Pediatric Hemoptysis without Bronchiectasis or Cardiac Disease: Etiology, Recurrence, and Mortality

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Objectives To describe the etiologies of hemoptysis in patients without pre-existing bronchiectasis or cardiac disease; to assess odds of recurrent hemoptysis by diagnostic category; and to assess odds of mortality by diagnostic category.

Study design This retrospective case series included all patients with hemoptysis documented during an admission to Boston Children's Hospital from January 1, 2007 to June 1, 2017. Patients with bronchiectasis, congenital heart disease, primary pulmonary hypertension, bleeding above the glottis, hemoptysis before 38 weeks of corrected gestational age, hematemesis, foreign body, and trauma were excluded. Patients were also characterized by coagulation status. Primary outcomes were recurrent hemoptysis and death. Univariate analysis was performed to determine ORs for recurrence and death per diagnostic category with infection as the reference category.

Results In total, 257 patients met study criteria and were analyzed. The most common causes of hemoptysis were infection (n = 122), neoplasm (n = 58), and other diagnoses (n = 49). Of the patients with infection, recurrence was 28% and all-cause mortality was 12%. Neoplasm had lower odds of recurrence (OR 0.3, $P = .012$) but higher odds of mortality (OR 15.8, $P < .001$). Thrombocytopenia had lower odds of recurrence (OR 0.2, $P = .005$) but higher odds of mortality (OR 5.9, $P < .001$). Patients with a tracheostomy had higher odds of recurrence (OR 6.3, $P < .001$), but lower odds of death (OR 0.4, $P = .042$).

Conclusions This study confirms that infection is the most common cause of hemoptysis in patients without severe underlying pulmonary or cardiac disease. Hemoptysis associated with neoplasm and/or thrombocytopenia confers mortality risk. Tracheostomy confers risk of recurrence. Future prospective research on diagnoses associated with hemoptysis is warranted. *(J Pediatr 2019;214:66-70)*.

Hemoptysis is a potentially life-threatening event that necessitates that pediatricians have an understanding of its etiology, management, and prognosis.[1] The incidence of hemoptysis in pediatrics is difficult to estimate as children present both to primary care providers and to a variety of subspecialists with this symptom.[2] Previous retrospective studies have identified infection[3-9] and cystic fibrosis[10] as frequent causes of pediatric hemoptysis. Other causes include cardiac disease, foreign body, trauma, neoplasm, coagulopathy, diffuse alveolar hemorrhage, environmental, idiopathic, and factitious.[2,10-12] Pediatric hemoptysis is associated with significant mortality. Coss-Bu et al estimated 13% mortality associated with this chief complaint and identified age, volume of hemoptysis, receipt of blood products, and fever as risk factors for mortality in a retrospective chart review of 228 patients, 186 of whom had cystic fibrosis or congenital heart disease.[10] Similarly, a retrospective chart review of infants with pulmonary hemorrhage demonstrated that congenital heart disease was the most common associated diagnosis.[13]

We decided to evaluate a large group of patients with hemoptysis but without known trauma, cardiac disease, or bronchiectasis, as these underlying diagnoses are distinct, require unique subspecialty management, and are less frequently seen in the community. The aims of this study are to describe the etiologies of hemoptysis in a large cohort of patients at a tertiary care hospital without bronchiectasis (eg associated with cystic fibrosis), congenital heart disease, pulmonary hypertension, bleeding above the glottis, hematemesis, foreign body, hemoptysis before 38 weeks of corrected gestational age, or known trauma; define odds of recurrence of hemoptysis by diagnosis in this population; and define odds of mortality by diagnosis in this population.

Methods

This case series included all patients <26 years of age with a diagnosis of hemoptysis or pulmonary hemorrhage documented at any time during an admission to Boston Children's Hospital from January 1, 2007 to June 1, 2017. These patients were initially identified based on billing codes and were subsequently confirmed to have had documented production of frank blood, bloody sputum or blood

EMR	Electronic medical record
IPEX	Immunodysregulation, polyendocrinopathy, enteropathy, X-linked

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expectorated, or suctioned from tracheostomy or endotracheal tubes on review of the electronic medical record (EMR). Patients excluded from this study were those with pre-existing diagnoses of bronchiectasis, congenital heart disease, primary pulmonary hypertension, known trauma, foreign body, and those found to have bleeding above the glottis. We also excluded patients with administrative codes for hemoptysis, but only documentation of hematemesis on review of the EMR. Preterm infants who developed hemoptysis prior to 38 weeks of corrected gestational age were also excluded, although patients born preterm who developed hemoptysis thereafter were included.

