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Respiratory viral infections in patients with inherited metabolic disorders: Pathogen distribution and clinical outcomes

Kubra Aykac[1], Ozkan Uzunoglu[2], Aylin I. Kuruc[1], Osman O. Demir[1], Yilmaz Yildiz[3], Serap Sivri[3], Ali Dursun[3], Ali B. Cengiz[1], Yasemin Ozsurekci[1]

ABSTRACT

Introduction: Children with inborn errors of metabolism (IEMs) are at increased risk for severe viral infections, which may precipitate acute metabolic decompensation, PICU admission, and death. Pathogen-specific outcomes in this population remain poorly defined. The objective was to evaluate the epidemiology, viral etiology, and clinical severity of respiratory viral infections in hospitalized children with IEMs.

Method: This single-center retrospective study included children with IMDs hospitalized with acute infectious illness and laboratory-confirmed respiratory viral detection during 2018-2024. Demographic features, underlying metabolic diagnoses, viral pathogens, and outcomes were evaluated.

Result: A total of 45 infection episodes among 41 children were included; median age was 4 years (IQR:0.5–9.5), and 31 patients (75.6%) were male. The most common IEMs categories were amino acid metabolism disorders (36.6%) and complex molecule degradation and processing defects (26.8%). Respiratory disease was the predominant presentation (77.8%), followed by gastroenteritis (8.9%), sepsis (6.7%), and meningoencephalitis (6.7%). Acute metabolic decompensation occurred in 11/23 infection episodes in metabolically vulnerable patients (47.8%). Influenza was the most frequently identified virus (35.6%), followed by rhinovirus (22.2%), seasonal coronavirus (sCoV) (13.3%), and respiratory syncytial virus (11.1%). PICU admission was required in 13.3% (6/45) of cases. Infection-related mortality was 6.7% (n = 3), and all fatal cases had sCoV infection.

Conclusion: Influenza was the most frequently identified pathogen, while sCoV was detected in all three infection-related deaths. Our results suggest that respiratory viral infections may be associated with clinical burden in children with IMDs, highlighting the importance of close clinical monitoring and supportive management in this vulnerable population.

Keywords: *metabolism, inborn errors; respiratory tract infections; virus diseases; influenza, human; coronavirus.*

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[1] Department of Pediatric Infectious Diseases; [2] Department of Pediatrics; [3] Department of Pediatric Metabolism. Hacettepe University Faculty of Medicine, Ankara, Turkey.

Correspondence to *Yasemin Ozsurekci: yas.oguz99@yahoo.com*

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INTRODUCTION

Inherited metabolic disorders (IMDs) comprise a heterogeneous group of genetic conditions in which the impairment of a metabolic pathway is intrinsic to the pathophysiology of the disease process. These may result in accumulation, deficiency or impaired processing of small or complex molecules, or disrupt energy production, with a wide spectrum of clinical and biochemical manifestations.[1] Owing to their fundamental role in cellular metabolism, these disorders frequently affect multiple organ systems and follow a multisystemic clinical course. In this setting, the close relationship between immune function and cellular energy metabolism places individuals with IMDs at increased risk for infections, which substantially influence the clinical course of disease.[2]

In addition to their direct clinical impact, respiratory tract infections are among the most common triggers of acute metabolic decompensation (AMD) in patients with IMDs, primarily through disruption of metabolic homeostasis and induction of a catabolic state.[2,3] At the molecular level, respiratory viruses can reprogram host cell metabolism to support viral replication, increasing metabolic demands. In patients with IMDs, this additional stress may overwhelm limited metabolic reserve and precipitate AMD.[4,5]

Despite the well-recognized role of infections as major triggers of AMD in IMDs, data on the epidemiology and clinical impact of respiratory viral infections in this population remain limited, highlighting an important gap in the literature that this study aims to address. Therefore, the aim of this study was to evaluate the epidemiology, viral etiology, and clinical severity of respiratory viral infections in children with IMDs, with particular emphasis on pediatric intensive care unit admission, respiratory support requirements, and infection-related outcomes.

