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The role of respiratory viruses in children with humoral immunodeficiency on immunoglobulin replacement therapy

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Abstract

Background: The role of viruses in children with respiratory tract infections and humoral immunodeficiencies has hardly been studied. We have evaluated these infections in children with humoral immunodeficiencies who required immunoglobulin replacement therapy, considering their relationship with symptoms, lung function, bacterial co-infection, and outcomes.

Methods: We conducted a prospective case-control study during a 1-year period, including children with humoral immunodeficiencies receiving immunoglobulin replacement therapy. For each patient, at least one healthy family member was included. Respiratory samples for viral detection were taken every 1-3 months, and in case of respiratory tract infections. Symptoms questionnaires were filled biweekly. Spirometry and sputum culture were performed in every episode.

Results: Sixty-six episodes were analyzed in 14 patients (median age 12 years; IQR 7-17), identifying 18 respiratory viruses (27.3%), being rhinovirus the most frequently isolated one (12/18; 66%). Positive viral episodes were associated with clinical symptoms (89% vs 43%), more frequent antibiotic treatment (44% vs 15%) or hospital admission (22% vs 0%) than negative ones. Patients with positive viral detection showed impaired lung function, with lower FEV1 and FVC values.

Conclusions: In our experience, viral respiratory tract infections can cause significant respiratory symptoms and impaired lung function, in children with HID, despite immunoglobulin replacement therapy. These patients could benefit from the monitoring of viral infections, as these may be a gateway for ongoing lung damage.

KEYWORDS
humoral immunodeficiency, immunoglobulin replacement therapy, lung function, respiratory tract infection, virus

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Marta Benavides-Nieto and Ana Méndez-Echevarría are share first authorship.

1 | INTRODUCTION

Children with severe T-cell immunodeficiencies present impaired clearance of respiratory viruses, and pulmonary complications of viral infections are leading causes of morbidity and mortality in this group of patients.[1]

However, the role of respiratory viruses in children with other types of primary immunodeficiency (PID), mainly those with humoral immunodeficiencies (HID) or diseases of immune dysregulation, has hardly been studied.

Children with HID usually suffer from recurrent bacterial respiratory infections, resulting in progressive bronchiectasis and chronic lung disease.[2–5] Immunoglobulin replacement therapy (IRT) reduces the frequency of these infections. However, despite adequate IRT, recurrent respiratory infections are still one of the leading causes of morbidity and mortality in these patients.[2–4]

Little data are currently available regarding the susceptibility to respiratory viruses of hypogammaglobulinemic patients receiving IRT.[4,6,7] However, some other viruses have been described which play significant roles in these patients.[8–11] Human herpesvirus 8 (HHV-8) has been associated with granulomatous/lymphocytic interstitial lung disease (GLILD) in patients with common variable immunodeficiency (CVID),[8] and enterovirus is a known cause of fatal meningoencephalitis in patients with X-linked agammaglobulinemia (XLA).[9,10] In addition, there are several recent reports showing an increased susceptibility to viral respiratory infections in adults with CVID receiving IRT,[4–7] that can contribute to chronic and persistent pulmonary inflammation.[2,7]

We report, to the best of our knowledge, the first study that analyses respiratory viruses in pediatric patients with predominantly antibody deficiency who required IRT, considering their relationship with clinical symptoms and pulmonary function, bacterial co-infection, treatment and outcomes.

2 | PATIENTS AND METHODS

We conducted a prospective case-control single-center study during 1 year (November 2016 to October 2017) in a National Reference Unit for PID in Madrid, Spain.

We included patients less than 18 years of age diagnosed with HID who required IRT. Patients with combined immunodeficiency and/or reduced proliferative responses to mitogens (PHA, PWM, ConA) were excluded. Patients with HID who did not require IRT and/or patients receiving immunosuppressive treatments other than rituximab were excluded.

The study was approved by the local Clinical Research Ethics Committee. Informed consents were obtained from patients and parents.

For each patient, a healthy control was included, usually one of their parents. Respiratory samples (nasopharyngeal aspirate [NPA] for patients and nasopharyngeal swab for controls) were obtained every one to three months, coinciding with intravenous immunoglobulin administration or outpatient clinic evaluations, both in the patient and in the control group. Other investigations performed during the same visit in the patient group included: spirometry (in patients older than 5 years), spontaneous sputum culture (in patients older than 10 years), IgG levels, full blood count (FBC), C-reactive protein, and erythrocyte sedimentation rate (ESR).