Primary outcomes were recurrence of hemoptysis and death. Mortality was defined as all-cause mortality at the time of data collection. Recurrence was defined as any additional episode of hemoptysis, production of bloody sputum, or blood suctioned from tracheostomy or endotracheal tubes as recorded in the medical record or any subsequent admission with diagnosis code of hemoptysis. Data were collected for each patient admission during the study period from existing sources including the EMR, institutional respiratory therapy database, ECMO database, and our institutional data warehouse. Additional chart review was performed to assign diagnostic category, determine recurrence, collate available microbiological diagnoses, and identify comorbidities. No additional patient testing or patient contact was performed. Institutional review board approval was obtained for this study prior to the collection of data.

Diagnostic categories evaluated included infection, pulmonary vascular abnormalities, neoplasm, diffuse alveolar hemorrhage, chronic lung disease, and other. Infections included in this study were pneumonia, upper respiratory infection, tracheobronchitis, tuberculosis, sepsis, sinusitis, or tonsillitis. Infection category was determined by positive culture data or imaging, laboratory findings, and/or clinical picture strongly supportive of a bacterial vs viral infection. Pulmonary vascular abnormalities were defined as arteriovenous or venovenous malformations visualized on chest computed tomography with intravenous contrast. Neoplasm included hematologic malignancies, solid tumors, and primary and metastatic lung tumors. Diffuse alveolar hemorrhage was determined by the documenting provider, based on a combination of clinical presentation and evidence on chest computed tomography and/or flexible bronchoscopy with bronchoalveolar lavage. Chronic lung diseases were asthma, emphysema, and bronchopulmonary dysplasia or chronic lung disease of prematurity. Other diagnoses identified included Stevens-Johnson syndrome, granulomatosis with polyangiitis (formerly Wegener granulomatosis), hemophagocytic lymphohistiocytosis, other autoimmune disorders, nonaccidental trauma, inborn errors of metabolism, and idiopathic pulmonary hemorrhage.

Coagulation status was identified for all patients. The categories used were normal (no identified risk), Von Willebrand disease, thrombocytopenia, patients on therapeutic anticoagulation at the time of presentation, and other congenital or acquired coagulopathies. Prophylactic vs treatment dosing of anticoagulants was not evaluated.

Statistical Analyses

Descriptive statistics were obtained and examined according to the following categories: all patients, recurrence, and deceased patients. Descriptive statistics for the "Other diagnoses" category were also obtained. Outcomes were obtained for subgroups and univariate analysis performed using logistic regression. Results were reported as ORs without adjustment. A P value of $< .05$ was considered significant. Infection was used as the reference for the diagnosis categories in logistic regression.

Results

In total, 257 patients met inclusion criteria (Table I). Recurrence occurred in 61 (23.7%) patients; 74 patients (28.8%) were deceased at the time of data collection. A slight majority of patients (n = 146, 56.8%) were male. Ethnicity information was obtained for 233 of 257 patients with the majority of white/Caucasian descent (64.4%). Forty patients (15.6%) had a tracheostomy with 57.5% of those patients experiencing a recurrence.

The most common diagnosis was infection, n = 122 (47.4%). Of patients with the diagnosis of infection, 34 (27.9%) had recurrence and 15 (12.3%) were deceased at the time of data collection. The second most frequent diagnosis was neoplasm, n = 58 (22.6%). Of patients with the diagnosis of neoplasm, 6 (10.3%) had recurrence and 40 (69.0%) were deceased at the time of data collection. There were 3 patients described as having multiple diagnoses; these are patients in whom there was more than 1 possible reason for hemoptysis but no clearly predominant cause. The remaining diagnoses, recurrence, and all-cause mortality rates are reported in Table I.