MATERIALS AND METHODS

Study design and population

This retrospective observational study was conducted at a tertiary pediatric referral center in Türkiye. The study period spanned from January 2018 to December 2024. Children aged 0–18 years with a diagnosis of an IMDs and laboratory-confirmed respiratory viral detection at admission, presenting with acute infectious symptoms during hospitalization, were eligible for inclusion. Eligibility was based on laboratory-confirmed respiratory viral detection rather than on the primary admission diagnosis. Patients were identified through the hospital electronic medical record system, and demographic characteristics, underlying metabolic diagnoses, clinical presentations, laboratory findings, treatment requirements, influenza vaccination history, and outcomes were extracted.

Patients with incomplete clinical data or inconclusive viral test results were excluded. The unit of analysis was the infection episode rather than the individual patient. Accordingly, multiple admissions from the same patient were included as separate infection episodes. Duplicate specimens obtained within a 2-week period were excluded to avoid counting the same infection episode multiple times. Viral detection was interpreted in the clinical context of acute infection at admission. In some cases, particularly in children with IMDs, infections presented with non-respiratory syndromes (e.g., sepsis-like or neurological manifestations); all were evaluated in the clinical context, with viral detection considered potentially contributory. Respiratory viral infections in children with IMDs may present predominantly with extrapulmonary manifestations or trigger systemic illness and metabolic decompensation.

The study was approved by the Ethics Committee of Hacettepe University Faculty of Medicine (SBA 25/2025), which waived the requirement for informed consent due to its retrospective design.

Definitions

Inherited metabolic disorders were classified according to the primary affected metabolic pathway, including amino acid metabolism, carbohydrate metabolism, mitochondrial disorders, and other relevant categories.[6] Primary diagnoses at admission were categorized as respiratory disease, gastroenteritis, sepsis, or meningoencephalitis. Respiratory support was defined as the requirement for supplemental oxygen via face-mask, non-invasive mechanical ventilation, or invasive mechanical ventilation at any point during hospitalization. Pediatric intensive care unit admission was recorded when patients required close monitoring or advanced respiratory support. Infection-related mortality was defined as death occurring within the first 30 days after laboratory confirmation of viral infection and directly attributable to the infectious episode.[7]

For the purposes of this study, AMD of an IMD was defined as an acute, potentially life-

threatening episode, characterized by rapid onset or deterioration of the clinical or biochemical status directly in relation to the underlying metabolic defect (eg., lactic acidosis in disorders of gluconeogenesis or mitochondrial disorders, ketosis or acidosis in branched-chain organic acidemias, acute symptoms accompanying leucine elevation in maple syrup urine disease, acute encephalopathy in glutaric aciduria type 1, etc.). Acute presentations of the chronic complications of the underlying disorder (eg., new seizure in an IMD patient with accompanying epilepsy, aspiration pneumonia and resultant sepsis in an IMD patient with hypotonia and feeding dysfunction, etc.) that were not a direct consequence of an acute exacerbation of the metabolic defect were not regarded as acute metabolic decompensations.[8–10]

Inherited metabolic disorders were classified as being at risk of acute metabolic decompensation (AMD) according to the pathophysiological classification of inborn errors of metabolism, in which intoxication-type and energy-deficiency disorders predispose to acute decompensation during catabolic stress such as intercurrent illness, whereas disorders of complex molecules typically do not.[9] The AMD-prone category included aminoacidopathies (e.g., maple syrup urine disease), organic acidemias (e.g., propionic acidemia, methylmalonic acidemia, glutaric aciduria type 1), urea cycle disorders (e.g., argininosuccinic aciduria), disorders of carbohydrate metabolism and gluconeogenesis (e.g., glycogen storage disease type Ib, fructose-1,6-bisphosphatase deficiency), and selected mitochondrial disorders. Disorders not typically associated with acute decompensation, such as lysosomal storage disorders (e.g., mucopolysaccharidoses, Pompe disease, Niemann-Pick disease) and Menkes disease, were classified as non-AMD. This classification was applied retrospectively based on the patients' confirmed diagnoses recorded in the medical files.

