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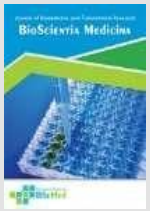

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Fatal Lung-Kidney Crosstalk in Bronchopulmonary Dysplasia: A Case of Refractory Weaning Unmasking Confirmed Williams Syndrome and Severe Obstructive Nephrolithiasis

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A B S T R A C T

Background: Bronchopulmonary dysplasia (BPD) is the most common, serious morbidity of prematurity, frequently complicated by a protracted and difficult weaning process from respiratory support. Refractory weaning failure, defined as a lack of response to conventional BPD therapies, should trigger a broad investigation for non-pulmonary, systemic confounders. **Case presentation:** We present the case of a 1,480-gram, 35+4 weeks' gestation female infant with severe hyaline membrane disease who subsequently developed moderate-to-severe BPD. The infant exhibited refractory respiratory failure, failing multiple extubation attempts, and showing no clinical improvement despite standard BPD management, including a 15-day course of furosemide. On day 58, investigation for worsening cholestasis incidentally revealed a 1.3 cm obstructive right renal calculus with severe hydronephrosis and acute pyelonephritis. This finding, coupled with evolving "elfin" facies, prompted a systemic workup. Key confirmatory data included severe hypercalcemia (13.4 mg/dL) and an echocardiogram revealing supravalvular aortic stenosis (SVAS). These findings, along with a characteristic phenotype, established a clinical diagnosis of Williams Syndrome. The infant rapidly developed urosepsis and anuric acute kidney injury (AKI), culminating in irreversible respiratory failure. **Conclusion:** This case provides a definitive clinico-pathological correlation for a rare and fatal triad. The severe nephrolithiasis is explained by a "two-hit" mechanism: baseline idiopathic hypercalcemia from Williams Syndrome, massively amplified by iatrogenic hypercalciuria from furosemide therapy. The patient's demise was a direct consequence of lung-kidney crosstalk, wherein the obstructive urosepsis and AKI induced a fatal inflammatory and hydrostatic pulmonary edema that overwhelmed the infant's BPD-compromised lungs.

1. Introduction

Bronchopulmonary dysplasia (BPD), a chronic lung disease of prematurity, remains a formidable challenge in modern neonatal-perinatal medicine.[1] Despite significant advances in perinatal care, including the widespread adoption of antenatal corticosteroids, surfactant replacement therapy, and non-invasive ventilation strategies, BPD continues to be the most prevalent and serious long-term morbidity for survivors of extreme prematurity. Its incidence is inversely proportional to gestational age, affecting the majority of infants born before 28 weeks' gestation.[2] The pathophysiology of this "new" BPD, a paradigm distinct from the "old" BPD driven by high-pressure barotrauma and oxygen toxicity, is now understood as a complex disorder of failed lung development. It is characterized by a profound arrest of alveolar simplification, leading to a lung with fewer, larger alveoli, and a dysregulated, underdeveloped pulmonary vascular bed.[3] This structural immaturity

results in a decreased surface area for gas exchange, increased airway resistance, and a high propensity for developing pulmonary hypertension (PHTN), which significantly increases mortality.

Clinically, BPD manifests as a persistent oxygen dependency beyond 36 weeks' postmenstrual age (PMA), but this simple definition belies the clinical reality of managing a chronic, multi-system inflammatory disease. The primary clinical battleground in BPD is the arduous, protracted, and often frustrating process of weaning from mechanical ventilation and supplemental oxygen.[4] Failure to wean is traditionally and appropriately attributed to a constellation of pulmonary-limited factors. These include high airway resistance from inflammation and remodeling, poor lung compliance from interstitial fluid and atelectasis, ventilation-perfusion (V/Q) mismatch, structural anomalies like tracheobronchomalacia, recurrent respiratory infections, and the insidious development of PHTN.[5] Consequently, conventional management strategies are aimed at optimizing this compromised pulmonary system. This "BPD cocktail" typically involves fluid restriction, nutritional optimization, aggressive use of diuretics (predominantly loop diuretics like furosemide), administration of systemic or inhaled corticosteroids, and bronchodilator therapy.[6]

However, a subset of infants with BPD exhibits a refractory respiratory failure, failing to progress or even deteriorating despite the meticulous optimization of these standard pulmonary therapies. In such cases, the diagnostic lens must widen to consider that the primary driver of respiratory dependency may lie entirely outside the pulmonary system. Well-established extrapulmonary confounders include hemodynamically significant patent ductus arteriosus (PDA) causing pulmonary overcirculation, and severe gastroesophageal reflux disease (GERD) with microaspiration. Less commonly recognized, yet potentially catastrophic, are systemic genetic disorders that create metabolic predispositions and acute end-organ damage, particularly to the neonatal kidney.

