# Natural History of Perinatal and Infantile Hypophosphatasia: A Retrospective Study

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**Objective** To report clinical characteristics and medical history data obtained retrospectively for a large cohort of pediatric patients with perinatal and infantile hypophosphatasia.

**Study design** Medical records from academic medical centers known to diagnose and/or treat hypophosphatasia were reviewed. Patients born between 1970 and 2011 with hypophosphatasia and any of the following signs/symptoms at age <6 months were eligible: vitamin B6–dependent seizures, respiratory compromise, or rachitic chest deformity (NCT01419028). Patient demographics and characteristics, respiratory support requirements, invasive ventilator–free survival, and further complications of hypophosphatasia were followed for up to the first 5 years of life.

**Results** Forty-eight patients represented 12 study sites in 7 countries; 13 patients were alive, and 35 were dead (including 1 stillborn). Chest deformity, respiratory distress, respiratory failure (as conditioned by the eligibility criteria), failure to thrive, and elevated calcium levels were present in >70% of patients between birth and age 5 years. Vitamin B6–dependent seizures and respiratory distress and failure were associated significantly ($P < .05$) with the risk of early death. Serum alkaline phosphatase activity in all 41 patients tested (mean [SD]: 18.1 [15.4] U/L) was below the mean lower limit of normal of the reference ranges of the various laboratories (88.2 U/L). Among the 45 patients with relevant data, 29 had received respiratory support, of whom 26 had died at the time of data collection. The likelihood of invasive ventilator–free survival for this cohort decreased to 63% at 3 months, 54% at 6 months, 31% at 12 months, and 25% at 5 years.

**Conclusions** Patients with perinatal or infantile hypophosphatasia and vitamin B6–dependent seizures, with or without significant respiratory distress or chest deformities, have high morbidity and mortality in the first 5 years of life. *(J Pediatr 2019;209:116-24)*.

**Trial registration** ClinicalTrials.gov: NCT01419028.

Hypophosphatasia is the rare inborn-error-of-metabolism characterized enzymatically by low activity of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP).[1-3] In hypophosphatasia, deficient activity of TNSALP on cell surfaces leads to extracellular accumulation of its natural substrates: inorganic pyrophosphate (PPi), a potent inhibitor of hydroxyapatite crystal growth; pyridoxal 5′-phosphate (PLP), the major circulating form of vitamin B6; and phosphoethanolamine (PEA), a degradation product of cell-surface phosphatidylinositol–glycan anchors for various ectoproteins like TNSALP.[1,2,4] Because PPi inhibits hydroxyapatite crystal propagation, sufficiently high extracellular PPi levels in hypophosphatasia can impair mineralization of the growing skeleton, causing rickets, and can lead to osteomalacia in adults.[1,2,5] TNSALP dephosphorylates PLP to pyridoxal to cross the blood–brain barrier and enter neurons. Thus, profound TNSALP deficiency in the most severely affected patients with hypophosphatasia also can compromise neurotransmitter synthesis and cause vitamin B6–dependent seizures.[1,6]

Largely owing to genetic heterogeneity, hypophosphatasia severity is broad-ranging, featuring a continuum from essentially no skeletal mineralization at birth

| | |
|---|---|
| ALP | Alkaline phosphatase |
| IVFST | Invasive ventilator–free survival time |
| PEA | Phosphoethanolamine |
| PLP | Pyridoxal 5′-phosphate |
| PPi | Inorganic pyrophosphate |
| TNSALP | Tissue-nonspecific isoenzyme of alkaline phosphatase |
| ULN | Upper limit of normal |

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to arthropathies and/or dental complications without skeletal abnormalities in adult life.[1,2] The clinical nosology of pediatric hypophosphatasia, aiming to organize this continuum, now includes (by increasing severity) odonto-hypophosphatasia, mild childhood hypophosphatasia, severe childhood hypophosphatasia, infantile hypophosphatasia, and perinatal hypophosphatasia.[1,7,8] Benign prenatal hypophosphatasia also has been described; it is characterized by skeletal manifestations detected in utero or at birth that improve spontaneously ex utero, with outcomes ranging from odonto-hypophosphatasia to infantile hypophosphatasia.[9]

Information concerning the prevalence and nature of hypophosphatasia complications and survival rates with supportive care alone is incomplete for perinatal hypophosphatasia, which manifests in utero and is apparent at birth, and infantile hypophosphatasia, which presents before 6 months of age.[1,2] Death from these 2 life-threatening forms of hypophosphatasia seems to result most often from respiratory complications caused by poor mineralization of the bones of the thorax.[1,10,11] Perinatal hypophosphatasia is considered almost always fatal within a few days after birth, and mortality in infantile hypophosphatasia has been estimated as approximately 50% during the first year of life.[1,2] However, no published comprehensive retrospective or prospective studies include a global compilation of the features of life-threatening perinatal and infantile hypophosphatasia.

Herein we describe the natural history of patients with perinatal or infantile hypophosphatasia receiving supportive care born between 1970 and 2011. They were selected for this study because they displayed the severe manifestations of hypophosphatasia (eg, respiratory compromise, seizures, chest deformity) of a cohort of patients who began a clinical study of enzyme replacement therapy in 2008 (asfotase alfa; Strensiq, Alexion Pharmaceuticals, Inc, Boston, Massachusetts).[12] A portion of the data from that study regarding overall survival and ventilatory support requirements was published in 2016,[13] and the findings after an average of 7 years of treatment were published in 2019.[14] Now we report unpublished data concerning clinical characteristics including signs, symptoms, and complications; medical history (including respiratory support, medications, and hospitalizations); and routine clinical laboratory values and *ALPL* mutations in this natural history cohort of patients with perinatal or infantile hypophosphatasia.

## Methods

This multinational, noninterventional, retrospective chart review of the natural history of perinatal and infantile hypophosphatasia (ClinicalTrials.gov: NCT01419028) was performed at academic medical centers that had diagnosed and/or managed severe pediatric hypophosphatasia. The study was conducted in accordance with guidelines set by the World Medical Association Declaration of Helsinki and the International Conference on Harmonisation Guideline for Good Clinical Practice and in compliance with national, state, and local laws of the appropriate regulatory authorities. The study protocol and subsequent amendments were approved at each institution by the institutional review board, independent ethics committee, or research ethics board. Details regarding patient informed consent are provided in **Appendix 2, Methods** (available at www.jpeds.com).

