracture [38].

Furthermore, Andronikou *et al.* assessed the usefulness of skull radiographs in detecting skull fracture and other abnormalities in children with minor head injury (MHI). Three-hundred and eighty-one children were included with a mean age of 6 years. Retrospective review of CT scans and skull X-rays (SXR) showed 49% of all children had fractures either on CT or SXR [39].

12. The likely causes of rib fractures observed in Averial's case

The ME performed an autopsy on Averial's body on August 18 and found four healed rib fractures on the right side (3^{rd}, 5^{th}, 6^{th}, 7^{th}) and two healed rib fractures on the left side (4^{th} and 5^{th}) as described in Table 21. He alleged that these rib fractures were caused by trauma resulting from child abuse. My review of the medical evidence in Averial's case indicates that these fractures occurred at different intervals during Averial's stay in the hospital. Averial suffered from acidosis and protein deficiency that increased her risk for rib fractures. Below are the clinical observations and medical data that support my conclusions.

12.1 Clinical observations that indicate Averial's rib fractures occurred in the hospital

1) Dr. Reghuram examined Averial in the emergency room following her admission on August 6 and he did not see evidence of any surface bruising, petechia, ecchymosis or purpura over the skin of her body.

2) No evidence of rib fracture was observed on Averial's 3 chest X-rays taken on August 6 at 0251 and August 7^{th} at 0538 and 0653 (Table 21).

3) Evidence of acute rib fractures without evidence of healing was noted on Averial's chest X-ray performed on August 10 at 0920. These fractures were associated with extra-pleural hematoma, which was caused by the fractures (Table 21). These observations indicate that the fractures occurred within a few hours prior to taking this X-ray.

4) The healed fractures of the right costovertebral junctions of 3^{rd} and 4^{th} ribs noted on the chest X-ray of August 10 were not observed on three chest X-rays taken on August 6 and 7. These observations indicate that these fractured ribs occurred on August 7 after 0653.

5) The ME found three additional healed rib fractures (right 5^{th} and left 4^{th} and 5^{th}) that were not seen on Averial's four chest X-rays taken on August 6, 7, and 10 (Table 21). These data indicate that these ribs were fractured between August 10 and 17.

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Table 21. Results of Averial's chest X-rays and microscopical examination of the fractured ribs

Date	Test type	Findings
8/06/04 at 0251	Chest-X-ray	• No rib fracture seen
8/07/04 at 0538	Chest-X-ray	• No rib fracture seen
8/07/04 0653	Chest-X-ray	• No rib fracture seen
8/10/04 at 0920	Skeletal survey (X-rays)	• Fractures without evidence of healing in the right lateral 6th and 7th associated with extra-pleural hematoma. • Healing fractures of the right costovertebral junctions of 3rd and 4th ribs.
8/17/04	Chest and abdomen X- rays	• Healing lateral right-sided rib fractures as well and older posterior superior rib fracture.
8/18/04	Histopatholgy	• Healing fractures of the right anterolateral ribs (5th, 6th and 7th). • Healing fracture of the posterior right 3rd rib. • Healing fractures of the left lateral ribs # 4, 5

12.2 Metabolic acidosis and its influences on bone metabolism

Averial's blood analysis at the time of admission on August 6 showed that she suffered from severe metabolic and respiratory acidosis. Her blood pH was critically low (6.882) and her PCO_2 and HCO_3 levels were 70.1 mmol/L and 12.9 mmol/L, respectively. Averial was also suffering from hyperglycemia with blood glucose level of 347 mg/dL. Her urine was also positive for glucose (Table 9). Published medical studies show that acidosis and hyperglycemia have negative influences on bone metabolism and increase the risk for bone fracture.

For example, Topaloglu *et al.* 2005 evaluated 16 children with diabetic ketoacidosis due to new onset type 1 diabetes and 25 children with acute metabolic acidosis due to dehydration complicating acute gastroenteritis before and after the correction of acidosis.