The neonatal kidney, especially in the preterm infant, is an organ of exquisite vulnerability. It is characterized by an immature glomerular filtration rate (GFR) and impaired tubular reabsorptive and concentrating capacities.[7] This intrinsic fragility makes it highly susceptible to insults from hemodynamic instability, hypoxia, and the numerous nephrotoxic medications that are mainstays of neonatal intensive care, including aminoglycosides and, most notably, loop diuretics. Furosemide, while essential for managing the pulmonary edema component of BPD, is a powerful iatrogenic catalyst for renal complications. By inhibiting the Na-K-2Cl cotransporter in the thick ascending loop of Henle, furosemide not only induces diuresis but also disrupts the electrochemical gradient responsible for paracellular calcium reabsorption. This effect leads directly to significant, dose-dependent hypercalciuria. In the immature kidney, this massive calcium load, coupled with a low urine flow state, can rapidly lead to urinary supersaturation, crystallization, and the formation of nephrocalcinosis (parenchymal deposits) or frank nephrolithiasis (stones in the collecting system).

While iatrogenic factors alone can explain nephrolithiasis, the development of exceptionally large or rapidly-forming calculi should raise suspicion for an underlying metabolic or genetic driver. Williams Syndrome (WS), also known as Williams-Beuren Syndrome, is a multisystem genetic disorder caused by a microdeletion on the long arm of chromosome 7 (7q11.23). This deletion removes approximately 25-28 genes, including the ELN gene, which encodes elastin. The loss of elastin explains the classic cardiovascular manifestations, such as supravalvular aortic stenosis (SVAS) and peripheral pulmonary artery stenosis (PPS), as well as the characteristic "elfin" facies. Critically, a hallmark of WS in infancy is idiopathic infantile hypercalcemia, which can be severe and persistent. The exact mechanism remains debated but is thought to involve dysregulated vitamin D metabolism or hypersensitivity.[8] This genetically-driven hypercalcemia creates a baseline state of

profound, chronic hypercalciuria, establishing a "ticking time bomb" within the renal system.[9]

This case report details a scenario wherein this precise "perfect storm" occurred. We describe the confluence of an iatrogenic catalyst (furosemide) superimposed upon a potent, underlying genetic predisposition (WS-driven hypercalcemia), leading to the formation of a massive, obstructive renal calculus. When acute renal pathology—specifically, obstructive uropathy and secondary acute pyelonephritis—develops, it initiates a catastrophic cascade of systemic inflammation and fluid dysregulation. This process, termed "lung-kidney crosstalk," involves the bidirectional injury of these two vital organs. Acute kidney injury (AKI) is not a silent, kidney-limited event; it is a potent source of systemic inflammation, cytokine release, and volume overload that can directly induce or exacerbate pulmonary edema and inflammation, thereby perpetuating ventilator dependency.[10]

This case report aims to: (1) provide a detailed clinico-pathological narrative of a fatal case of refractory BPD where the clinical course was dictated by this precise "two-hit" (WS + furosemide) mechanism; (2) offer a deep pathophysiological exploration of the "lung-kidney crosstalk" that was the ultimate mechanism of death; and (3) highlight the critical importance of expanding the differential diagnosis to include systemic, non-pulmonary causes when BPD weaning fails. The novelty of this report lies in its definitive clinico-pathological correlation of this rare triad (BPD, confirmed WS, severe nephrolithiasis) and its detailed mechanistic analysis of the fatal organ-crosstalk, made possible by a critical, multidisciplinary diagnostic re-evaluation.

2. Case Presentation

Initial presentation and acute phase (Days 1-10)

A female infant weighing 1,480 grams was born at 35+4 weeks' gestation to a 34-year-old G4P1A2 mother. The pregnancy was complicated by a lack of antenatal care, and the infant was delivered via emergency cesarean section, indicated for transverse lie and premature rupture of membranes. Antenatal steroids had not been administered. At birth, the infant was limp and cyanotic, with Apgar scores of 6 at one minute and 8 at five minutes.

In the delivery room, the infant presented with immediate, severe respiratory distress, characterized by tachypnea (82 breaths/minute), deep subcostal and intercostal retractions, prominent nasal flaring, and audible grunting. Initial oxygen saturation was 70% on room air. Her temperature was 35.0°C. The Downes score was 8, indicating impending respiratory failure. The Ballard score was 25, consistent with the 35–36 week gestational age. Initial diagnoses included very low birth weight (VLBW) preterm neonate, severe respiratory distress syndrome (RDS) secondary to hyaline membrane disease (HMD), and neonatal hypothermia.

The patient was immediately intubated with a 3.0 mm endotracheal tube, stabilized, and transferred to the Neonatal Intensive Care Unit (NICU). She was placed on synchronized intermittent mandatory ventilation with pressure control (SIMV-PC) with initial settings of: PEEP 6 cmH_2O, PIP 18 cmH_2O, respiratory rate 40 breaths/min, and FiO_2 80%. Umbilical venous and arterial catheters (UVC, UAC) were placed. The initial arterial blood gas (ABG) from the UAC showed a mixed respiratory and metabolic acidosis: pH 7.22, pCO_2 68 mmHg, pO_2 55 mmHg, and HCO_3 20 mEq/L. The initial chest X-ray (CXR) was classic for severe HMD, revealing diffuse bilateral reticulogranular opacities ("ground-glass" appearance) with prominent air bronchograms.