### Study Design and Patients

Physicians with access to records of patients with hypophosphatasia were identified and contacted via e-mail by the study sponsor. Examples of recruitment efforts included outreach to physicians with experience in metabolic bone diseases and genetic testing laboratories to obtain lists of physicians who had referred DNA samples that were positive for *ALPL* mutation(s). Medical records from patients (living or dead) were reviewed if the diagnosis of hypophosphatasia had included at least 1 of the following: (1) *ALPL* mutation(s); (2) serum alkaline phosphatase (ALP) activity below the normal range and either plasma PLP or urinary PEA levels above the laboratory's upper limit of normal (ULN); or (3) serum ALP activity below the normal range and report of hypophosphatasia-related radiographic abnormalities. In addition, patients were required to have signs and symptoms characteristic of hypophosphatasia before 6 months of age and at least 1 of the following hypophosphatasia characteristics associated with significant clinical compromise and poor outcomes: (1) respiratory complications that required respiratory support measures or medication(s) and/or that were associated with other pulmonary problems (eg, pneumonia, respiratory tract infection, respiratory failure); (2) vitamin B6–dependent seizures (ie, responsive to supplemental pyridoxine); or (3) rachitic chest deformity. These represent features of "severe" pediatric hypophosphatasia and therefore would likely exclude benign prenatal hypophosphatasia[9] and less severe instances of infantile hypophosphatasia. Thus, the medical records evaluated in our study represented patients with perinatal or infantile hypophosphatasia likely to show high morbidity and mortality. Exclusion criteria included any other clinically significant disease or other treatment with asfotase alfa at any time before data abstraction.

### Data Collection

Abstraction of the medical record onto case report forms by trained personnel occurred at a single time point between September 2012 and April 2013. Data from up to the patient's fifth birthday were collected. This included demographics; diagnostic history, including age at hypophosphatasia diagnosis; clinical laboratory results (serum ALP, urine PEA, and plasma PLP) obtained closest to the date of diagnosis; *ALPL* gene mutation analysis results; and clinical course including comorbidities, mention of developmental delays, hospitalizations, medications, therapies, and procedures. Additional data collected included date, cause, and age of death. Details regarding data collection are provided in **Appendix 2, Methods**.

### Outcome Measures

Information regarding the primary outcome measure of overall survival and the tertiary outcome measure of ventilatory support status was published in 2016.[13] Secondary and tertiary assessments, reported herein, include the proportion of patients requiring invasive ventilation (mechanical via intubation or tracheostomy) or noninvasive respiratory support (continuous or bilevel positive airway pressure or supplemental oxygen) stratified by mortality, and by invasive ventilator–free survival time (IVFST). IVFST is henceforth defined as time to first invasive ventilation or death. Respiratory "distress" and "failure" were defined as transient vs chronic respiratory difficulty, respectively. Additional assessments included radiographic findings reported at the time of hypophosphatasia diagnosis, medication history, hospitalizations, prevalent and clinically important signs, symptoms, and complications of hypophosphatasia (stratified by mortality) and association with death.

### Statistical Analyses

All available data were included in the statistical analyses. Because data collection was retrospective, not all patients had complete information. No imputation was performed for missing data except when only a partial birthdate was provided (ie, if the day was missing, it was set to 15, and if the month was missing, it was set to June). Data were censored, if applicable, at date of data collection for living patients and at date of last contact for patients whose status was unknown at data collection. All statistical analyses were conducted using SAS release 9.2 (SAS Institute, Inc, Cary, North Carolina). IVFST estimates were quantified using the Kaplan–Meier method. Survival and invasive respiratory support data (ie, mechanical via intubation or tracheostomy) were considered simultaneously and used to calculate the time to first invasive ventilation or death. CIs were generated using the Greenwood formula for variance, and CIs for proportions were generated using the normal approximation to the binomial distribution. All CIs were 2 sided, with a significance level set at alpha = .05. Any *P* values, if generated, were nominal. The association of the relative risk of death with select hypophosphatasia complications was also individually and separately examined post hoc without considering mutual correlation and confounding effects. Similarly, CIs for relative risks were obtained by assuming the normal approximation to the binomial distribution. Percentages of patients were calculated and are provided below only when the denominator was 48 (representing the entire enrolled group). All other data are presented as n/N. Further details regarding the statistical methods are provided in **Appendix 2, Methods**.

## Results

### Patient Demographics and Characteristics

Of the 65 patients screened, 48 were eligible and enrolled from 12 sites (6 in the US [n = 26] and 1 each in Australia [n = 2], Canada [n = 11], Germany [n = 6], Spain [n = 1], Switzerland [n = 1], and Taiwan [n = 1]). The first patient was born in 1970 and the last in 2011. Among the 48 patients, 13 (27%) were diagnosed with hypophosphatasia before 1990, 14 (29%) between 1990 and 1999, and 21 (44%) during or after 2000. Thirteen (27%) were alive (median [min, max] age: 7.7 [2, 20] years), and 35 (73%) had died (Kaplan–Meier median [95% CI] age at death: 0.7 [0.4, 1.2] years) (**Figure 1**; available at www.jpeds.com). Patients who had died comprised 100% (13/13) of those diagnosed before 1990, 71.4% (10/14) of those diagnosed between 1990 and 1999, and 57.1% (12/21) of those diagnosed in 2000 or later, suggesting some improvement in survival with better availability and/or advances in supportive care. Their demographic and disease characteristics are summarized in **Table I**. As required for study inclusion, all presented with at least 1 of the specified key characteristics of hypophosphatasia before 6 months of age (median [min, max] age: 1 [0, 179] days). Median (min, max) age of hypophosphatasia diagnosis was 0.2 (0, 3) years. Consistent with the range of severity of their hypophosphatasia, median (min, max) age of hypophosphatasia diagnosis among the 13 patients who were alive at the time of chart review was 0.4 (0, 3) years, and among the 34 patients who were dead and had this information recorded was 0.04 (0, 0.8) years. Among the total patient group, 14 (29%) were reported to have prenatal ultrasound scan manifestations of hypophosphatasia, 15 (31%) were not reported to have evidence of hypophosphatasia on prenatal ultrasound scan, and 19 (40%) had no available ultrasound scan data. In the 29 patients whose charts had sufficient information (23/35 dead and 6/13 alive), signs of hypophosphatasia reported on prenatal ultrasound scan were similar between those who would die and those who would live (12/23 vs 2/6, respectively).

One patient was stillborn, and 13 patients died within the first month of life; 9 on the first day, and 4 on days 5, 11, 27, and 31. In total, 10 of these 14 patients received respiratory support before death. Of the 14, 7 (50%) were diagnosed before 1990 (and only 1 was diagnosed before 1980), 3 (21%) were diagnosed between 1990 and 2000, and 4 (29%) were diagnosed after 2000. The infant who was stillborn could not be assessed for the key inclusion characteristics but was enrolled based on his profoundly low serum ALP activity, radiographic findings, and respiratory compromise that was attributed to pulmonary hypoplasia (cause of death). Among the 35 patients who would die, the most prevalent complication, as anticipated, was respiratory compromise (33/35).