Virological testing

Respiratory viral pathogens were detected from nasopharyngeal swabs by multiplex RT-PCR, with the panel covering influenza (IFV), parainfluenza (PIV), adenovirus (ADV), seasonal coronavirus (sCoV), enterovirus (EV), rhinovirus (HRV), bocavirus (HBoV), metapneumovirus (hMPV), and RSV.

Statistical analysis

The analyses were conducted using the SPSS for Windows Version 23.0 statistical package (Chicago, IL). Continuous variables are presented as medians with interquartile ranges (Q1–Q3), and categorical variables as frequencies and percentages. Descriptive statistical analyses were performed to characterize demographic data, underlying metabolic diagnoses, clinical presentations, laboratory findings, virological results, and clinical outcomes. Given the limited sample size, the analyses were primarily descriptive. The unit of analysis was the infection episode (45 episodes in 41 patients). Some patients contributed more than one episode, and each episode was analyzed as an independent observation. Given the descriptive nature of the study and the limited sample size, no adjustment for within-patient clustering was performed.

RESULTS

Patient characteristics

A total of 45 viral infection episodes among 41 children with IMDs were included in the study *(Figure 1*). The median age was 4.0 years. The most common metabolic disorder categories were amino acid metabolism disorders (n = 15, 36.6%) and complex molecule degradation and processing defects (n = 11, 26.8%). Respiratory disease was the predominant primary diagnosis, observed in 35 episodes (77.8%). The remaining episodes fulfilled the inclusion criteria based on laboratory-confirmed respiratory viral detection despite presenting with extrapulmonary infectious syndromes. The baseline characteristics of the cohort are summarized in *Table 1.*

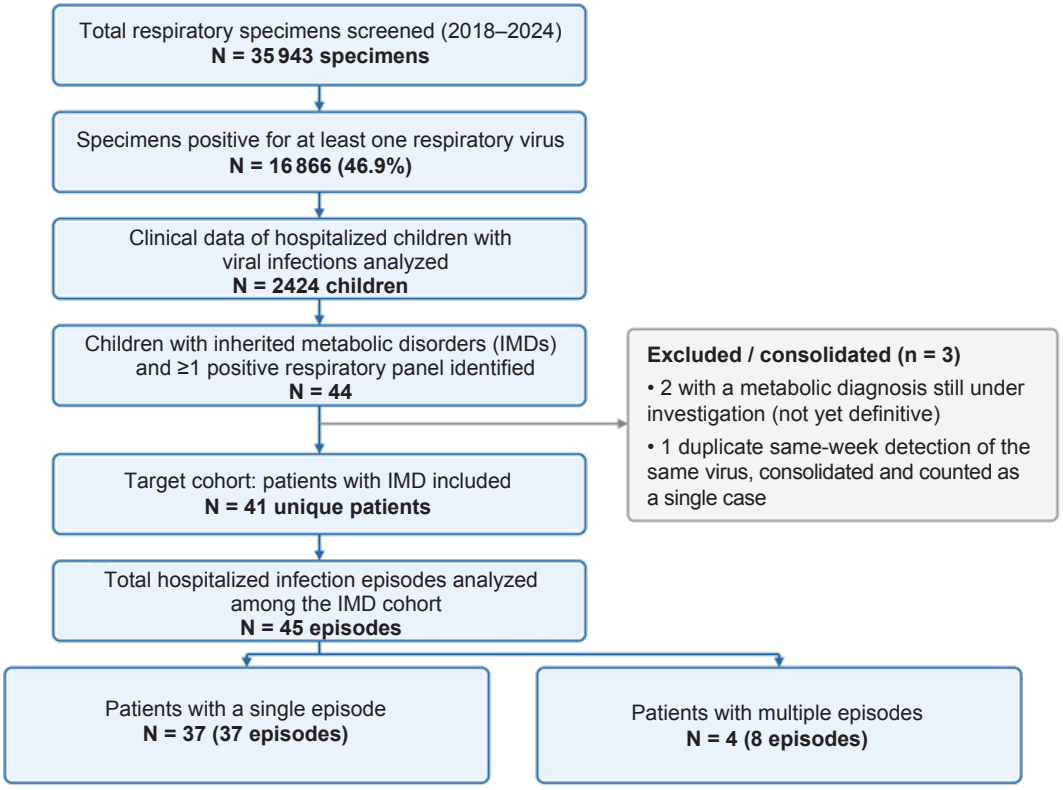
Viral pathogens

Influenza was the most frequently detected viral pathogen, identified in 16 episodes (35.6%), followed by rhinovirus in 10 episodes (22.2%), sCoV in 6 episodes (13.3%), and respiratory syncytial virus in 5 episodes (11.1%), *(Table 2)*. No documented influenza vaccination was identified in any patient included in the study.