Initial laboratory findings were significant for severe thrombocytopenia (platelet count 8 $\times 10^3/\mu L$), with a normal leukocyte count (13.63 $\times 10^3/\mu L$) and hemoglobin (13 g/dL). A full sepsis workup was initiated, and the patient was started on intravenous ampicillin (100 mg/kg/q12h) and gentamicin (4 mg/kg/q36h). She received a platelet transfusion (10 mL/kg) and packed red cells (PRC, 15 mL/kg). A single dose of porcine surfactant (Curosurf, 100 mg/kg) was administered endotracheally, resulting in a rapid and significant improvement in oxygenation; FiO_2 was

weaned to 40% within two hours. Total parenteral nutrition (TPN) was initiated via the UVC.

Despite the initial improvement post-surfactant, her clinical course was complicated by persistent septic physiology. The platelet count remained low (17 $\times 10^3/\mu L$ on day 3), requiring two further platelet transfusions. Blood cultures ultimately remained negative, but C-reactive protein (CRP) was elevated at 18 mg/L (normal < 5 mg/L). Given the severe thrombocytopenia and persistent inflammatory state, antibiotics were escalated on day 3 to meropenem (40 mg/kg/q12h) and vancomycin (15 mg/kg/q12h) for suspected culture-negative neonatal sepsis.

The refractory weaning struggle (days 11-35)

The infant's respiratory status slowly stabilized, and she was successfully extubated to bubble CPAP on day 12 (PEEP 6 cmH_2O, FiO_2 35%). However, this success was short-lived. She exhibited persistent desaturation episodes (SpO_2 < 85%) and recurrent central apnea (requiring > 3 stimulations per hour), which did not respond to caffeine therapy. This culminated in a significant apneic episode with bradycardia on day 14, necessitating re-intubation.

A second extubation attempt was made on day 20 to CPAP. This attempt also failed, with the infant developing identical issues of persistent, severe apnea and progressive desaturations by day 22, again requiring re-intubation. The infant was now clearly developing a persistent oxygen dependency and an inability to maintain her own respiratory drive, consistent with a developing chronic lung disease. From this point, she remained on invasive ventilation. Weaning attempts were repeatedly complicated by high oxygen requirements (FiO_2 fluctuating between 35-50%) and persistent, compensated hypercapnia (pCO_2 55-65 mmHg) despite moderate ventilator settings.

During this period, she also developed significant TPN-associated cholestatic jaundice. On day 12, labs showed total bilirubin 12.49 mg/dL and direct bilirubin 3.47 mg/dL. Liver function tests (LFTs) on day 30 were markedly elevated (SGOT 319 U/L, SGPT 157 U/L). Ursodeoxycholic acid was initiated, and attempts were made to cycle TPN, but her nutritional and fluid status were precarious.

BPD diagnosis and unresponsive therapy (Days 36-57)

On day 36 of life, at 41+1 weeks' postmenstrual age, the infant remained oxygen-dependent (FiO_2 45%) and on invasive mechanical ventilation. A diagnosis of moderate-to-severe BPD was formally established based on the National Institute of Child Health and Human Development (NICHD) 2001 criteria.

A CXR on day 37 showed persistent bilateral coarse infiltrates, areas of hyperinflation alternating with atelectasis, and mild cardiomegaly. This picture was consistent with BPD and a significant component of fluid overload. Echocardiography was requested to evaluate for PDA and pulmonary hypertension; however, the patient was deemed clinically unstable for transport to the echocardiography lab. A limited, bedside study on Day 38 was difficult due to the hyperinflated lungs but suggested a small, restrictive, left-to-right PDA shunt and no clear evidence of significant pulmonary hypertension at that time. Given the lack of a large shunt, the persistent respiratory failure was attributed to severe parenchymal BPD.

To manage the presumed pulmonary edema component of BPD, a 15-day course of intravenous furosemide (1 mg/kg/q12h) was initiated on day 36. Concurrently, a 10-day tapering course of low-dose dexamethasone (0.15 mg/kg/day, tapering) was administered to facilitate weaning. Nebulized salbutamol and ipratropium bromide were also trialed.

Despite this aggressive, multi-modal BPD regimen, the patient's respiratory status showed no significant improvement. Weaning attempts continued to fail. In fact, over the following two weeks, her oxygen requirements began to increase to 50-60%. She continued to have apneic episodes despite being on mechanical ventilation, and her CO_2 retention worsened, requiring higher mean airway pressures.

This refractory, unresponsive clinical course was highly atypical and signaled that the primary driver of her deterioration was being missed.