At hypophosphatasia diagnosis, serum ALP was available for 85% (41/48) of patients (mean ± SD [min, max]: 18.1 ± 15.4 [0, 55.0] U/L). ALP reference ranges were provided for 26 of these patients; all 26 patient values were below the mean lower limit of normal of the reference ranges of the various laboratories (88.2 U/L). Among the 13 patients who were alive at the time of chart review, 12 (92%) had recorded serum ALP activity (mean ± SD [min, max]: 34.0 ± 14.5 [2.0, 55.0] U/L). Among the 35 patients who were dead at

**Table I. Patient demographics and diagnostic history**

| Characteristics | Overall | Alive | Dead |
|---|---|---|---|
| Demographics | | | |
| Gestational age at birth | n = 36 | n = 12 | n = 24 |
| Median (min, max), wk | 39 (30, 41) | 38.5 (35, 41) | 39.0 (30, 41) |
| Age at data collection for living patients | n = 13 | n = 13 | |
| Median (min, max), y | 7.7 (2, 20) | 7.7 (2, 20) | — |
| Sex, n (%) | n = 48 | n = 13 | n = 35 |
| Male | 26 (54) | 6 (46) | 20 (57) |
| Female | 22 (46) | 7 (54) | 15 (43) |
| Region of birth, n (%) | n = 48 | n = 13 | n = 35 |
| North America | 33 (69) | 5 (39) | 28 (80) |
| Europe | 8 (17) | 7 (54) | 1 (3) |
| Australia | 2 (4) | 0 | 2 (6) |
| Middle East | 1 (2) | 1 (8) | 0 |
| Asia | 1 (2) | 0 | 1 (3) |
| Unknown* | 3 (6) | 0 | 3 (9) |
| Race, n (%) | n = 48 | n = 13 | n = 35 |
| White | 40 (83) | 11 (85) | 29 (83) |
| Black or African American | 3 (6) | 0 | 3 (9) |
| Asian | 2 (4) | 1 (8) | 1 (3) |
| American Indian or Alaska Native | 1 (2) | 1 (8) | 0 |
| Unknown | 2 (4) | 0 | 2 (6) |
| Ethnicity, n (%) | n = 48 | n = 13 | n = 35 |
| Not Hispanic or Latino | 41 (85) | 12 (92) | 29 (83) |
| Hispanic or Latino | 1 (2) | 0 | 1 (3) |
| Unknown | 6 (13) | 1 (8) | 5 (14) |
| Diagnostic history | | | |
| Signs of in utero skeletal disease on ultrasound scan, n (%) | n = 48 | n = 13 | n = 35 |
| Yes | 14 (29) | 2 (15) | 12 (34) |
| No | 15 (31) | 4 (31) | 11 (31) |
| Unknown | 19 (40) | 7 (54) | 12 (34) |
| Age at onset of signs/symptoms, mo | n = 47 | n = 13 | n = 34 |
| Mean (SD) | 1.1 (1.7) | 2.3 (2.1) | 0.7 (1.2) |
| Median (min, max) | 0.03 (0, 5.9) | 2.4 (0, 5.9) | 0.03 (0, 5.2) |
| Age at hypophosphatasia diagnosis, mo | n = 47 | n = 13 | n = 34 |
| Mean (SD) | 5.2 (9.3) | 13.7 (14.3) | 1.9 (2.5) |
| Median (min, max) | 2.0 (0, 40.9) | 4.4 (0.2, 40.9) | 0.5 (0, 10.1) |
| Criteria that formed the basis for diagnosis of hypophosphatasia,† n (%) | n = 48 | n = 13 | n = 35 |
| Clinical laboratory results | | | |
| Serum ALP | 41 (85) | 11 (85) | 30 (86) |
| Plasma PLP | 6 (13) | 7 (54) | 6 (17) |
| Urinary PEA | 12 (25) | 7 (54) | 5 (14) |
| Other: serum calcium | 3 (6) | 0 | 3 (9) |
| Radiographic findings | 38 (79) | 11 (85) | 27 (77) |
| Signs and symptoms | 25 (52) | 11 (85) | 14 (40) |
| *ALPL* gene mutation | 17 (35) | 9 (69) | 8 (23) |
| Laboratory test results | | | |
| Serum ALP activity, U/L | n = 41 | n = 12 | n = 29 |
| Mean (SD) | 18.1 (15.4) | 34.0 (14.5) | 11.6 (10.3) |
| Median (min, max) | 15.0 (0, 55.0) | 34.0 (2.0, 55.0) | 10.0 (0, 42.0) |
| Plasma PLP, ng/mL | n = 6 | n = 5 | n = 1 |
| Mean (SD) | 623 (1154) | 154 (93) | 2972 (NA) |
| Median (min, max) | 150 (43, 2972) | 150 (43, 300) | 2972 (2972, 2972) |
| Serum calcium, mmol/L | n = 32 | n = 11 | n = 21 |
| Mean (SD) | 2.8 (0.4) | 2.7 (0.3) | 2.8 (0.4) |
| Median (min, max) | 2.6 (2.3, 4.0) | 2.6 (2.4, 3.5) | 2.7 (2.3, 4.0) |

*NA*, not available.
*Recorded as unknown.
†Diagnosis was based on a combination of laboratory findings, a combination of laboratory and radiographic findings, or genetic analysis (see inclusion criteria). *ALPL* gene mutation analysis was not required for diagnosis. Reference ranges for each laboratory varied.

the time of chart review, 29 (83%) had substantially lower recorded serum ALP activity (mean ± SD [min, max]: 11.6 ± 10.3 [0, 42.0] U/L), suggesting correlation with hypophosphatasia severity. Plasma PLP level was elevated above the mean ULN of the various laboratories (31.3 ng/mL) in all of the few patients with such data (n = 6), with a mean ± SD (min, max) of 623 ± 1154 (43, 2972) ng/mL. Mean ± SD (min, max) serum 25-hydroxyvitamin D (84.8 ± 13.5 [73.9, 99.8] nmol/L; n = 3) was within the normal reference ranges of the various laboratories (mean lower limit of normal: 53.2 nmol/L; mean ULN: 172.0 nmol/L). Hypercalcemia had been documented in 14 of 21 patients, and hyperphosphatemia had been reported in 10 of 21 patients with available data. Mean ± SD (min, max) serum calcium concentration (2.8 ± 0.4 [2.3, 4.0] mmol/L [11.2 mg/dL]; n = 32) was above the mean ULN

of the various laboratories (2.6 mmol/L; 10.4 mg/dL), with a mean 1.1-fold elevation. Mean ± SD (min, max) serum phosphate concentration (2.0 ± 0.4 [1.1, 3.1] mmol/L [6.19 mg/dL]; n = 29) matched the mean ULN of the various laboratories (2.0 mmol/L; 6.19 mg/dL). Mean ± SD (min, max) serum creatinine concentration (136.6 ± 325.5 [0.1, 1246.4] μmol/L [1.55 mg/dL]; n = 23) was elevated at the time of hypophosphatasia diagnosis compared with the mean ULN of the various laboratories (68.3 μmol/L; 0.77 mg/dL) because of 2 especially high values. The values were proportionately distributed as "low" (5/16), "normal" (7/16), and "high" (4/16) within the reference ranges.