They found that plasma ionized calcium levels were increased in both groups, significantly more so in diabetic ketoacidosis. While osteoblastic markers, osteocalcin and alkaline phosphatase were depressed to a comparable degree in both groups, urinary calcium/creatinine ratio and hydroxyproline excretion were significantly greater in diabetic ketoacidosis. These data suggested that acidosis diminished bone formation and increased bone mineral dissolution and bone resorption [40].

Furthermore, Yildizdas *et al.* studied bone mineral metabolism changes in individuals who suffered from metabolic acidosis due to acute gastroenteritis. They observed hypercalcemia, hypercalciuria, and elevated urinary hydroxyproline excretion. The study subjects' serum magnesium and plasma osteocalcin, alkaline phosphatase, and IGF-1 levels were decreased. Hypercalcemia seems to be the result of increased calcium efflux from bone due to metabolic acidosis-induced catabolism of type 1 collagen and decreased osteoblastic activity. All abnormalities disappeared with the correction of acidosis [41].

12.3 Protein deficiency and its impact on bone metabolism

Averial's blood analysis at the time of admission on August 6 revealed that her serum albumin and total protein levels were below normal. Her albumin and total protein levels were 2.5 g/dL and 3.9 g/dL, respectively (Table 5). Averial lost 130 g during her 11-day stay in the hospital because she was critically ill. Her weight at the time of admission was 4.29 kg and her weight at autopsy was 4.16 kg. Her average daily weight gain prior to her hospitalization was 25.7 g (Table 22). The average daily weight gain for a healthy infant similar to Averial's age is about 28 g [11, 32].

These data clearly indicate that Averial suffered from protein deficiency during her stay in the hospital and this contributed to her rib fractures. Tanaka *et al.* stated that protein malnutrition increases fracture risk due to decreased bone mineral density and muscle weakness [42]. Rizzoli *et al.* also reported that protein deficiency contributes to the occurrence of osteoporotic fractures not only by decreasing bone mass but also by altering muscle function [43].

Table 22. Averial's growth measurements prior to and during her hospitalization

Date	Age (days)	Weight [1] (g)	Height (cm)	Head Circumference (cm)
6/21/04	birth	3107	49.5	33.0
7/01/04	10	3145	52.0	34.3
7/07/04	16	3380	-	-
7/23/04	32	3882	54.5	36.3
8/06/04	46	4290	54.0	37.0
8/17/04	57	4190	56.0	37.0

[1] Averial's average daily weight gain was 25.7 g.

13. Conclusions

Review of the clinical data and the pertinent medical literature to Averial's case revealed the following:

1) Averial suffered from acute bronchopneumonia and respiratory distress syndrome on August 6, 2004 that led to hypoxemia, severe metabolic and respiratory acidosis, hyperkalemia, loss of consciousness, respiratory failure, and cardiac arrest.

2) Averial's intracranial bleeding, pulmonary bleeding, and bleeding in other locations occurred during her stay in the hospital. These lesions were caused by the use of epinephrine and sodium carbonate, and hypoxia.

3) Averial's brain edema was caused by hypoxia, the use of sodium carbonate, and bleeding.

4) Averial's brain necrosis occurred during her stay in the hospital and it was caused by hypoxia, bleeding, and infarction.

5) Averial's skull fracture occurred in the hospital due to the increase in the intracranial pressure caused by bleeding and brain edema.

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6) Averial's subretinal bleeding in both eyes occurred during her stay in the hospital and it was caused by hypoxia, anemia, thrombocytosis, and increased intracranial pressure.

7) Averial's rib fractures occurred in the hospital due to acidosis, protein deficiency, illness, and handling.

8) The ME knew that Averial suffered from bronchopneumonia and respiratory distress syndrome but he did not consider these serious and fatal illnesses in her case.

9) The ME did not take into consideration the overwhelming clinical data described in this report that show Averial's bleeding and skull and rib fractures occurred in the hospital and were caused by infection, acidosis, medications, and hypoxia.

10) There is no evidence that shows Averial's injuries and death were caused by trauma and child abuse. The allegations against her father are false.

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