The diagnostic unmasking and confirmatory data (days 58-60)

On day 58, due to progressively worsening jaundice (Total bilirubin 24.88 mg/dL, Direct 16.28 mg/dL) and pale (though not acholic) stools, an abdominal ultrasound was ordered to rule out biliary atresia. The ultrasound provided a critical, unexpected, and catastrophic finding. The biliary tree and liver were abnormal (hepatomegaly, increased echotexture consistent with cholestasis/hepatitis), but the primary finding was in the renal system. The report detailed: (1) Right Kidney: A massive, 1.3 cm hyperechoic calculus was identified within the renal pelvis, casting a strong posterior acoustic shadow; (2) Obstruction: This stone was causing severe right-sided hydronephrosis (Grade IV) with marked dilatation of the renal pelvis and calyces, and significant thinning of the renal parenchyma; (3) Inflammation: The right renal parenchyma appeared thickened and hyperechoic, with echogenic debris within the collecting system and reduced corticomedullary differentiation. These findings were highly suggestive of obstructive uropathy complicated by acute pyelonephritis; (4) Left Kidney: Unremarkable (Figure 1).

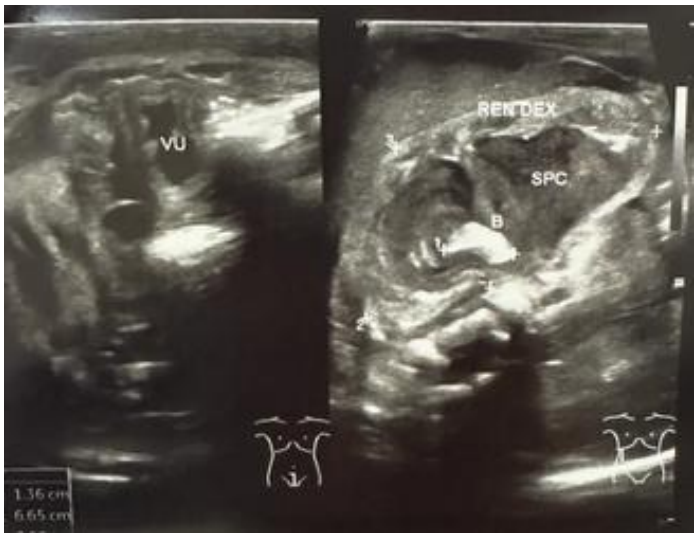

Figure 1. Abdominal Ultrasound. Left panel (VU): Transverse view of the urinary bladder (VU). Right panel (REN DEX): Sagittal view of the right kidney (REN DEX). A large, hyperechoic calculus (B, marked '1') measuring 1.36 cm is seen within the severely dilated collecting system (SPC), casting a posterior acoustic shadow. Marked hydronephrosis, parenchymal thinning, and echogenic debris are evident, consistent with obstructive pyelonephritis.

This "incidentaloma" immediately shifted the clinical paradigm from a pulmonary-limited problem to a multi-system crisis. A full metabolic and septic workup was sent. Laboratory tests returned confirming acute-on-chronic renal failure: (1) Renal Function: blood urea nitrogen (BUN) 90 mg/dL (markedly elevated), serum creatinine 0.31 mg/dl (deceptively low, reflecting poor muscle mass), serum potassium 6.8 mEq/L (severe hyperkalemia); (2) Sepsis: WBC 22.8 $\times 10^3/\mu L$ (leukocytosis), CRP 150 mg/L (profoundly elevated); (3) Urinalysis (from catheter): Specific Gravity 1.005 (isothenuria), pH 6.0, Leukocytes +++, Nitrites Positive, Protein +, Blood ++, RBCs 10-15/hpf, WBCs >50/hpf, numerous bacteria,

Calcium Oxalate crystals ++; (4) Urine; (5) Culture: Grew *Escherichia coli* >100,000 CFU/mL. Crucially, the full metabolic panel provided the etiological key; Severe hypercalcemia: serum calcium was 13.4 mg/dL (Reference: 8.6-10.2 mg/dL) with an ionized calcium of 1.7 mmol/L (Reference: 1.1-1.3 mmol/L). A spot urine calcium-to-creatinine ratio was >1.0 (highly elevated).

Coinciding with this discovery, clinicians re-examined the infant. The subtle dysmorphic features, previously overlooked or attributed to prematurity and edema, had become more distinct. The infant exhibited a classic "elfin-like" facies with a broad forehead, bilateral epicanthal folds, periorbital fullness, a short, upturned nose, a long philtrum, and micrognathia (See Figure 2). A new, or previously unappreciated, 2/6 continuous systolic murmur was auscultated at the left upper sternal border, radiating to the back.