One hundred three of the 122 patients diagnosed with infection had positive testing for bacterial, bacterial and viral, viral, or mycobacteria tuberculosis infections or a clinical picture and imaging findings strongly suggestive of bacterial or viral infection. There were 19 patients who were thought to have infection but in whom determination of a viral or bacterial process could not be made. Bacterial infection had the highest rate of recurrence, 19 of 72 (26.4%); 72.5% of patients with tracheostomy were found to have infection associated with hemoptysis.

Seventy-six (29.6%) patients had increased bleeding risk. Patients with thrombocytopenia and "other coagulopathies" had a significant number of deaths, 28 of 50 and 10 of 16 (56.0% and 62.5%), respectively. Of note, there is overlap between the neoplasm and thrombocytopenia group, with 37.9% of the neoplasm group thrombocytopenic at the time of admission.

Other underlying diagnoses (n = 49, 19.1%) are described in Table II. The most predominant (n = 27, 55.1%) were systemic disorders associated with autoimmunity or immune dysregulation, including systemic lupus erythematosus, juvenile idiopathic arthritis, inflammatory bowel disease, CTLA4 deficiency, Evans syndrome, and immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. In the patients with systemic disorders associated with

Table I. Patient characteristics, diagnoses, and outcomes

Patient characteristics and diagnoses	All patients, n (%)	Recurrence, n (%)	Deceased, n (%)
n	257 (100)	61 (23.7)	74 (28.8)
Sex			
Male	146 (56.8)	29 (19.9)	41 (28.1)
Female	111 (43.2)	32 (28.8)	33 (29.7)
Ethnicity:	n = 233	n = 60	n = 62
White	150 (64.4)	42 (28.0)	38 (25.3)
Black or African American	34 (14.6)	9 (26.5)	7 (20.6)
Other	34 (14.6)	7 (20.6)	8 (23.5)
Asian	13 (5.6)	2 (15.4)	8 (61.5)
Hispanic or Latino	2 (0.8)	0 (0)	1 (50.0)
Age, y	Mean = 10.5 (0-25.9)	Mean = 12.4 (0.1-25.9)	Mean = 10.2 (0-25.3)
Tracheostomy	40 (15.6)	23 (57.5)	6 (15.0)
Diagnosis	n = 257	n = 61	n = 74
Infection	122 (47.4)	34 (27.9)	15 (12.3)
Infection category			
Bacterial	72 (59.0)	19 (26.4)	10 (13.9)
Bacterial and viral	15 (12.3)	4 (26.7)	3 (20.0)
Viral	15 (12.3)	2 (13.3)	0 (0)
Tuberculosis	1 (0.8)	0 (0)	0 (0)
Clinical suspicion of infection	19 (15.6)	9 (47.4)	2 (10.5)
Neoplasm	58 (22.6)	6 (10.3)	40 (69.0)
Other*	49 (19.1)	14 (28.6)	16 (6.2)
Diffuse alveolar hemorrhage	13 (5.0)	3 (23.1)	1 (7.7)
Chronic lung disease, emphysema, asthma	10 (3.9)	4 (40.0)	0 (0)
Multiple	3 (1.2)	0 (0)	1 (33.3)
Vascular anomaly	2 (0.8)	0 (0)	1 (50.0)
Coagulation status:	n = 257	n = 61	n = 74
No identified bleeding risk	181 (70.4)	52 (28.7)	32 (12.4)
Thrombocytopenia	50 (19.5)	4 (8.0)	28 (56.0)
Other	16 (6.2)	2 (12.5)	10 (62.5)
Therapeutic anticoagulation	9 (3.5)	2 (22.2)	4 (44.4)
Von Willebrand disease	1 (0.4)	1 (100)	0 (0)

HLH, hemophagocytic lymphohistiocytosis.
*Autoimmune or immune dysregulation, granulomatosis with polyangiitis, idiopathic, inborn error of metabolism, nonaccidental trauma, HLH, Stevens-Johnson syndrome, factitious.

autoimmunity or immune dysregulation, 25.9% of these patients had a recurrence and 40.7% were deceased at the time of data collection. Granulomatosis with polyangiitis had the highest recurrence rate (80.0%) but no mortalities. Four cases of nonaccidental trauma were identified. All of these patients were less than a year of age. The 2 patients with hemophagocytic lymphohistiocytosis are deceased. One case of factitious hemoptysis was discovered.