Laboratory findings and coinfections

Laboratory parameters at admission are presented in *Table 1*. Bacterial coinfections were identified in 7 of 45 infection episodes (15.6%), most commonly urinary tract infections (n = 5/45, 11.1%), followed by bacteremia and meningitis (n = 1/45, 2.2%). Coinfection patterns were heterogeneous. Viral–bacterial

Figure 1. Study flowchart illustrating patient selection and infection episode analysis



A total of 35 943 respiratory specimens collected between 2018 and 2024 were screened, of which 16 866 (46.9%) tested positive for at least one respiratory virus. Clinical data from 2424 hospitalized children with viral infections were analyzed. Among these, 41 patients with inherited metabolic disorders (IMDs) were identified and included in the study. A total of 45 infection episodes were analyzed, including 37 patients with a single episode and 4 patients with multiple episodes, contributing 8 additional episodes.

coinfections included combinations such as ADV with PIV associated with *Pseudomonas luteola* bacteremia, sCoV with *Klebsiella pneumoniae* urinary tract infection, and rhinovirus with *Escherichia coli* meningitis. In addition, viral–viral coinfections without bacterial co-infection included combinations such as rhinovirus with sCoV, ADV with PIV, ADV with SARS-CoV-2, and RSV with influenza.

Clinical outcomes

Among the 45 episodes, 23 occurred in patients with AMD-prone disorders. During the infection episode, AMD developed in 11 of these 23 episodes (47.8%). Six episodes (13.3%) required admission to the pediatric intensive care unit. Respiratory support requirements according to viral pathogen are summarized in *Table 2*. Among patients with influenza infection, 10 (62.5%) required respiratory support, including invasive mechanical ventilation (IMV) in 2 cases. Invasive mechanical ventilation was required in 8 episodes (17.8%) and was most frequently needed in patients with sCoV (3/6) and coinfections (2/5), followed by RSV (1/5) and influenza (2/6). Because several pathogen groups comprised very few episodes, these proportions are presented for descriptive purposes only and should not be used to infer differences in severity between viral pathogens.

The median length of hospital stay was 6 days (Q1–Q3: 3–14). Infection-related mortality occurred in 3 episodes (6.7%); all three deaths occurred in episodes with detected sCoV (two in mono-detected sCoV episodes and one in a rhinovirus–sCoV coinfection), and none had a concurrent bacterial infection. One fatal episode occurred in a patient with an AMD-prone disorder who decompensated, the other two in non-AMD disorders. As this observation is based on a very small number of cases, it may be influenced by chance.

Table 1. Demographic and clinical characteristics of children with inherited metabolic disorders hospitalized with viral infections