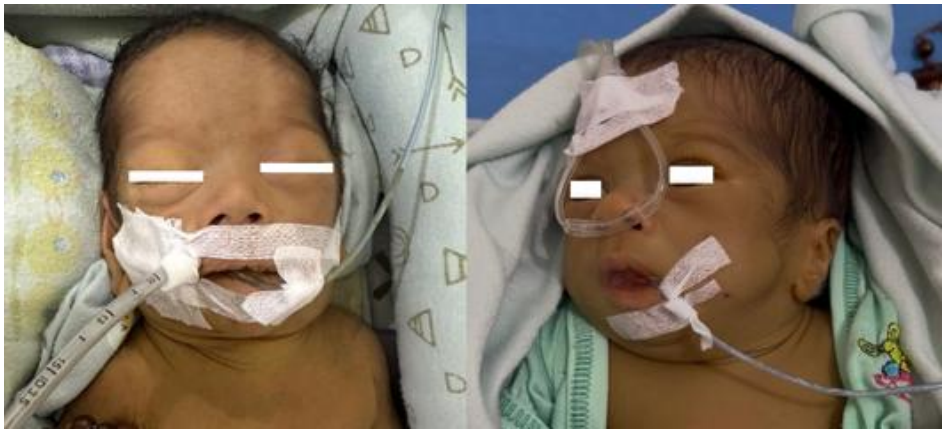

Figure 2. Facial dysmorphism. The patient displays characteristic facial features, including a broad forehead, periorbital puffiness, epicanthal folds, a short upturned nose, a long philtrum, and micrognathia. These features, collectively known as "elfin facies," are pathognomonic for Williams syndrome.

The combination of severe hypercalcemia, massive nephrolithiasis, characteristic dysmorphic features, and a new murmur made Williams Syndrome the primary unifying diagnosis. An urgent, formal echocardiogram was performed by a pediatric cardiologist on Day 60. The study confirmed the clinical suspicion, revealing supravalvular aortic stenosis (SVAS) with a peak gradient of 40 mmHg, as well as peripheral pulmonary artery stenosis (PPS), the classic cardiovascular findings of Williams Syndrome. A diagnosis was made of severe BPD complicated by acute-on-chronic respiratory failure, secondary to severe right-sided obstructive pyelonephritis and urosepsis from a large renal calculus, in the setting of Williams Syndrome.

Final decline (Days 60-62)

The patient was immediately started on broad-spectrum antibiotics (meropenem and vancomycin), and an urgent pediatric urology consult was placed. However, her condition deteriorated rapidly. She developed refractory septic shock, requiring high-dose vasopressor support (Dopamine 15 mcg/kg/min, Dobutamine 10 mcg/kg/min). Her respiratory failure worsened, requiring maximum ventilator settings (FiO_2 100%, PEEP 8, PIP 28). She developed severe, refractory metabolic acidosis (ABG: pH 7.15, pCO_2 70, HCO_3 12) and became completely anuric, consistent with irreversible multisystem organ failure. Following extensive counseling with the family regarding the grave prognosis, a decision was made to redirect care. Comfort measures were instituted. The infant passed away peacefully on day 62 of hospitalization.

Table 1. Timeline of key clinical events and confirmatory data.

A detailed timeline illustrating the patient's clinical course, key interventions, and critical diagnostic findings.

DAY OF LIFE	CLINICAL EVENT / FINDING	RESPIRATORY SUPPORT	KEY INTERVENTION / FINDING
1	Birth (1480g, 35+4 wks). Severe RDS.	Intubated (SIMV-PC, FiO_2 80%)	Surfactant, Amp/Gent, TPN, Transfusions
3	Persistent thrombocytopenia.	SIMV-PC, FiO_2 40%	Escalate to Meropenem/Vancomycin
12-14	First extubation failure. Cholestasis noted.	Extubated to BCPAP → Re-intubated	Ursodeoxycholic acid
20-22	Second extubation failure.	Extubated to BCPAP → Re-intubated	-
36	BPD Diagnosis.	SIMV-PC, FiO_2 45%	**Furosemide (15 days)**, Dexamethasone (10 days)
38	Refractory Weaning.	SIMV-PC, FiO_2 50%	**Bedside Echo:** No large PDA or PHTN.
58	**DIAGNOSTIC UNMASKING. Worsening jaundice.**	SIMV-PC, FiO_2 60%	**Abdominal US: 1.3cm renal stone, hydronephrosis.**
59	**AKI & Urosepsis. Dysmorphism noted.**	SIMV-PC, FiO_2 70%	**Labs: BUN 90, K+ 6.8, Serum Ca 13.4 mg/dL.** +Urine Culture.
60	**ETIOLOGY CONFIRMED. Clinical decline.**	SIMV-PC, FiO_2 100%	**Formal Echo: Confirmed SVAS & PPS.**
61	**Refractory shock. Clinical decline.**	(Maximal support)	Vasopressor support.
62	**Multisystem Organ Failure.**	**(Maximal support)**	**Comfort measures instituted. Patient deceased.**

Color Key:

Critical Event / Deterioration · Confirmatory Diagnosis · Final Outcome · Standard Timeline (Alternating)

Table 2. Selected laboratory data.

Key laboratory values from admission to the final critical days, highlighting the development of multisystem failure.