Table II. Diagnoses and patient characteristics in "other" category

Diagnoses	Number	Age, y	Sex	Recurrence	Death
Autoimmune or immune dysregulation	27	11.3 (0.01-22.8)	F12/M15	7	11
Granulomatosis with polyangiitis	5	16.5 (14.8-17.7)	F3/M2	4	0
Idiopathic	5	10.3 (3.6-17.6)	F2/M3	2	0
Inborn error of metabolism	4	3.0 (0.01-11.7)	F1/M2	0	3
Nonaccidental trauma	4	0.1 (0.1-0.2)	F2/M2	1	0
HLH	2	3.1 (0.8-5.3)	F2	0	2
Stevens-Johnson Syndrome	1	13.4	F1	0	0
Factitious	1	17.2	F1	0	0

F, female; *M*, male.

Univariate Analyses

Univariate predictors for recurrence found to be statistically significant using logistic regression with infection as the reference were tracheostomy (OR 6.3, $P < .001$), neoplasm (OR 0.3, $P = .01$), and thrombocytopenia (OR 0.2, $P = .005$) (Table III). Statistically significant predictors for death were tracheostomy (OR 0.4, $P = .04$), neoplasm (OR 15.8, $P < .001$), thrombocytopenia (OR 5.9, $P < .001$), and coagulation status category 'other' (OR 7.8, $P < .001$).

Discussion

We describe the clinical presentation and outcomes of 257 patients with hemoptysis or pulmonary hemorrhage at presentation or during a tertiary hospital admission. This study is unique in its focus on patients without the common predisposing conditions of cardiac disease, bronchiectasis, pulmonary hypertension, bleeding above the glottis, hematemesis, prematurity, foreign body, and trauma. We selected this population because there is a paucity of data about the causes of hemoptysis and risk factors for mortality and recurrence in these patients. In addition, the diagnostic and therapeutic approach to hemoptysis in this subgroup likely varies from the approach to other patients with underlying conditions known to contribute to hemoptysis.

The most common etiologies for hemoptysis in our population were infection, neoplasm, and a combination of other

Table III. Predictors of recurrence or death

Patient characteristics and diagnoses	Recurrence OR [CI] (*P* value)	Death OR [CI] (*P* value)
Sex (m)	0.6 [0.3-1.1] (.1)	0.9 [0.5-1.6] (.8)
Tracheostomy	6.3 [3.1-13.1] (<.001)	0.4 [0.1-1.0] (.04)
Diagnosis category		
Infection	1 (reference)	1 (reference)
Neoplasm	0.3 [0.1-0.8] (.01)	15.8 [7.3-34.4] (<.001)
Other*	1.0 [0.5-2.2] (.9)	3.5 [1.5-7.7] (.003)
Diffuse alveolar hemorrhage	0.8 [0.2-3.0] (.7)	0.6 [0.1-4.9] (.6)
Chronic lung disease	1.7 [0.5-6.5] (.4)	
Pulmonary vascular anomaly		7.1 [0.4-120.1] (.2)
Multiple		3.6 [0.3-42.8] (.3)
Infection category		
Bacterial and viral	1.0 [0.3-3.6] (1.0)	1.5 [0.4-6.5] (.5)
Viral	0.4 [0.1-2.1] (.3)	
Coagulation status		
Thrombocytopenia	0.2 [0.1-0.6] (.005)	5.9 [3.0-11.7] (<.001)
Therapeutic anticoagulation	0.7 [0.1-3.5] (.7)	3.7 [0.9-14.6] (.06)
Other	0.4 [0.1-1.6] (.2)	7.8 [2.6-22.9] (<.001)

*Autoimmune or immune dysregulation, granulomatosis with polyangiitis, idiopathic, inborn error of metabolism, nonaccidental trauma, HLH, Stevens-Johnson syndrome, factitious.

very rare diagnoses. Nearly one-half of the cases were attributed to infection. The finding of infection as a common cause of pediatric hemoptysis is concordant with existing literature, particularly in centers where cystic fibrosis and congenital cardiac disease are less commonly seen.[3-8] Similarly, the finding in the present study that the majority of infectious cases were presumed to be bacterial in origin is in agreement with previous studies.[4,8] Although we, like others, found that tuberculosis is a relatively rare cause of hemoptysis,[3,4,8,10] this result should be interpreted with caution compared with other literature in populations where tuberculosis is more prevalent.[7] Neoplasm as a cause for hemoptysis has been previously recognized as the most common in patients without cystic fibrosis, congenital heart disease, or pneumonia in a large retrospective chart review.[10] The present study identified an interesting subgroup of patients with autoimmune disorders and immune dysregulation syndromes.