*ALPL* mutation analysis results obtained using early sequencing techniques at a variety of commercial and research laboratories between March 1995 and November 2011 were reported for 21 patients; mutations were detected in 19. Most patients were compound heterozygotes (12/19), and the remainder carried homozygous mutations (5/19) or seemed to carry heterozygous mutations (2/19). For the 2 patients without an identified *ALPL* mutation, copy number variation or reverse transcriptase polymerase chain reaction had not been performed. Because these 2 patients had laboratory and radiographic findings characteristic of severe hypophosphatasia, they were included in the study.

At the time of hypophosphatasia diagnosis, radiographic findings had been reported in the medical record for 77% of patients (37/48). Multiple skeletal abnormalities were common and often included mention of osteopenia (33/37) as well as the study inclusion criterion of rachitic chest deformity (32/37) (**Table II**; available at www.jpeds.com). Radiographic absence of some or all bones was described in 7 of 30 patients. Of these 7 patients, 5 had signs and symptoms of hypophosphatasia at birth or reported within 1 day of birth.

### Respiratory Support Requirements and Invasive Ventilation-Free Survival

Forty-five (94%) of the 48 patients had documented respiratory status. Of the 45, 29 had received either "noninvasive" or "invasive" respiratory support. At the time we collected their data, 26 of the 29 patients had died (**Figure 2**). Respiratory support was necessary within the first 6 days of life for most of these patients (17/29). Invasive ventilation was necessary for 19 of the 29 patients, supplemental oxygen was necessary in 9, and continuous positive airway pressure was necessary in 1. Death occurred for 18 of the 19 who received invasive ventilation (**Figure 2**).

Among the 48 patients, the median IVFST was 7.8 months (95% CI 2.6-9.9; **Figure 3**). The Kaplan–Meier estimate of probability of being alive and not invasively ventilated during the first year of life was 63% at 3 months, 54% at 6 months, and 31% at 12 months. Only 25% of patients were alive at 5 years of age (**Figure 3**). Rates of respiratory support–free survival (data not shown) were comparable with rates of IVFST, as respiratory support was invasive in most patients. Additional information concerning

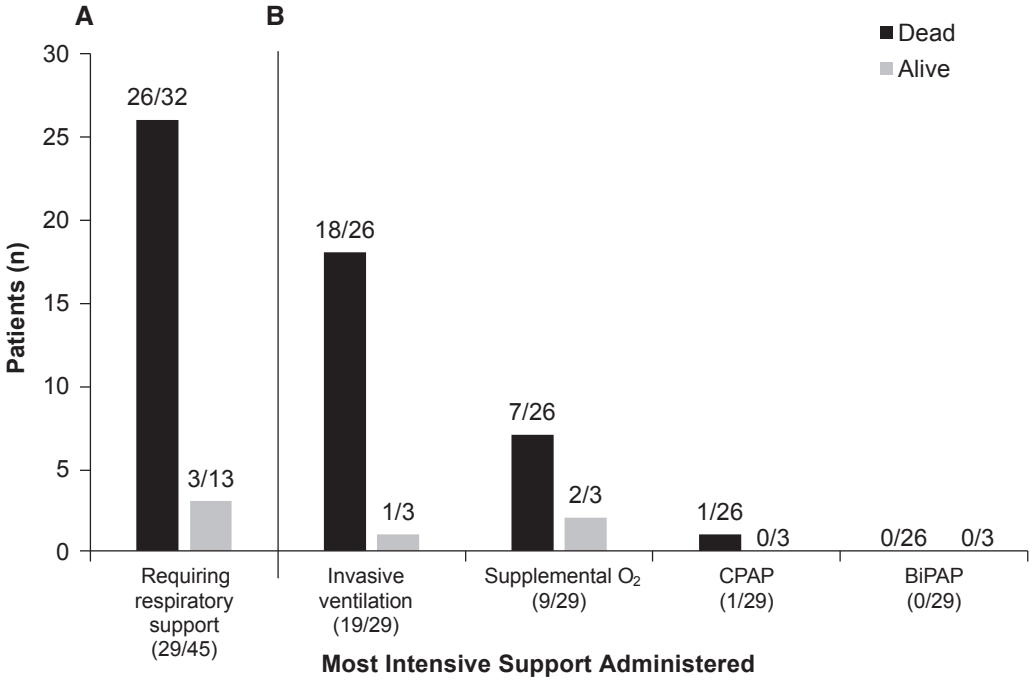


**Figure 2.** Respiratory support administration. **A,** Distribution of living and dead patients who had required respiratory support. **B,** Greatest required support stratified by type and number of patients alive vs dead at data collection. Values along the x-axis represent the total number of patients (dead and alive combined) who received the specific type of support compared with the total number of patients for whom data were available. *BiPAP*, bilevel positive airway pressure; *CPAP*, continuous positive airway pressure.

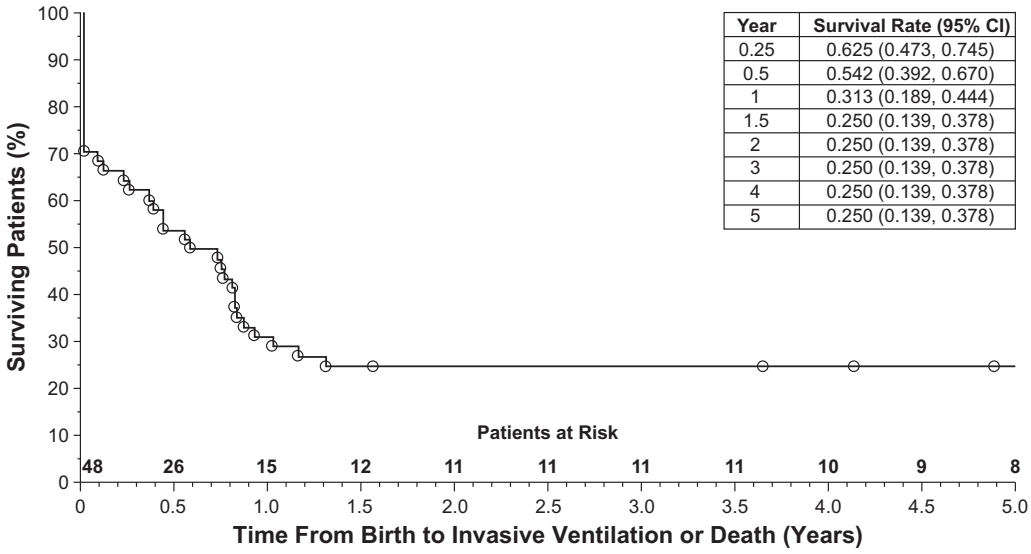


**Figure 3.** Kaplan–Meier plot of time from birth during which patients were not mechanically ventilated by intubation or tracheostomy; 36 patients had an event of invasive ventilation or death, and 12 were censored. *Inset:* cumulative probability of invasive ventilation-free survival.

individual patient ventilation status is in **Table III** (available at www.jpeds.com).