PARAMETER	DAY 1	DAY 30	DAY 59 (POST-US)	REFERENCE RANGE
Hematology				
WBC (×10³/μL)	13.63	10.5	**22.8 (Leukocytosis)**	5.0 - 19.5
Hemoglobin (g/dL)	13.0	**9.8**	**8.5 (Anemia)**	14.0 - 22.0
Platelets (×10³/μL)	**8 (Severe)**	120	**95 (Thrombocytopenia)**	150 - 450
CRP (mg/L)	**8**	**12**	**150 (Very High)**	< 5
Chemistry				
Sodium (mmol/L)	138	135	133	133 - 146
Potassium (mmol/L)	5.0	4.5	**6.8 (Severe Hyperkalemia)**	3.7 - 5.9
BUN (mg/dL)	15	**25**	**90 (Uremia)**	4 - 18
Creatinine (mg/dL)	0.8	0.4	0.31*	0.3 - 1.0
Serum Calcium (mg/dL)	9.2	9.5	**13.4 (Severe Hypercalcemia)**	8.6 - 10.2
Ionized Ca (mmol/L)	1.15	1.18	**1.7 (Severe Hypercalcemia)**	1.1 - 1.3
Liver Function				
Total Bilirubin (mg/dL)	1.5	**18.2**	**24.88 (High)**	< 5.0
Direct Bilirubin (mg/dL)	0.2	**10.1**	**16.28 (High)**	< 0.3
SGOT (AST) (U/L)	45	**319 (High)**	**215 (High)**	10 - 55
SGPT (ALT) (U/L)	30	**157 (High)**	**167 (High)**	7 - 55

***Note on Creatinine:** A low serum creatinine in a VLBW infant with high BUN is deceptive. It reflects poor muscle mass and should not be interpreted as normal renal function; the high BUN, hyperkalemia, and anuria confirm severe AKI.

3. Discussion

This complex and tragic case provides a powerful, high-fidelity illustration of diagnostic overshadowing, where all clinical signs of deterioration in a patient with BPD were erroneously attributed to pulmonary pathology. The refractory nature of the respiratory failure was, in fact, a sentinel sign of a catastrophic, systemic "second hit" originating from the renal system.[11] The subsequent, multidisciplinary diagnostic pivot unmasked a definitive, lethal triad of (1) underlying Williams syndrome, (2) iatrogenically-accelerated severe nephrolithiasis, and (3) a fatal lung-kidney crosstalk mechanism. This discussion will deconstruct the pathophysiology of this case (Figure 3).