If patients developed respiratory symptoms between visits, additional sputum culture and nasopharyngeal aspirates were performed in the first 3 days after symptom onset, as well as an additional spirometry. In children older than 10 years of age who needed antibiotic for treating respiratory infections, the sputum samples were obtained before starting the therapy. Every moment in which a respiratory sample was obtained from a patient was defined as an episode.

Symptoms questionnaires elaborated ad hoc were filled out systematically biweekly by patients and controls, recording fever, increased respiratory secretions, cough, respiratory distress, sputum (increased production, change in its characteristics), absenteeism from school and/or work, need for steroids, bronchodilators or antibiotic therapy, and hospital admission. Respiratory symptoms for each subject in each episode were classified as none, mild or moderate/severe using a score based on the questionnaire (See supplementary file). Respiratory symptoms were classified as asymptomatic (0 points), mild symptoms (2 point or less), or moderate/severe symptoms (3 or more points).

Values are expressed as percentages for discrete variables, and as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Due to the small number of patients included in both groups, no statistical comparisons were made.

2.1 | Respiratory tract infections and viruses: Microbiological analysis

NPA and nasopharyngeal swabs were sent for virological investigation to the Influenza and Respiratory Viruses Laboratory at the National Center for Microbiology (ISCIII), Madrid, Spain. Samples were processed within 24 h after collection. Upon reception, three aliquots were prepared and stored at −80°C. Both the reception and the NPA sample processing areas are separated from those defined as working areas.

Three independent RT-PCR assays were performed to detect sixteen respiratory viruses as previously published by our group.[12–14] Influenza A, B, and C viruses were detected by using previously described primer sets only to amplify influenza viruses in a multiplex PCR assay.[12] A second multiplex PCR was used to detect parainfluenza viruses 1-4, human coronaviruses 229E and OC43, enteroviruses, and rhinoviruses (RV).[13] Presence of respiratory syncityal virus (RSV) A and B types, human metapneumovirus, human bocavirus, and adenoviruses were investigated by a third multiplex RT-nested PCR-BRQ method.[14]

Spontaneous sputum samples were collected using sterile specimen containers and immediately processed or stored at 4°C until

processing was feasible. Samples were cultured on standard media, and potential respiratory tract pathogens were identified and tested for antimicrobial susceptibility.

2.2 | Lung function testing

Pulmonary function tests were performed on all patients at study entry and repeated with every sample collection. Spirometry was performed according to established guidelines[15] using a Jaeger MasterScope-PC spirometer (VIASYS HealthCare GmbH, Hoechberg, Germany). The Z-scores were derived for each participant using norms from the Global Lung Function Initiative (GLI) basing specially on developed software (GLI-2012 desktop software for individual calculations; http://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools/desktop-individual-calculator.aspx). The GLI severity classification based on the FEV1 Z score was employed: mild (≥−2.0), moderate (−2.5 to −2.0), moderately severe (−3.0 to −2.5), severe (−4.0 to −3.0), and very severe (<−4.0)].[16]

3 | RESULTS

During the study period, 14 patients with predominantly antibody deficiency were included (5 girls and 9 boys). Their main immunological diagnoses are reported in Table 1.

The median age of patients was 12 years (IQR 7-17), and only two of them were younger than 5 years. Eleven patients were receiving intravenous IRT and three patients, subcutaneous IRT. Immunological status at inclusion is described in Table 2.

Eighteen healthy adult family members (mother and/or father) of the patients were included as healthy control subjects (at least one control per case included).

Sixty-six episodes were analyzed in 14 patients (median number of samples per patient: 4; IQR 1-6). There were 18 (27.3%) with a positive viral detection: 12 rhinovirus, 3 adenovirus, and 1 case each of influenza-A, respiratory syncytial virus (RSV), and coinfection rhinovirus-coronavirus (Table 1). Six patients had no positive samples, coinciding with those who had fewer number of samples collected. The median of positive samples per patient was 1 (IQR 0-3).