### Common Signs, Symptoms, and Complications Associated with Hypophosphatasia

**Table IV** summarizes the incidence/prevalence of the most common complications of perinatal and infantile hypophosphatasia noted in this study population, as well as their association with mortality. The eligibility criteria conditioned the high prevalence of chest deformity (39/43), respiratory distress (30/39), and respiratory failure (26/36). Respiratory distress and failure and vitamin B6–dependent seizures were associated significantly ($P < .05$) with the risk of early death independent of other confounding risk factors (**Table IV**). In addition, 24 of 27 patients with appropriate data for age reportedly had developmental delays, including gross motor skills (23/24), walking (10/24), and fine motor skills (2/24). Cognitive delays were documented for 3 of 19 of patients with available data.

### Medication Histories and Hospitalizations

Treatment histories were positive for medications or other therapies for hypophosphatasia signs and symptoms for most patients (65% [31/48]). Medications included adrenergic

**Table IV. Hypophosphatasia presentation stratified by age interval and association with death**

| | Observed incidence, % (n/N)* | | | | | Death rate, % (n/N) | |
|---|---|---|---|---|---|---|---|
| | | By age at occurrence | | | | | |
| Signs, symptoms, or complications | Overall | <6 mo (n = 48) | 6 mo–3 y (n = 27) | 3–5 y (n = 13) | Relative risk (95% CI) of death in patients with vs without the manifestation | With manifestation† | Without manifestation‡ |
| Respiratory failure | 72 (26/36) | 47 (18/38) | 42 (8/19) | 0 (0/11) | 10 (1.56-64.20)§ | 100 (26/26) | 10 (1/10) |
| Respiratory distress | 77 (30/39) | 64 (25/39) | 50 (10/20) | 18 (2/11) | 2.6 (1.02-6.62)§ | 87 (26/30) | 33 (3/9) |
| Decreased oxygen saturation | 67 (22/33) | 53 (16/30) | 53 (10/19) | 0 (0/10) | 1.8 (0.92-3.54) | 82 (18/22) | 45 (5/11) |
| Tachypnea | 63 (20/32) | 53 (17/32) | 47 (8/17) | 18 (2/11) | 1.7 (0.94-3.08) | 85 (17/20) | 50 (6/12) |
| Vitamin B6–dependent seizures | 26 (10/38)¶ | 17 (6/36) | 14 (3/21) | 0 (0/11) | 1.6 (1.18-2.06)§ | 100 (10/10) | 64 (18/28) |
| Elevated serum or urine calcium | 72 (28/39) | 68 (26/38) | 74 (14/19) | 18 (2/11) | 1.2 (0.72-1.94) | 75 (21/28) | 64 (7/11) |
| Pneumonia | 42 (15/36) | 18 (6/34) | 50 (10/20) | 18 (2/11) | 1.1 (0.72-1.69) | 73 (11/15) | 67 (14/21) |
| Nephrocalcinosis | 52 (16/31) | 36 (11/31) | 63 (10/16) | 40 (4/10) | 1.0 (0.63-1.68) | 69 (11/16) | 67 (10/15) |
| Chest deformity | 91 (39/43) | 80 (28/35) | 96 (22/23) | 83 (10/12) | 0.7 (0.54-0.84)§ | 67 (26/39) | 100 (4/4) |
| Respiratory tract infection | 64 (21/33) | 42 (13/31) | 79 (15/19) | 46 (5/11) | 0.7 (0.49-1.13) | 62 (13/21) | 83 (10/12) |
| Craniosynostosis | 61 (19/31) | 50 (15/30) | 74 (14/19) | 64 (7/11) | 0.7 (0.41-1.20) | 53 (10/19) | 75 (9/12) |
| Failure to thrive | 76 (28/37) | 67 (24/36) | 91 (19/21) | 64 (7/11) | 0.6 (0.45-0.82)§ | 61 (17/28) | 100 (9/9) |
| Early tooth loss | 44 (10/23) | 0 (0/24) | 71 (10/14) | 78 (7/9) | 0 (–, –) | 0 (0/10) | 92 (12/13) |

*Calculated as the number of patients with disease history (n) divided by the number of patients with available data (N) × 100. Patients for whom status was unknown or missing were not included.
†Number of patients who were dead (n) divided by the total number of patients (both alive and dead) with the complication (N).
‡Number of patients who were dead (n) divided by the total number of patients (both alive and dead) without the complication (N).
§Relative risk significantly different from 1 ($P < .05$).
¶Seven patients had documented vitamin B6–dependent seizures; an additional 3 patients had a history of vitamin B6–dependent seizures based upon hospitalization and medication records (age was not available for these 3 patients).

inhalants, nonsteroidal anti-inflammatory drugs, systemic corticosteroids, loop diuretics, anticonvulsants, and vitamin B6. Two patients, both alive at the time of chart review, had been our research subjects and received a bone marrow transplantation during infancy,[15,16] followed soon after by stromal cell transplantation in one.[15] Thirty-nine (81%) of the 48 patients had hospitalizations during their first 5 years of life, 22 from respiratory compromise complications and 7 from seizure-related complications. Multiple hospitalizations, some prolonged, had occurred for most living and dead patients. Approximately one-half of the patients who had died (18/35) and one-third of the living patients (4/13) had hospitalization(s) for respiratory compromise. (Additional information concerning the hospitalizations is shown in **Table V** [available at www.jpeds.com].)

## Discussion

This chart review collected natural history data from patients with perinatal or infantile hypophosphatasia (ie, hypophosphatasia-related findings apparent at birth or manifesting in the first 6 months of life, respectively). Data were collected up to 5 years of life. In earlier reports, we described the natural history of hypophosphatasia selectively in 15 Manitoban patients with perinatal hypophosphatasia[10] and documented the natural history of hypophosphatasia spanning an average of 6.5 years in children with odonto-, mild childhood, severe childhood, and infantile hypophosphatasia.[17] Our current study is a multinational systematic assessment of the natural history of specifically perinatal and infantile hypophosphatasia caused by a wide variety of *ALPL* mutations. Patients selected for this study were required to have a history of rachitic chest deformity, respiratory compromise, or vitamin B6–dependent seizures to represent the extreme end of the hypophosphatasia disease spectrum and, therefore, to reflect the perinatal and infantile hypophosphatasia patient population involved in a clinical study of asfotase alfa treatment.[12,14] Patients with benign prenatal hypophosphatasia[9] were excluded, as shown by the severe clinical course of the study subjects.