We add to other reports by assessing risk factors for recurrence of hemoptysis. In line with previous studies,[4,9] the presence of a tracheostomy was found to confer increased risk of hemoptysis. We found that though recurrence risk was higher in this subgroup, mortality risk was not. Prior literature has shown that bleeding from patients with tracheostomy may be related to mucosal abrasion or granuloma formation,[4] which may explain lower mortality compared with other diagnoses.

This study showed an all-cause mortality rate at the time of data collection of 28.8%. Neoplasm, thrombocytopenia, and other coagulation abnormalities increased the odds of mortality. Prior literature has suggested a hemoptysis-associated mortality rate of 13%.[10] The discrepancy between our study and prior literature is likely related to our examination of all-cause mortality over a longer time interval. Our finding that coagulation abnormalities increase the odds of mortality is similar to prior literature describing transfusion of blood products in the setting of hemoptysis as a risk factor for death.[10] The increased odds of mortality with neoplasm needs to be further examined to understand the role of hemoptysis in conferring increased odds of mortality vs the underlying disease process itself.

This study is limited by its retrospective nature and reliance on the electronic medical record and diagnostic coding. Many of the patients had multiple comorbidities, which could not be completely controlled for in the statistical analyses and are likely confounders. This study was unable objectively to quantify volume of hemoptysis because of inconsistent documentation of volume of hemoptysis in the medical record. Classification within our medical record of small-volume bleeding may not have been consistent, leading to under- or over-estimates of some events. Upper airway bleeding may have been incorrectly documented as hemoptysis in the medical record. Origin of bleeding, particularly in patients with tracheostomy, may be difficult to determine and local trauma or infection could not be excluded, likely leading to overestimation of hemoptysis and/or recurrence events. Recurrence was determined based on documentation in our electronic medical record; patients may have had recurrence of hemoptysis and sought medical attention elsewhere and thus may not have been captured. We used all-cause mortality as our endpoint. Under-reporting of mortality is possible as patients may have been lost to follow-up. Coagulation status was based on admission laboratory findings; at times, hemoptysis may have occurred later in a prolonged admission. Diagnoses including diffuse alveolar hemorrhage and idiopathic pulmonary hemosiderosis may have been given by providers without expertise in this diagnosis, and, thus, their accuracy is uncertain.

An important future direction would be to work toward an analysis of the utility of different diagnostic tests—including laboratory studies, imaging, bronchoscopy, cardiac catheterization—and subspecialty consultation when children present with hemoptysis. By identifying causes and risk factors for recurrence and death, we have laid the foundation for future research to create evidence-based standardization of diagnostic testing on presentation. In our group, we found significant variability in the approach used, and to our knowledge, there is no published consensus approach. We found significant variation in testing done. Additional future directions for research include further describing which types of neoplasm, including primary and metastatic cancers, put patients most at risk for hemoptysis and increase odds of mortality. Similarly, a more detailed chart review to better understand which coagulopathies increase odds of mortality would be useful. Further evaluation of whether infection in isolation or infection as a trigger of an underlying condition provokes hemoptysis would be interesting. Additional research into the time to recurrence of hemoptysis may help clarify the morbidity associated with the different diagnoses. Prospective studies to better characterize hemoptysis in patients with underlying immune dysregulation and autoimmune disorders, including risk factors based on clinical and laboratory findings is necessary, in light of the high mortality rate in this subgroup. Prospective studies to understand how to distinguish between

worrisome and benign bleeding in patients with tracheostomy should be considered to optimize the diagnostic and therapeutic interventions in these patients. ■