A total of 57 respiratory samples were collected from healthy controls, and viruses were identified in 12 (21%): eight rhinovirus, three coronavirus, and one influenza. Only in two occasions (2/18; 11%) the same virus (rhinovirus) was simultaneously identified in both patient and control episodes. No significant differences were found regarding the viral isolation rate between patients and healthy controls.

Sputum cultures were available in 19 episodes of older children, being positive in 16 (84%). Haemophilus influenzae was isolated in all cases but one (co-isolation of Streptococcus pneumoniae/Pseudomonas aeruginosa).

IgG levels were available in 47 episodes. In six of them (15%) they were <600 mg/dL.

Median IgA level was 0 (IQR 0-14.7).

3.1 | Comparison between episodes with positive and negative viral detection

Episodes with positive viral detection (n = 18) were associated with respiratory symptoms in 89% of cases (16/18) and 44% of controls.

Regarding respiratory symptoms in the viral positive cases, 27.8% (5/18) of them were mild, 61.1% moderate/severe (11/18) and, only 2 (11%) were asymptomatic. Episodes with negative viral detection were less frequently associated with respiratory symptoms than positive episodes 42.5% (20/47) versus 89% (16/18) with 25.5% of them presenting mild symptoms and 38.3% severe. Episodes with positive viral detection were associated with impaired lung function, higher levels of antibiotic prescribing and hospital admission (Table 3).

4 | DISCUSSION

Our results suggest that viral respiratory tract infections may play an important role in children with predominantly antibody deficiencies. In our experience, presence of respiratory symptoms, negative bacterial sputum culture, impaired lung function, antibiotic prescription, and hospital admission were significantly associated with viral detection.

Some authors have already reported how respiratory viral infections seem to play a role in adults with HID.[7–17] These studies have reported viral detection rates in 41-56% of respiratory exacerbations, being rhinovirus the most frequently identified.[4,5,7] These episodes are more frequently symptomatic in HID patients compared to healthy controls,[6,7] as we have observed.

However, the role of viral respiratory infections in children with HID has hardly been analyzed, and the mechanisms of increased susceptibility to some viral respiratory infections in these patients are not well known.[17]

IRT may not offer protection at the mucosal surface, as IgA and IgM are not replaced with immunoglobulin products.[4] IgM is highly effective for agglutination, especially of viruses.[17] In addition, Duraisingham et al observed that patients with HID and respiratory viral infection presented lower levels of IgA than patients with negative viral results.[4] In our series, patients with positive viral detection presented adequate IgG levels, but very low IgA levels, which could favor these infections.

Some authors have also suggested that antibodies originating in the lymphatic tissue of the respiratory mucosa may play a more important role than systemic antibodies against pulmonary and sinus infection.[3,17] In addition, persistent viral infections could result in chronic antigen stimulation in the context of a dysregulated immune system, and could exacerbate inflammatory disorders.[4,7]

In our study, bacterial sputum cultures were more frequently positive in children with negative virological tests. However, antibiotic prescription was higher in patients with viral respiratory infection, as an important percentage of our patients with positive viral episodes associated respiratory symptoms, and the results of viral tests were not available early during the episode. Duraisingham et al observed that most positive viral samples of their study were obtained from patients with negative bacteriologic results.[4] Sperlich

TABLE 1 Patients, diagnoses, pulmonary status at enrolment, and positive episodes

Case	Diagnosis	Bronchiectasis at enrolment	Lung function at enrolment	Gender	Age: years	Positive episodes	Symptomatic during viral episodes
1	CTLA-4 haploinsufficiency	No	Restrictive	Female	11.7	ADV (January)	Yes
						RV (April)	Yes
						Coronavirus + RV (September)	No
2	CVID	No	Restrictive	Female	12.5	RV (December)	Yes
						RV (April)	Yes
						RV (June)	Yes
3		No	Restrictive	Female	16.9	-	
4	XLA	No	Normal	Male	18.8	RV (December)	Yes
						Influenza A (February)	Yes
						RV (September)	Yes
5		No	Normal	Male	5.7	-	
6		Yes	Normal	Male	17.8	-	
7	ARA	No	Normal	Female	7.8	RV (November)	Yes
						RV (June)	Yes
8		No	NA	Male	4.8	ADV (September)	Yes
						RV (October)	Yes
						ADV (November)	Yes
9	B-cell lymphopenia after HSCT due to CID more than 3 years ago	Yes	Normal	Male	7.6	-	
10		No	Normal	Male	15.3	RSV(January)	Yes
11		No	Normal	Male	18	-	
12	APDS2	No	Normal	Male	14.9	-	
13	AD-HIES	Yes	Normal	Female	12	RV (November)	No
						RV (September)	Yes
14	Secondary HID after rituximab for refractory nephrotic syndrome	No	NA	Male	4.7	RV (December)	Yes