Our data from 48 patients manifesting complications of hypophosphatasia before 6 months of life, and frequently within the first month of life, showed that skeletal disease in utero was suspected based on prenatal ultrasound scan in only one-third. Perhaps this has changed with more advanced and prevalent use of this technology, or it indicates that postnatal presentation of the disorder is common. Although the median age at diagnosis of hypophosphatasia was 0.2 years, diagnosis also was made as late as 3 years of age. Patients who had died at the time of chart review had been diagnosed earlier than those who were alive at chart review and had numerically lower mean serum ALP activity. However, these results should be interpreted with caution, as statistical comparisons of ALP activity between alive and dead patients seemed problematic because of differences in sample collection (eg, sites, time periods, assays). Delays in diagnosis for some patients that occurred despite the presence of the most severe characteristics of hypophosphatasia underscore the need for better appreciation of the signs, symptoms, and biochemical and radiographic hallmarks of hypophosphatasia, especially now that an effective treatment is available for patients with hypophosphatasia, including for severely affected newborns and infants.[14,18]

The 13 surviving patients in our study nevertheless suffered significant morbidity during their first 5 years of life. Those with available data had failure to thrive and chest deformity, but reportedly none had vitamin B6–dependent seizures, which in hypophosphatasia is considered a sign of impending death.[6,19] At least one-half of the 13 surviving patients went on to manifest early deciduous tooth loss, respiratory tract infection, respiratory compromise, craniosynostosis, hypercalcemia, and/or nephrocalcinosis. Respiratory complications that troubled these survivors included decreased oxygen saturation, distress, pneumonia, and tachypnea, although none progressed to chronic respiratory failure during the time frame of data collection and only 1 transiently was given ventilation. All patients with vitamin B6–dependent seizures and respiratory failure died, as did most requiring any respiratory support (26/32). Finally, within the time frame of this study, all but 1 surviving patient reportedly had developmental (motor) delays and 2 reportedly had cognitive delays. The motor delays were readily attributed to their skeletal abnormalities and muscle weakness.[12,14,20]

We focused in 2016[13] on the overall mortality rate of 73% by 5 years of age in this current study population, with the greatest relative risks for death noted among patients with the inclusion criteria of respiratory failure, respiratory distress, and vitamin B6–dependent seizures. Most of the 48 patients (58%) died within 12 months of birth, and median time to death was 8.9 months.[13] Thus, our current analysis adds to what is known about mortality among these patients. Although mortality was greatest among patients diagnosed before 1990 (100%), the rate remained high for those diagnosed between 1990 and 1999 (71%) and those diagnosed in 2000 and later (57%), suggesting that mortality rates for patients with perinatal and infantile hypophosphatasia with the aforementioned inclusion criteria remain high even with modern neonatal and pediatric intensive care units. The proportion of patients surviving without invasive ventilation decreased during the first year, from 63% at 3 months to 31% at 12 months. The median time from birth to invasive ventilation or death was 7.8 months. Thus, these observations confirm published reports of high mortality in general among patients with perinatal and infantile hypophosphatasia receiving supportive care.[1,2]

As first published in 2012, asfotase alfa treatment in the similar population of patients improved survival,[12] with 84% (31/37) of patients alive at 5 years of age[13] vs 27% (13/48) in the current study. This emphasizes the importance of prompt diagnosis of perinatal and infantile hypophosphatasia so that supportive measures and effective treatment can

begin. A rapidly worsening clinical course often occurs in perinatal or infantile hypophosphatasia, and therefore either form of hypophosphatasia requires close monitoring. Chest deformities and failure to thrive are common acquired features of infantile hypophosphatasia[12] but, in the current study, were associated with a somewhat-lower risk of death compared with respiratory failure or compromise or, as published in 2007, with vitamin B6–dependent seizures.[6] These latter 2 characteristics of severe hypophosphatasia were associated with greater mortality in this study, likely because pulmonary compromise is understandably life-threatening and vitamin B6–dependent seizures likely signal the most profound deficiency of TNSALP activity. In fact, a similar finding was recently reported among Japanese patients with perinatal hypophosphatasia, where failure to thrive did not correlate with a poorer prognosis.[20] However, a rachitic chest and failure to thrive are typically diagnosed in infants who have survived at least several weeks, permitting these complications to manifest.[10,12,21] Possibly, chest deformity or failure to thrive affected some patients in our study but went unreported. The relatively small number of patients in the multinational study reported herein may have been insufficient to identify further signs and symptoms that influenced mortality.

Our study was retrospective and often limited by the available data in case files. Data concerning motor and cognitive delays were collected from chart review and had not been assessed with standardized tools. Furthermore, the eligibility criteria were such that patients would be excluded if their signs and symptoms represented relatively mild infantile hypophosphatasia, which therefore likely increased the overall relative risks. In addition, the study included data reflecting a timeframe of perhaps 41 years (the first patient was born in 1970, and the last in 2011) and enrolled 48 patients. This small number of study subjects representing many years of follow-up may not have provided sufficient statistical power to identify correlations between outcomes and additional insidious features of hypophosphatasia. Furthermore, the broad time span for data acquisition did not fully reflect recent advances in pediatric intensive care, including respiratory support and ventilation. Lastly, the associations between risk factors and mortality were analyzed individually without considering mutual correlation and potentially confounding aspects among risk factors. Importantly, the most common complications of hypophosphatasia are subject to survivorship bias, such as tooth loss and, therefore, might take longer to develop.

In conclusion, this retrospective natural history study confirmed a high rate of morbidity and mortality among patients with perinatal and infantile hypophosphatasia within the first 5 years of life. Respiratory failure and vitamin B6-dependent seizures are comorbidities highly predictive of early death. Our observations are of particular significance because with the availability of an effective enzyme replacement therapy (asfotase alfa)[14,18] future natural history studies in this population of young children are unlikely. ■

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## Data Statement

Data sharing statement available at www.jpeds.com.

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## 50 Years Ago in *THE JOURNAL OF PEDIATRICS*

# Funduscopic Photography and Fluorescein Angioretinography in Evaluation of Children with Neurologic Handicaps

Baird HW, Pileggi AJ, Harley RD. J Pediatr 1969;6:937-45.

Baird et al obtained funduscopic photographs with fluorescein angioretinography in 80 of 300 neurologically handicapped children referred for ophthalmoscopic examination. Macular degenerative disease was present in 20. The authors further described 6 cases with different diagnoses and concluded that fundoscopic photography is a useful tool for retinal examination of handicapped children. In the following years, however; a restricted field of view, reflection artefacts, universal need for general anesthesia, and specific positioning, cost, and availability were recognized as major limitations to regular and widespread use of fundus photography and fluorescein angiography in children.