Patient-level characteristics (n = 41)	
Age, year, median (Q1–Q3)	4.0 (0.5-9.5)
Male sex, n (%)	31 (75.6)
Metabolic disorders, n (%)	
Amino acid metabolism	15 (36.6)
Complex molecule degradation and processing defects	11 (26.8)
Phospholipid remodelling	1 (2.4)
Carbohydrate metabolism	4 (9.8)
Mineral/cofactor metabolism	3 (7.3)
Mitochondrial	4 (9.8)
Protein synthesis	1 (2.4)
Peptide metabolism	1 (2.4)
Neurotransmitter defect	1 (2.4)
Episode-level characteristics (n = 45)	
Primary diagnosis, n (%)	
Respiratory disease	35 (77.8)
Gastroenteritis	4 (8.9)
Sepsis	3 (6.7)
Meningoencephalitis	3 (6.7)
Laboratory parameters, median (Q1–Q3)	
White blood cell count, x10^3/µL	6.9 (5.4-11)
Absolute neutrophil count, x10^3/µL	4.1 (2.6-6.7)
Absolute lymphocyte count, x10^3/µL	1.7 (1.0-3.0)
Platelet count, x10^3/µL	224 (139-376)
C-reactive protein, mg/L	2.35 (0.37-11.42)
Alanine aminotransferase, U/L	33 (18-48)
Aspartate aminotransferase, U/L	49 (30-101)
Co-infections (n, %)	
Bacteremia,	1 (2.2)
Urinary tract infection	5 (11.1)
Meningitis	1 (2.2)
Pediatric intensive care unit, n/(%)	6 (13.3)
Respiratory support, n (%)	
None	21 (46.7)
Oxygen via face mask	14 (31.1)
Non-invasive mechanical ventilation	2 (4.4)
Invasive mechanical ventilation	8 (17.8)
Length of hospital stay, median (Q1–Q3)	6 (3-14)
Infection-related mortality, n/(%)	3 (6.7)

Table 2. Respiratory support requirements according to respiratory viral pathogen

Respiratory viral pathogen	No support	Supplemental oxygen	NIMV	IMV
Influenza (n = 16)	6	8	0	2
Rhinovirus (n = 10)	7	3	0	0
Seasonal coronavirus (n = 6)	2	0	1	3
Respiratory syncytial virus (n = 5)	2	2	0	1
Parainfluenza (n = 2)	0	1	1	0
Adenovirus (n = 1)	1	0	0	0
Coinfection (n = 5)	3	0	0	2
Total (n = 45)	**21 (46.7)**	**14 (31.1)**	**2 (4.4)**	**8 (17.8)**

Data are presented as number of cases within each pathogen group. NIMV, non-invasive mechanical ventilation; IMV, invasive mechanical ventilation. Given the small number of patients in several groups, values should be interpreted with caution.

DISCUSSION

In this study, we evaluated the clinical impact of respiratory viral infections in children with IMDs and demonstrated that these infections are associated with a substantial clinical burden, frequently requiring respiratory support and, in a notable proportion of cases, pediatric intensive care unit admission. Our findings emphasize that viral infections in this population are not benign intercurrent events.

Respiratory viral infections are increasingly recognized to cause extrapulmonary manifestations, including neurological, cardiovascular, and gastrointestinal involvement.[11–13] This explains why a minority of patients in our cohort presented with gastroenteritis, sepsis-like illness, or neurological syndromes despite laboratory-confirmed respiratory viral infection.

Children with IMDs are particularly vulnerable to infections due to the close interdependence between energy metabolism and immune function.[2] Many IMDs are associated with chronic multisystem involvement predisposing patients to ineffective airway clearance and reduced respiratory reserve.[14,15] Therefore, our results highlight the importance of investigating respiratory viruses, as they represent one of the most common causes of lower respiratory tract infections in children.

Influenza was the most frequently identified virus and was frequently associated with the need for respiratory support, including invasive mechanical ventilation, underscoring its potential severity in children with IMDs. The strong inflammatory and catabolic response induced by influenza can rapidly overwhelm the limited metabolic reserve of children with IMDs, driving clinical deterioration.[2–4,16] This may be contextualized by the immunometabolic role of the liver: influenza-triggered innate immune activation can depress vital pathways such as fatty acid oxidation and ureagenesis, precipitating the acute decompensations observed in our cohort.[17,18]

In our previous study about the outcome predictors of influenza for hospitalization and mortality in children, IMD constituted 9.1% of the underlying conditions among children admitted to the intensive care unit with influenza. Although metabolic disorders were not evaluated as a distinct risk group in multivariable analyses, our current findings build upon these data by specifically demonstrating the substantial clinical burden of influenza in children with IMDs.[19] The American Academy of Pediatrics recommends prioritizing influenza vaccination for individuals with chronic metabolic diseases due to their high complication risk.[20] Unfortunately, none of the patients with influenza infection in our cohort had documented influenza vaccination prior to hospitalization. This finding is consistent with previously reported low vaccination rates in Türkiye, both in the general pediatric population and in high-risk groups.[21] This suboptimal vaccine uptake is further mirrored in international multicenter data, which demonstrate that even in developed healthcare settings, influenza immunization coverage remains critically low (around 30–35%) among at-risk children with IMDs, leaving them highly exposed to vaccine-preventable metabolic crises.[22]