AD-HIES, autosomal dominant Hyper IgE syndrome; ADV, adenovirus; APDS2, activated PI3 kinase delta syndrome; ARA, autosomal recessive agammaglobulinemia; CID, combined immunodeficiency; CVID, common variable immunodeficiency; HID, humoral immunodeficiency; HSCT, hematopoietic stem cell transplantation; NA, not available (young children); RSV, respiratory syncytial virus; RV, rhinovirus; XLA, X-linked agammaglobulinemia.

et al also reported that viruses are commonly present in adults with CVID and upper respiratory tract symptoms that respond poorly to antibiotics,[5] suggesting that antibiotic usage could be better targeted.

On the other hand, other authors have hypothesized that persistent and recurrent viral respiratory infections could adversely affect the microbiome, leading to an increased bacterial density in children's nasopharyngeal tract, predisposing to sinopulmonary bacterial infections.[17,18] As other authors,[4] we recommend screening for viral infection in children with HID and acute respiratory symptoms to avoid unnecessary antibiotic treatment. However, viral testing is routinely performed only in children with severe combined immunodeficiency (SCID).[1,4] Regarding HID, protocols present a great deal of variation across Europe in the management of lung complications.[19]

There is an urgent need for consensus guidelines on how to monitor lung complications and how to treat respiratory infections in HID patients.[19]

Not all our patients were typical HID such as XLA or CVID. Three of our cases were SCID patients who had received a hematopoietic cell transplant, but presented persistent B-cell lymphopenia and hypogammaglobulinemia. Although most children with SCID recover cellular immunity 1 year after transplantation, many patients are likely to be on IRT for a considerable period until full reconstitution of B-cell immunity has been achieved.[20,21] B-cell immune reconstitution and its consequences regarding viral respiratory infections have not been deeply investigated in these patients. Our data support that these patients are also prone to viral respiratory infections, which impact lung function and lead to antibiotic consumption.

TABLE 2 Immunologic studies of cases at the moment of inclusion (n = 14)

	Median values
Median neutrophil count	3400/µL (IQR; 1355-4970)
Median lymphocyte count	1470/µL (IQR; 1092-2185)
Median T-cells	
CD3+ % (count)	89.5% (1347/µL; IQR 830-1977)
CD4+ % (count)	44.5% (555/µL; IQR 400-975)
CD8 + % (count)	38% (706/µL; IQR 257-825)
Median B-cells CD19+ % (count)	4% (53/µL; IQR 0-164)
Median NK-cells CD56 + CD3− % (count)	7% (89/µL; IQR 47-210)
Median IgA	0 mg/dL (IQR; 0-16)
Median IgM	42 mg/dL (IQR; 1-150)

Another patient was an AD-HIES. Regarding humoral immunity, many patients with AD-HIES require immunoglobulin infusions due to memory B-cell lymphopenia and decline in specific antibody titers.[22] Recurrent respiratory tract infections have been described in these children, and more than 90% of them develop pneumonia.[22] Although bacteria are detected in 44% of respiratory exacerbations, viral pneumonia has also been reported.[22] Lung sequelae in these patients are frequent, mainly as bronchiectasis.[22] Thus, monitoring viral infections in these children may be important.

One patient in our series suffered from APDS2. While the disease is heterogeneous, respiratory infections and their complications are frequent and often severe.[23] The spectrum of pathogens is highly reminiscent of other primary antibody deficiency syndromes such as CVID.[23] Coulter et al[24] noted that significant adenovirus infections occurred in 17% of their cohort; other viruses commonly identified during respiratory exacerbations included RSV, parainfluenza, echovirus, and coxsackie.