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References

1. Gaude GS. Hemoptysis in children. Indian Pediatr 2010;47:245-54.
2. Godfrey S. Pulmonary hemorrhage/hemoptysis in children. Pediatr Pulmonol 2004;37:476-84.
3. Abu-Kishk I, Klin B, Eshel G. Hemoptysis in children: a single institutional experience. Pediatr Emerg Care 2012;28:1206-10.
4. Batra PS, Holinger LD. Etiology and management of pediatric hemoptysis. Arch Otolaryngol Head Neck Surg 2001;127:377-82.
5. Sim J, Kim H, Lee H, Ahn K, Lee SI. Etiology of hemoptysis in children: a single institutional series of 40 cases. Allergy Asthma Immunol Res 2009;1:41-4.
6. Tom LWC, Weisman RA, Handler SD. Hemoptysis in children. Ann Otol 1980;89:419-24.
7. Wong KS, Lien R, Hsia SH. Major hemoptysis in adolescents. Indian J Pediatr 2005;72:537-8.
8. Wong KS, Wang CR, Lin TY. Hemoptysis in children. Chang Gung Med J 1998;21:57-61.
9. Fabian MC, Smitheringale A. Hemoptysis in children: the hospital for sick children experience. J Otolaryngol 1996;25:44-5.
10. Coss-Bu JA, Sachdeva RC, Bricker JT, Harrison GM, Jefferson LS. Hemoptysis: a 10-year retrospective study. Pediatrics 1997;100:E7.
11. Susarla SC, Fan LL. Diffuse alveolar hemorrhage syndromes in children. Curr Opin Pediatr 2007;19:314-20.
12. Cassimos CD, Chryssanthopoulos C, Panagiotidou C. Epidemiologic observations in idiopathic pulmonary hemosiderosis. J Pediatr 1983;102:698-702.
13. Welsh SK, Casey A, Fishman MP. Pulmonary hemorrhage in infancy: a 10-year-single-center experience. Pediatr Pulmonol 2018;53:1559-64.

50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Idiopathic Hypoglycemia: A Study of Twenty-Six Children

Kogut MD, Blaskovics M, and Donnell GN. J Pediatr 1969;74;6:853-871.

In 1956, Cochrane et al first reported hypoglycemia precipitated by a leucine-rich diet in susceptible individuals.[1] In 1969, Kogut et al followed up this observation with systematic characterization of 26 patients with idiopathic hypoglycemia using a battery of tolerance and provocative tests. The study identified and characterized 5 patients who developed hypoglycemia after receiving a leucine-rich diet. Some evidence suggested that amino acids, especially leucine, stimulate insulin secretion, and dysregulation of this pathway leads to hyperinsulinism and hypoglycemia. Multiple subsequent studies confirmed these findings and further clarified the mechanisms of insulin regulation. The phenomenon described in the 1950s and 1960s as protein-sensitive hypoglycemia or leucine-sensitive hypoglycemia is now considered a subset of congenital hyperinsulinism.[2]

A major complication of congenital hyperinsulinism is brain injury secondary to severe or persistent hypoglycemia. Since the initial case reports more than 50 years ago, the rate of brain injury remains high owing to delays in diagnosis and treatment.[2] To address this issue, the Pediatric Endocrine Society published guidelines to facilitate screening and early treatment of neonates with persistent hypoglycemia.[3] In contrast with the battery of tolerance and provocative testing by Kogut's group, we now use quick and easy tests for hypoglycemia. A critical sample that includes blood glucose, bicarbonate, beta-hydroxybutyrate, and lactate, among others, is the initial step to classify hypoglycemia.[3] Based on the results, specific biochemical, genetic, or imaging studies can further narrow the diagnosis. Clinical management of congenital hyperinsulinism remains challenging, and most patients require intensive continuous tube feeding. Advancements in genetic diagnosis allows identification of patients who would benefit from diazoxide treatment or pancreatectomy. Efforts are ongoing to identify additional genetic mutations associated with congenital hyperinsulinism. Development and testing are also ongoing for new treatments, including long-acting somatostatin injections, glucagon-like peptide-1 receptor reverse agonist, and sirolimus.

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References

1. Cochrane WA, Payne WW, Simpkiss MJ, Woolf LI. Familial hypoglycemia precipitated by amino acids. J Clin Invest 1956;35:411-22.
2. Stanley CA. Perspective on the genetics and diagnosis of congenital hyperinsulinism disorders. J Clin Endocrinol Metab 2016;101:815-26.
3. Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, et al. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr 2015;167:238-45.