Fifty years later, the world of retinal imaging has surpassed most barriers. With the use of wide field and ultra-widefield (UWF) imaging systems, it is possible to obtain ora-to-ora view of the retina.[1] UWF has allowed to expand the field of view of imaging from 30° to 60° to up to 200° in a single image, capturing more of the periphery at retina.[2] Most pediatric retinal diseases manifest in peripheral retina and UWF angiography has proved to be extremely useful to diagnose the proliferative and exudative changes. Although most cases still require general anesthesia or light sedation, UWF fundus photography and angiography can be done as an outpatient procedure without the need for anesthesia, using "flying-baby" technique to position the child primarily for retinopathy of prematurity screening.[2] Confocal scanning laser ophthalmoscopy, allows for elimination of artefact reflections. Portable wide-angle cameras are now available for fundus photography, which allow direct visualization and capture in pediatric patients unable to position themselves.[3] These, and the advent of smart phone fundus photography, have opened up new gateways for telemedicine consulting and screening programs.[3]

Fundus imaging now plays an important role in retinopathy of prematurity, familial exudative vitreoretinopathy, Coats disease, Incontentia pigmenti, X-linked retinoschisis, Stargardt disease, Best disease, toxoplasmosis chorioretinitis, juvenile sarcoidosis, choroidal melanoma, juvenile idiopathic arthritis, pars planitis, and traumatic retinal detachment.[2] Recent imaging tools have not only allowed improved diagnosis, screening, documentation, monitoring, and image-guided treatment of these diseases. They have also widened the scope of research.

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# Appendix 1

## Additional Members of the Study 011-10 Investigators

The authors gratefully acknowledge the help of the following individuals: Michael Beck, MD, Children's Hospital, University of Mainz, Mainz, Germany; Linda DiMeglio, MD, Indiana University School of Medicine, Indianapolis, IN; Paul Wuh-Liang Hwu, MD, PhD, National Taiwan University Hospital, Taipei, Taiwan; Katherine L. Madson, MD, PhD, and Upasana Nanda, MPH, Shriners Hospital for Children, St. Louis, MO, USA; Peter Simm, MD, Royal Children's Hospital, Parkville, Victoria, Australia; Jill Simmons, MD, Vanderbilt University Medical Center, Nashville, TN; Joel Steelman, MD, Cook Children's Health Care System, Fort Worth, TX; Robert D. Steiner, MD, Oregon Health & Science University, Portland, OR; and Andrea Superti-Furga, MD, Centre Hospitalier Universitaire, Lausanne, Switzerland.

## Disclosures

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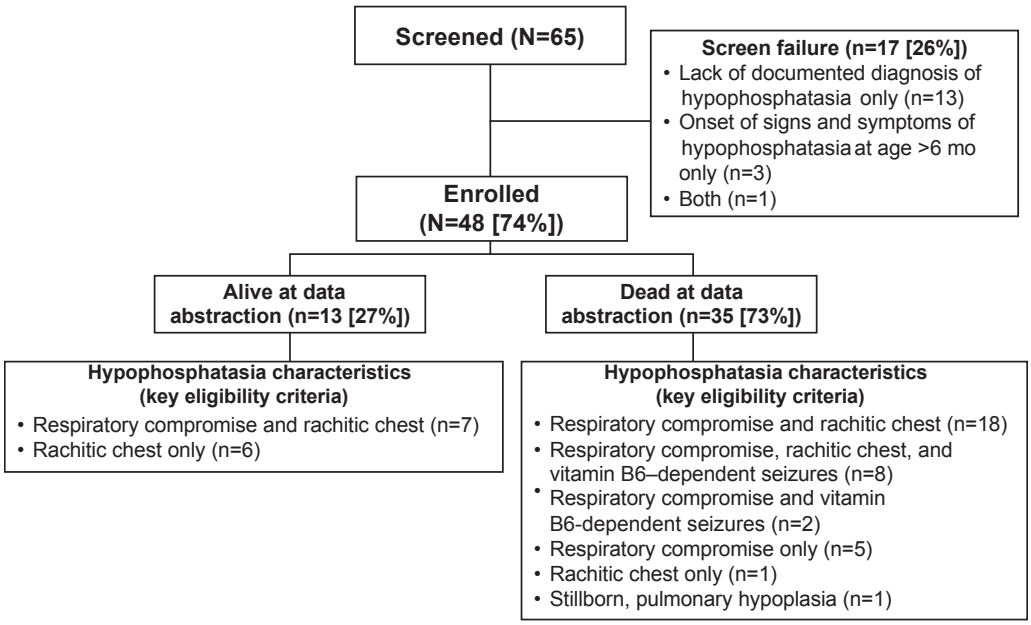


**Figure 1.** Patient disposition flowchart.

**Table II. Radiographic findings reported at hypophosphatasia diagnosis**

| Radiographic findings | %* (n/N) |
|---|---|
| Osteopenia | 89 (33/37) |
| Rachitic chest/deformed ribs | 86 (32/37)† |
| Metaphyseal fraying | 68 (19/28) |
| Metaphyseal flaring | 67 (20/30) |
| Metaphyseal radiolucencies (tongues) | 63 (15/24) |
| Metaphyseal widening | 55 (12/22) |
| Long bone bowing | 48 (14/29) |
| Thin, gracile bones | 44 (12/27) |
| Sclerosis | 30 (6/20) |
| Bony spurs | 26 (6/23) |
| Fracture (nonunion) | 23 (7/30) |
| Absence of some/all bones | 23 (7/30) |

*Percent calculated as the number of patients with the finding (n) divided by the number of patients with available data (N) × 100. Patients for whom status was "unknown" or missing were not included.

†A total of 39 patients had chest deformity documented in disease history (Table IV in the main text) and 32 patients had radiographic evidence of rachitic chest at the time of diagnosis.