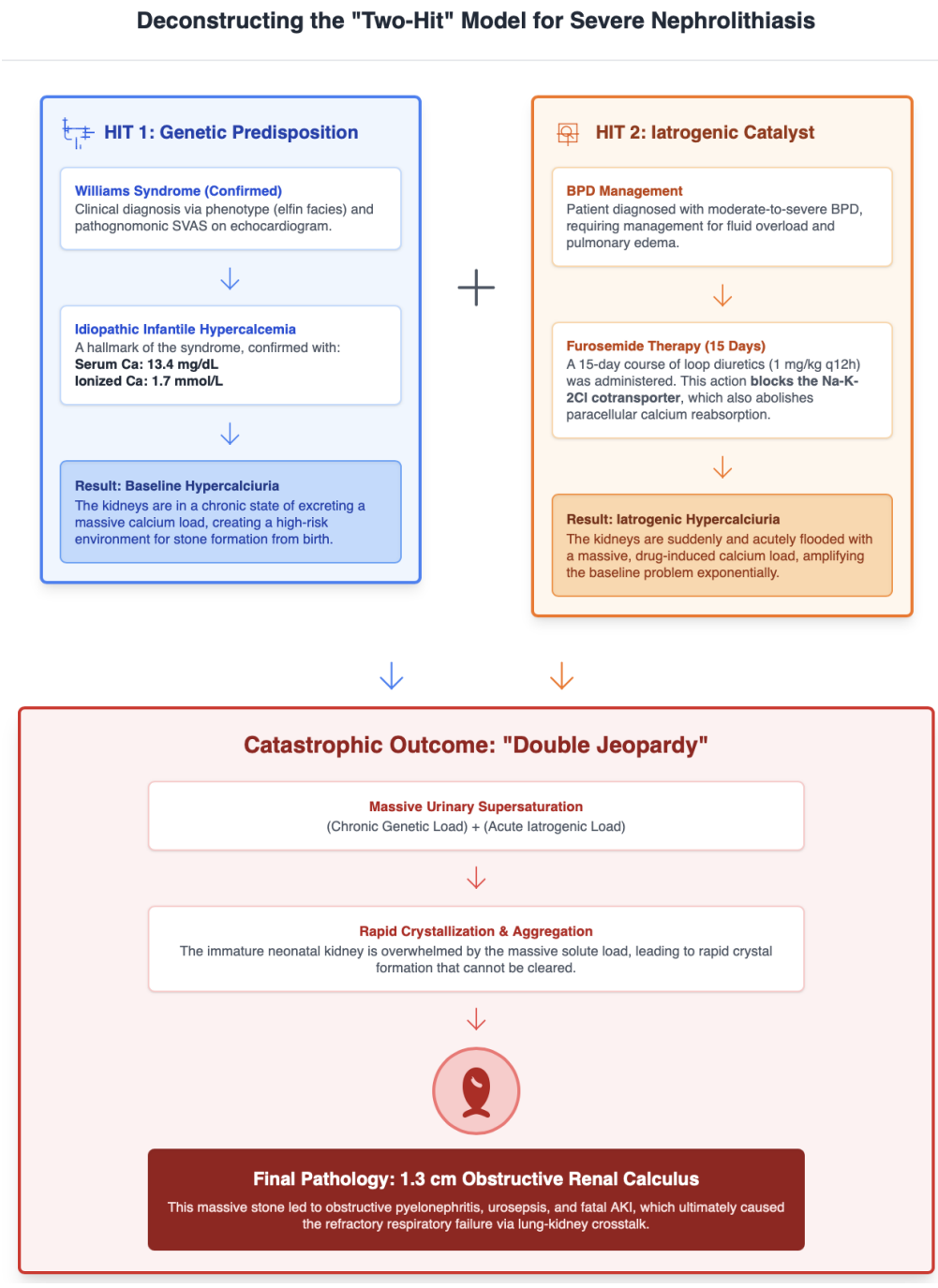

Figure 3. Deconstructing the "Two-Hit" model for severe nephrolithiasis.

The discovery of a 1.3 cm renal calculus—a massive stone for a neonate—is the central pathological finding that bridges the genetic, iatrogenic, and septic components of this case. Such a severe stone, formed in under 60 days, cannot be explained by a single factor; it is the product of a "perfect storm." Our findings provide definitive evidence for a "two-hit" mechanism: (1) Hit 1: The Genetic Predisposition (Confirmed Williams Syndrome); The clinical diagnosis of Williams Syndrome, based on the triad of severe hypercalcemia, pathognomonic SVAS, and characteristic facies, is the root cause of the entire pathology.[12] The underlying 7q11.23 microdeletion, which defines the syndrome, removes the ELN gene, explaining the cardiovascular findings (SVAS and PPS). The critical metabolic feature is idiopathic infantile hypercalcemia. Our patient's serum calcium of 13.4 mg/dL on Day 59 confirms she was in a state of severe, active hypercalcemia.[13] While the exact mechanism of hypercalcemia in WS is still debated, it is believed to involve a complex dysregulation of vitamin D metabolism and calcium sensing. This genetically-driven hypercalcemia leads to a state of obligatory, profound hypercalciuria. In effect, the patient's kidneys were, from birth, being forced to excrete a massive, chronic calcium load, creating a "baseline" state of urinary supersaturation and a high-risk environment for crystallization; (2) Hit 2: The iatrogenic catalyst (furosemide therapy): Into this high-risk environment, we introduced a powerful iatrogenic catalyst. The patient received a 15-day course of intravenous furosemide (1 mg/kg q12h) to manage the pulmonary edema of BPD. Furosemide, a loop diuretic, functions by inhibiting the Na-K-2Cl cotransporter in the thick ascending loop of Henle. While this action is highly effective for diuresis, it has a critical, off-target effect: it abolishes the transepithelial electrical potential that drives the paracellular reabsorption of divalent cations, including calcium and magnesium. The result is a massive, dose-dependent increase in urinary calcium excretion (hypercalciuria). This patient was therefore in a state of "double jeopardy": she possessed a baseline, genetically-driven hypercalciuria (from WS) which was then massively amplified by an acute, iatrogenic, drug-induced hypercalciuria (from furosemide). This "two-hit" model perfectly explains the rapid development of such a severe, obstructive calculus. The genetic hit provided the supersaturated solution, and the iatrogenic hit provided the acute, overwhelming solute load that precipitated catastrophic crystallization.[14]

The final and most critical piece of the puzzle is understanding how a kidney stone led to a respiratory death. The stone itself was not the direct driver; it was the consequences of the stone—obstruction, infection, and acute kidney injury—that initiated a fatal cascade of multi-system organ failure via the mechanism of lung-kidney crosstalk; (1) Step 1 (obstruction, stasis, and urosepsis); The 1.3 cm stone created a high-grade, physical obstruction of the right renal pelvis, leading to urinary stasis (Grade IV hydronephrosis). Stagnant urine in an immunocompromised preterm infant is an ideal culture medium. As confirmed by the urinalysis and culture, the patient developed acute obstructive pyelonephritis and *E. coli* urosepsis. This infection was the "second hit" on the kidney, transforming a chronic structural problem (the stone) into an acute, life-threatening inflammatory and septic crisis; Step 2 (the septic-inflammatory lung injury (non-cardiogenic edema)); This urosepsis was the primary engine of the patient's rapid decline. Sepsis is a potent cause of respiratory failure, initiating a Type 1 lung-kidney crosstalk.[15] The systemic release of bacterial endotoxins (lipopolysaccharide from *E. coli*) and a flood of pro-inflammatory cytokines (including TNF-α, IL-1β, and IL-6) from the infected kidney caused a massive, systemic increase in capillary permeability. This systemic inflammation directly targeted the pulmonary capillary endothelium, "a remote organ," causing a profound increase in permeability. This led to a non-cardiogenic, inflammatory, protein-rich pulmonary edema. This inflammatory exudate flooded the alveoli, inactivated surfactant, and caused severe V/Q mismatch.[16] The patient's escalating oxygen requirement from 50% to 100% was a direct reflection