Finally, one patient had no PID, but he developed persistent B-cell lymphopenia with secondary hypogammaglobulinemia requiring IRT 1 year after receiving rituximab for treating steroid-resistant nephrotic syndrome. Rituximab was the first anti-CD20 monoclonal antibody, and the development of persistent hypogammaglobinemia after its use has been reported in children.[25] Recent clinical studies highlight that some patients may develop a clinical condition similar to CVID, with the degree of hypogammaglobulinemia being directly associated with infection rates.[23] These infections, including severe respiratory tract infection, remain the most common non-hematological adverse effect of anti-CD20 monoclonal antibodies.[25] However, the clinical impact of hypogammaglobulinemia induced by CD20-targeted therapy remains unclear.

Our study has several limitations. We have included a small number of patients who suffer from different types of HID with

TABLE 3 Comparison between episodes with positive and negative viral detection in children with humoral immunodeficiencies

	Negative-virus episodes	Positive-virus episodes
Number of episodes	48	18
No symptoms	57% (27/47)	11% (2/18)
Bronchodilator treatment	15% (7/47)	2% (4/18)
Antibiotic treatment	15% (7/47)	44% (8/18)
Hospital admission	0% (0/48)	22% (4/18)
IgG levels <600 mg/dL	15% (5/34)	15% (2/13)
IgA levels mg/dL (mean ± SD)	7 ± 11	11 ± 13
Blood lymphocyte count (cells/mm^3) (mean ± SD)	1485 ± 598	1505 ± 632
C reactive protein (mg/L) (mean ± SD)	3.9 ± 3	2.6 ± 3
H influenzae in sputum culture	93% (13/14)	40% (2/5)
FEV1 < 80% and/or FEV1/FVC < 70	24% (9/37)	70% (7/10)
FVC < 80%	16% (6/37)	70% (7/10)
%FEV1 (mean ± SD)	96 ± 16	84 ± 11
%FVC (mean ± SD)	96.3 ± 18	82.5 ± 14
z score FEV1 (mean ± SD)	−0.9 ± 1.1	−1.8 ± 1.2
z score FVC (mean ± SD)	−0.7 ± 1.3	−1.8 ± 1.3
z score FEV1 < −2	19% (7/37)	50% (5/10)

FEV1, forced expiratory volume in first second; FVC, forced vital capacity; SD, standard deviation.

varying molecular mechanisms. Despite the heterogeneity of the cases, our results indicate the significant role of viral respiratory infections in these children, in terms of clinical symptoms, lung function, antibiotic prescription, and hospital admission. We have also observed that viral isolation is more frequently associated with symptoms in cases compared with healthy controls although both groups are different in terms of age and immunity and do not allow direct comparisons. Further studies should ideally include age-matched healthy controls, to better assess the impact of viral infections in children with humoral immunodeficiency. However, Peltola et al[6] have reported that the duration of symptoms and of rhinovirus shedding was longer in adults with HID than in healthy children. For this reason, we expect that respiratory viruses might cause more symptoms in these patients compared with healthy children, although we have not been able to prove it. In spite of the limitations, respiratory viral infections seem to play a role in children with HID, as has also been described in adults.[7,17]

Further studies are needed to improve our knowledge about the impact of respiratory viral infections, their prevention and management in children with IRT, with the aim of avoiding short- and long-term consequences.