**Table III. Respiratory support type* for each patient**

| Patient IDs | Initial type of respiratory support (Y/M/D)† | Most intensive type of respiratory support required (Y/M/D)† | Last recorded type of respiratory support (Y/M/D)†‡ | Patient alive at time of data collection (Y/M/D)§ |
|---|---|---|---|---|
| 1 | Supplemental $O_2$ (0/7/0) | IV (0/11/0, 1/0/3) | IV (2/9/28) | No (2/10/2) |
| 2 | No support provided | | | No (unknown) |
| 3 | Unknown | | | No (0/0/37) |
| 4 | No support provided | | | No (0/0/1) |
| 5 | IV (0/0/0) | IV (0/0/0) | IV (0/0/1) | No (0/0/1) |
| 6 | No support provided | | | No (0/8/23) |
| 7 | Unknown | | | No (0/0/1) |
| 8 | No support provided¶ | | | No (0/0/0) |
| 9 | No support provided | | | No (0/9/21) |
| 10 | IV (0/0/0) | IV (0/0/1) | IV (0/0/1) | No (0/0/1) |
| 11 | Supplemental $O_2$ (0/0/0) | Supplemental $O_2$ (0/0/0) | Supplemental $O_2$ (0/0/0) | No (0/4/5) |
| 12 | IV (0/0/0) | IV (0/0/0) | IV (0/0/0) | No (0/0/1) |
| 13 | IV (0/0/0) | IV (0/0/5) | IV (0/0/5) | No (0/0/5) |
| 14 | No support provided | | | Yes |
| 15 | No support provided | | | No (0/0/1) |
| 16 | IV (0/0/1) | IV (0/0/1) | IV (0/1/0) | No (0/1/0) |
| 17 | IV (0/0/1) | IV (0/0/1) | IV (0/0/1) | No (0/0/1) |
| 18 | IV (0/0/1) | IV (0/0/1) | IV (0/0/9) | No (0/0/11) |
| 19 | Supplemental $O_2$ (0/0/1) | IV (0/0/1) | IV (0/0/1) | No (0/0/1) |
| 20 | No support provided | | | Yes |
| 21 | Supplemental $O_2$ (0/7/6) | Supplemental $O_2$ (0/10/5) | Supplemental $O_2$ (0/10/5) | No (0/10/7) |
| 22 | Supplemental $O_2$ (0/5/5) | Supplemental $O_2$ (0/5/5) | Supplemental $O_2$ (0/5/5) | No (0/5/5) |
| 23 | IV (0/0/1) | IV (0/0/1) | Supplemental $O_2$ | Yes (not still on support) |
| 24 | Supplemental $O_2$ (0/0/5) | Supplemental $O_2$ (0/0/5) | Supplemental $O_2$ (0/0/5) | Yes (not still on support) |
| 25 | No support provided | | | Yes |
| 26 | Supplemental $O_2$ (0/0/0) | Supplemental $O_2$ (0/0/6) | Supplemental $O_2$ (0/0/6) | Yes (not still on support) |
| 27 | Supplemental $O_2$ (0/0/0) | Supplemental $O_2$ (0/0/0) | Supplemental $O_2$ (0/0/0) | No |
| 28 | Supplemental $O_2$ (0/9/0) | IV (0/9/0) | IV (3/0/6) | No (0/36/0) |
| 29 | IV (1/1/3) | IV (1/1/3) | IV (1/1/3) | No (1/2/1) |
| 30 | Supplemental $O_2$ (0/4/2) | IV (0/4/3) | IV (0/5/6) | No (0/5/27) |
| 31 | Supplemental $O_2$ (0/6/0) | Supplemental $O_2$ (0/6/0) | Supplemental $O_2$ (0/6/6) | No (0/6/27) |
| 32 | Supplemental $O_2$ (0/8/0) | Supplemental $O_2$ (0/8/0) | Supplemental $O_2$ (0/8/4) | No (0/8/0) |
| 33 | IV (0/3/0) | IV (0/3/0) | IV (0/3/0) | No (0/3/3) |
| 34 | Unknown | | | No (0/9/0) |
| 35 | IV (0/0/0) | IV (0/0/0) | Supplemental $O_2$ (0/0/0) | No (0/0/1) |
| 36 | IV (0/6/0) | IV (0/6/1) | IV (0/6/1) | No |
| 37 | CPAP (0/0/1) | CPAP (0/0/1) | CPAP (0/0/5) | No (0/0/27) |
| 38 | No support provided | | | Yes |
| 39 | No support provided | | | Yes |
| 40 | No support provided | | | Yes |
| 41 | No support provided | | | Yes |
| 42 | No support provided | | | Yes |
| 43 | No support provided | | | Yes |
| 44 | No support provided | | | Yes |
| 45 | CPAP (0/0/1) | IV (0/2/4, 0/4/4) | IV (0/5/5) | No (0/5/19) |
| 46 | CPAP (0/0/0) | IV (0/0/1, 0/5/5) | IV (0/5/0) | No (0/5/7) |
| 47 | Supplemental $O_2$ (0/9/6) | Supplemental $O_2$ (0/9/6) | Supplemental $O_2$ (0/9/6) | No (0/9/27) |
| 48 | Supplemental $O_2$ (0/8/26) | IV (0/11/1) | IV (1/0/6) | No (1/0/6) |

*BiPAP*, bilevel positive airway pressure; *CPAP*, continuous positive airway pressure; *IV*, invasive ventilation.
Types of respiratory support are color-coded, with each type of support appearing in the same color.
*Respiratory support types from greatest to least: IV, CPAP, BiPAP, and/or supplemental oxygen.
†Age (years/months/days) at which respiratory support was initiated, if available, is indicated in parentheses.
‡Last respiratory support is the type of support that was needed up to age 5 years for patients who were alive or the final support applied before death.
§Age (years/months/days) at death, if available, is indicated in parentheses. If patient was alive, requirement for respiratory support at age 5 years, if needed, is indicated.
¶Patient was stillborn.

**Table V. Hospitalizations for reasons consistent with a diagnosis of hypophosphatasia**

| Reasons | All patients (N = 48) | | Deceased patients (n = 35) | Living patients (n = 13) |
|---|---|---|---|---|
| | Hospitalizations, n | Patients, n (%)* | Patients, n (%)† | Patients, n (%)† |
| Hospitalizations for any reason | 133 | 39 (81) | 27 (77) | 12 (92) |
| All respiratory compromise | 46 | 22 (46) | 18 (51) | 4 (31) |
| Respiratory failure | 5 | 2 (4) | 2 (6) | 0 (0) |
| Respiratory distress | 21 | 12 (25) | 11 (31) | 1 (8) |
| Other‡ | 20 | 11 (23) | 7 (20) | 4 (31) |
| Craniosynostosis | 16 | 9 (19) | 4 (11) | 5 (39) |
| Seizure related | 8 | 7 (15) | 6 (17) | 1 (8)§ |
| Renal related | 3 | 2 (4) | 1 (3) | 1 (8) |
| Others¶ | 62 | 28 (58) | 16 (46) | 12 (92) |

*Percentage is calculated as n divided by 48, the number of enrolled patients, × 100.
†Percentage is calculated using the number of deceased or alive patients.
‡Includes pneumonia, asthma, tachypnea, dyspnea, tachydyspnea, asthma, ventilator use, labored respirations, ventilatory care.
§Reason was to eliminate possibility of seizures.
¶Reasons included hypercalcemia, infections, vomiting, failure to thrive/developmental delays, hypophosphatasia evaluation/diagnostics, orthopedic treatment (surgery, casts, fractures), experimental therapies (stem cell or bone marrow transplants, enzyme replacement using Paget's bone disease plasma infusions), abdominal pain, rehabilitation, icterus neonatorum, choking, head injury/concussion, nasal gastric tube placement, prematurity, cardiac failure, patent ductus arteriosus ligation. Patients may have had multiple hospitalizations. Patients and hospitalizations may be counted in multiple "reasons" categories.