of this septic, inflammatory lung injury, which was being "stacked" on top of her baseline chronic BPD; (3) Step 3 (The AKI-driven volume overload (hydrostatic edema)); Simultaneously, the combination of obstruction and infection led to severe, anuric AKI (BUN 90, K+ 6.8, anuria). This initiated a Type 2 lung-kidney crosstalk. The AKI directly thwarted the primary goal of BPD management: fluid restriction. The kidneys, now non-functional, could no longer excrete fluid, regulate electrolytes, or manage the severe metabolic acidosis. The patient became anuric and rapidly volume overloaded, leading to cardiogenic/hydrostatic pulmonary edema that *compounded* the non-cardiogenic, inflammatory edema from sepsis. The lungs were being "drowned" from two separate mechanisms. This explains why the patient was "unresponsive" to furosemide; the diuretic was being administered to a kidney that was obstructed, infected, and non-functional; (4) Step 4 (the irreversible vicious cycle); This created a fatal, self-amplifying loop: (i) Baseline BPD limited pulmonary reserve, (ii) The WS + furosemide "two-hit" caused the renal stone, (iii) The stone caused obstruction, leading to pyelonephritis (sepsis) and AKI, (iv) sepsis caused inflammatory lung injury (permeability edema), (v) AKI caused volume overload (hydrostatic edema), (vi) both forms of edema caused severe respiratory failure, requiring higher ventilator pressures, (vii) these high pressures (barotrauma) and hypoxia, in turn, can reduce renal perfusion, further worsening the AKI. The patient's respiratory system did not fail in isolation; it was destroyed by the systemic consequences of an infected, obstructed, and failing renal system.[17,18]

This case is a profound lesson in the dangers of "diagnostic overshadowing," a common cognitive bias in intensive care where all new symptoms in a patient with a chronic diagnosis are attributed to that known diagnosis. For 57 days, every apnea, desaturation, and new oxygen requirement was, understandably, attributed to "the BPD." The critical "red flag" that was present, but challenging to interpret, was the complete lack of response to standard, aggressive BPD therapy. The failure of dexamethasone and furosemide to produce any clinical improvement should have been the signal that the team was fighting the wrong "fire."

This case also highlights the perilous, double-edged sword of our most common therapies. The 15-day course of furosemide was a logical and standard intervention for BPD-associated pulmonary edema. However, in this *specific* patient, it was the final, fatal catalyst. This underscores the need for a low threshold to investigate for complications. A baseline renal ultrasound to screen for nephrocalcinosis should be considered in any BPD patient requiring prolonged (>14 days) or high-dose loop diuretic therapy.

Finally, the multi-system organ failure was comprehensive. The severe cholestatic jaundice (DBili 16.28) was likely multifactorial, arising from a combination of: (1) baseline TPN-associated cholestasis, (2) septic cholestasis from the *E. coli* endotoxemia, and (3) hepatic congestion from the AKI-driven volume overload. This, along with the AKI and respiratory failure, completed the picture of irreversible MSOF. The initial echocardiogram, which failed to show significant PHTN, was a "false-negative" that further anchored the team to a "pulmonary-parenchymal" diagnosis, when in fact the true driver was systemic and metabolic.[19,20]

4. Conclusion

This case of refractory bronchopulmonary dysplasia provides a compelling and definitive example of how a pulmonary presentation can be entirely driven by catastrophic, non-pulmonary pathology. We have described a rare triad of BPD, confirmed Williams Syndrome, and severe obstructive nephrolithiasis, where the clinical course was dictated by a "two-hit" mechanism. A genetic predisposition (WS-driven hypercalcemia) was massively amplified by an iatrogenic catalyst (furosemide), creating a severe renal calculus. The subsequent obstructive pyelonephritis and acute kidney injury initiated a fatal cascade of systemic inflammation and volume overload, perpetuating respiratory failure via the well-described mechanism of lung-kidney crosstalk.

The primary learning point for the neonatologist and intensive care clinician is that refractory weaning failure in BPD, especially when unresponsive to conventional therapies, must trigger a high index of suspicion for systemic confounders. A diagnostic "pause" and a willingness to look "beyond the pulmonary pathology" is essential. Early, multidisciplinary evaluation, including metabolic screening (serum calcium) and renal imaging, is critical to unmasking occult pathologies that may be silently antagonizing pulmonary recovery.

5. References

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