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REFERENCES

1. Méndez-Echevarría A, Del Rosal T, Pérez-Costa E, et al. Clinical features before hematopoietic stem cell transplantation or enzyme replacement therapy of children with combined immunodeficiency. *Pediatr Infect Dis J*. 2016;35:794–798.
2. Verma N, Grimbacher B, Hurst JR. Lung disease in primary antibody deficiency. *Lancet Respir Med*. 2015;3:651–660.
3. Jolles S. Subclinical infection and dosing in primary immunodeficiencies. *Clin Exp Immunol*. 2014;178:67–69.
4. Duraisingham SS, Manson A, Grigoriadou S, Buckland M, Tong CY, Longhurst HJ. Immune deficiency: changing spectrum of pathogens. *Clin Exp Immunol*. 2015;181:267–274.
5. Sperlich JM, Grimbacher B, Workman S, et al. Respiratory infections and antibiotic usage in common variable immunodeficiency. *J Allergy Clin Immunol Pract*. 2018;6:159–168.e3.
6. Peltola V, Waris M, Kainulainen L, Kero J, Ruuskanen O. Virus shedding after human rhinovirus infection in children, adults and patients with hypogammaglobulinaemia. *Clin Microbiol Infect*. 2013;19:E322–E327.
7. Kainulainen L, Vuorinen T, Rantakokko-Jalava K, Österback R, Ruuskanen O. Recurrent and persistent respiratory tract viral infections in patients with primary hypogammaglobulinemia. *J Allergy Clin Immunol*. 2010;126:120–126.
8. Park JH, Levinson AI. Granulomatous-lymphocytic interstitial lung disease (GLILD) in common variable immunodeficiency (CVID). *Clin Immunol*. 2010;134:97–103.
9. Bearden D, Collett M, Quan PL, Costa-Carvalho BT, Sullivan KE. Enteroviruses in X-linked agammaglobulinemia: update on epidemiology and therapy. *J Allergy Clin Immunol Pract*. 2016;4:1059–1065.
10. Winkelstein JA, Marino MC, Lederman HM, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. *Medicine (Baltimore)*. 2006;85:193–202.
11. Rezaei N, Hedayat M, Aghamohammadi A, Nichols KE. Primary immunodeficiency diseases associated with increased susceptibility to viral infections and malignancies. *J Allergy Clin Immunol*. 2011;127:1329–41.e2.
12. Coiras MT, Perez-Brena P, Garcia ML, Casas I. Simultaneous detection of influenza A, B, and C viruses, respiratory syncytial virus, and adenoviruses in clinical samples by multiplex reverse transcription nested-PCR assay. *J Med Virol*. 2003;69:132–144.
13. Coiras MT, Aguilar JC, Garcia ML, Casas I, Pérez-Breña P. Simultaneous detection of fourteen respiratory viruses in clinical specimens by two multiplex reverse transcription nested-PCR assays. *J Med Virol*. 2004;72:484–495.
14. Calvo C, Pozo F, García-García ML, et al. Detection of new respiratory viruses in hospitalized infants with bronchiolitis: a three-year prospective study. *Acta Pediatr*. 2010;99:883–887.
15. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:319–338.
16. Quanjer PH, Pretto JJ, Brazzale DJ, et al. Grading the severity of airways obstruction: new wine in new bottles. *Eur Respir J*. 2014;43:505–512.
17. Baumann U, Routes JM, Soler-Palacín P, Jolles S. The lung in primary immunodeficiencies: new concepts in infection and inflammation. *Front Immunol*. 2018;9:1837.
18. Molyneaux PL, Mallia P, Cox MJ, et al. Outgrowth of the bacterial airway microbiome after rhinovirus exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;188:1224–1231.
19. Jolles S, Sánchez-Ramón S, Quinti I, et al. Screening protocols to monitor respiratory status in primary immunodeficiency disease: findings from a European survey and subclinical infection working group. *Clin Exp Immunol*. 2017;190:226–234.
20. Heimall J, Logan BR, Cowan MJ, et al. Immune reconstitution and survival of 100 SCID patients post-hematopoietic cell transplant: a PIDTC natural history study. *Blood*. 2017;130:2718–2727.
21. Lev A, Simon AJ, Bareket M, et al. The kinetics of early T and B cell immune recovery after bone marrow transplantation in RAG-2-deficient SCID patients. *PLoS ONE*. 2012;7:e30494.
22. Chandesris MO, Melki I, Natividad A, et al. Autosomal dominant STAT3 deficiency and hyper-IgE syndrome: molecular, cellular, and clinical features from a French national survey. *Medicine (Baltimore)*. 2012;91:e1–19.
23. Condliffe AM, Chandra A. Respiratory manifestations of the activated phosphoinositide 3-kinase delta syndrome. *Front Immunol*. 2018;9:338.
24. Coulter TI, Chandra A, Bacon CM, et al. Clinical spectrum and features of activated phosphoinositide 3-kinase δ syndrome: a large patient cohort study. *J Allergy Clin Immunol*. 2017;139:597.e–606.e.
25. Mikulska M, Lanini S, Gudiol C, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). *Clin Microbiol Infect*. 2018;24:S71–S82.

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