In our cohort, sCoV accounted for 13.3% of all detected viral infections and represented the third most frequently identified respiratory virus after influenza and rhinovirus. Although typically mild in immunocompetent children, sCoV was detected with all three infection-related deaths in our cohort, suggesting that host metabolic vulnerability may play a role in modifying disease severity. Interestingly, AMD was documented in only one of the fatal cases, suggesting that severe viral infection itself, rather than metabolic decompensation alone, may primarily drive adverse outcomes in this population. Experimental data further show that coronaviruses significantly alter host cellular pathways to facilitate replication, which may exacerbate underlying metabolic vulnerabilities.[4] Given the limited data on sCoV infections in children with IMDs, our findings add novel information to the existing literature. Although the clinical impact of SARS-CoV-2 in patients with IMDs has been increasingly described,[3,23–26] evidence regarding sCoV in this population is still lacking. These results may highlight the importance of heightened clinical awareness, early supportive management, and close metabolic and respiratory monitoring when sCoV is detected, particularly in children with metabolically vulnerable disorders. However, given the limited number of sCoV episodes, this association should be interpreted with caution and regarded as a hypothesis-generating observation rather than evidence of pathogen-specific severity.

In a multicenter prospective study from Japan, children with IMD were included among rare disease groups targeted for palivizumab prophylaxis because of their vulnerability to severe RSV infection.[27] Although RSV-infected patients in our cohort (11.1%) experienced

relatively favorable short-term outcomes with no infection-related mortality, this well-recognized respiratory vulnerability strongly reinforces the critical importance of maintaining strict preventive strategies, including RSV immunoprophylaxis, to avert severe lower respiratory tract complications in this high-risk population.

Another notable finding in our cohort was the predominance of male patients. While most IMDs are not expected to show a sex-specific distribution, previous studies have suggested that viral respiratory infections, particularly in early childhood, may be more frequent or more severe in males.[9] This has been attributed to potential differences in airway anatomy and immune responses; however, the evidence remains inconsistent.[28,29] Therefore, the male predominance observed in our cohort may reflect a combination of these factors, as well as the relatively small sample size and cohort-specific characteristics.

This study has several limitations. Its small sample size precluded pathogen-specific multivariable analyses; the data are therefore purely descriptive, and the apparent clustering of fatal outcomes among sCoV episodes should be regarded as hypothesis-generating rather than evidence of a pathogen-specific difference in severity. Because the unit of analysis was the infection episode and some patients contributed more than one episode, these were treated as independent observations, and the potential non-independence of observations within patients could not be accounted for. Viral load, metabolic parameters reflecting acute metabolic decompensation, and long-term post-discharge outcomes were not systematically evaluated. The COVID-19 pandemic period may also have introduced bias, including lower hospitalization thresholds for high-risk patients, shifts in viral epidemiology, and wider use of multiplex PCR, which may have increased detection rates, including incidental findings. Finally, PCR detection of viral nucleic acid does not establish causality, and incidental detection or prolonged shedding cannot be excluded, particularly in young children.[30,31] Despite these limitations, the study provides valuable real-world data on respiratory viral infections in children with IMDs, a population for whom evidence remains limited.

CONCLUSION

In conclusion, respiratory viral infections in children with IMDs carry a considerable clinical burden. Influenza was the most common pathogen, all three infection-related deaths occurred in episodes with detected sCoV; however, given our small, single-center retrospective design, these pathogen-specific observations remain exploratory. These findings emphasize that respiratory viral infections in children with IMDs should not be considered as benign intercurrent events. Implementation of preventive strategies, particularly influenza vaccination, alongside early recognition, close metabolic and respiratory monitoring, and timely supportive care, are essential to improve clinical outcomes in this vulnerable population. ■

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