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EDITORIAL

The linguistic barrier of science for no-native english speakers

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In recent years, several papers have been published on the challenges faced by no-native English-speaking researchers in their publications in English-language journals. Journals with the highest Impact Factor are in English language, and researchers understand what it means to publish in such journals (1). Beyond prestige and personal satisfaction, this serves to attract new contributions for research, and is directly related with promotion, prestige, and academic positions (2).

In a study published in PLOS Biology in July 2023, a group of authors from various nationalities distributed a questionnaire to students and researchers for data collection, which was then processed in a centralized manner (3). Participants involved researchers from 8 countries, some native English speakers (including some from United Kingdom), and others no-native English speakers. The survey aimed to quantify the effort required by individual researchers to perform 5 types of scientific activities in English and in their first language (reading articles, writing, publishing and dissemination, participating in conferences) and compare the estimated effort among researchers with different linguistic and economic backgrounds.

The authors used the values of English-speaking countries as reference for data processing.

The paper had 908 participants with an average age of 39 years (range 18-77 years) and a median research dedication of 13 years. The results are surprising. No-native English speakers take 91% more time to read an article and 51% more time to write one in English. They experienced a rejection rate 2.6 times higher and a revision rate 12.5 times higher.

This is also clearly demonstrated in another study where authors made a randomized control study in which scholars judged the scientific quality of several scientific abstracts (4). Each abstract had two versions with identical scientific content, but the language in one version was conformed to standards for international academic English, and the language in the other version was not (but it was still comprehensible). Scholars may give abstracts lower ratings of scientific quality when the writing does not conform to standards of international academic English; and this leads to rejection of the paper in English-language journals. These results unequivocally demonstrate that fluent English speaker researches from economically affluent states have several advantages that make them publish more than others in prestigious journals.

KEY WORDS
Linguistic barrier; no-native English speakers; researchers.

Participation in Conferences

Regarding conference participation, the authors of the article published in PLOS (3) demonstrated that no-native English speakers need 94% more time

to prepare and practice an oral presentation, 30% often decide not to participate in the conference, and 50% decide not to give an oral presentation. This well-established habit causes a significant scientific loss, as researchers miss out on what they could contribute if they could present in their native language, different from English. There are no automatic translation systems (e.g., Google Translate) that can overcome this handicap. A solution proposed by the authors of this article is to encourage a greater use of languages from other nations in presentations and reports at conferences. The authors suggest efforts by journals and congress organizations of various scientific societies to avoid losing the additional contributions that researchers could bring, currently hampered by translations, in accordance with UNESCO's recommendations (5).

Preparation of Scientific Journals and Books

As for the translation of articles, since English writing will continue to dominate major scientific journals, the use of Artificial Intelligence (AI) in the near future could be of great utility. However, the debate on the use of AI in the scientific world is still very intense, particularly in opposing views. Some believe that the use of Large Language Models (LLM) like ChatGPT in producing scientific content should be excluded "a priori" as it would not produce "original" products (6). Others argue that, when used appropriately, these tools can improve equity in science, alleviating current linguistic disparities (7).

This perspective seems to be shared by many. In an interview conducted by Nature on the potential major benefits of generative AI for science, the most popular response among the 1600 respondents was that it would help researchers who do not have English as their first language (8).

We strongly agree with this position and we hope that a conscious use of these new technologies can simplify the dissemination of knowledge from researchers of all countries, mitigating the linguistic barriers that hinder the sharing of scientific research by no-native English speakers.

(Our is an example of a text translated with the assistance of the ChatGPT Chatbot)

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RESEARCH ARTICLE

Evaluation of platelet indices as early biomarkers for bacterial infections in pediatric emergency departments

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ABSTRACT

Discriminating bacterial from viral etiology of infectious diseases can be challenging in pediatric age, especially during the first year of life and even more in an emergency setting. Recent research has identified in platelet indices a potential biomarker for bacterial infections, nonetheless current results remain inconsistent. The primary objective of this retrospective observational study was to assess the ability of platelet indices to distinguish bacterial from viral infections in infants presenting to the emergency department. As secondary endpoints, it aimed to evaluate these indices in differentiating upper from lower urinary tract infections and bacterial from viral pneumonias. The present study included 236 patients younger than 12 months consecutively admitted for urinary tract infections, bronchiolitis, pneumonia or gastroenteritis to our Pediatric Emergency Department. Blood cells count was performed in each patient at admission and PLT indices (platelet count, mean platelet volume-MPV and platelet distribution width) were extracted from medical charts. Children with suspected bacterial diseases had slightly lower PLT and PLT/MPV ratio compared to those with suspected viral infections. None of the platelet indices showed significant differences between upper and lower urinary tract infections. A slight decrease in PLT, MPV and PLT/MPV was recorded in infants with bacterial pneumonias compared to those with viral forms. Platelet indices have not proved effective in defining the bacterial etiology of an infectious in children younger than 12 months. They do not discriminate between lower and upper urinary tract infections, nor between bacterial and viral pneumonias.

HIGHLIGHTS BOX

What is already known about this topic? Discriminating bacterial from viral etiology of infectious diseases can be challenging. Increasing evidence points out the role of platelet indices as biomarkers of bacterial infections. **What does this article add to our knowledge?** Platelet indices do not discriminate between lower and upper urinary tract infections, nor between bacterial and viral pneumonias. **How does this study impact current management guidelines?** The accuracy of the available biomarkers in discriminating the etiology of an infectious process in the paediatric population remains limited. More studies are needed to fill this gap.

ABBREVIATIONS

ANC: Absolute Neutrophil Count
AUC: Area Under the Curve
CRP: C-Reactive Protein
LP: Lymphocyte Percentage
MPV: Mean Platelet Volume
NP: Neutrophil Percentage
PCT: Procalcitonin
PDW: Platelet Distribution Width
PLT: Platelet
UTI: Urinary Tract Infection
WBC: White Blood Cells

KEY WORDS

Bacterial infection; children; infection biomarkers; platelet indices.

INTRODUCTION

Pediatric infectious diseases can develop through heterogeneous and mostly non-specific clinical pictures. This is particularly true and critical in infants younger than 12 months, whose clinical presentation is often unclear and who are at higher risk of invasive diseases. It is even more relevant in an emergency setting, where the presence of a temporal constraint to the diagnostic evaluation enhances the need for a timely etiological framework. The distinction between viral and bacterial infections defines the entire diagnostic and therapeutic path, since the latter correlate with a greater tendency to evolve into severe forms and require antibiotic treatments, ineffective and inappropriate in the management of viral diseases (1).

Several authors have identified multiple biomarkers and evaluated their efficacy in discriminating the etiology of an infectious process. Nevertheless, in pediatric age bacterial-viral co-infections are common and complicate the diagnostic path in the absence of a specific biomarker. Despite plenty of evidence suggesting the effectiveness of C-Reactive Protein (CRP) and procalcitonin (PCT) in identifying bacterial diseases (2, 3), their diagnostic accuracy in the pediatric population remains limited, especially regarding their negative predictive value. Furthermore, their routine dosage is limited due to its expensiveness (4, 5). Most recent research has identified promising alternatives to traditional biomarkers. An assay combining 3 circulating proteins (TRAIL, IP-10, and CRP), differently produced by the host in response to bacterial or viral infections, demonstrated superior effectiveness than CRP and PCT in detecting bacterial pathologies among children aged under 60 months (6). Preliminary studies have furthermore shown the ability of RNA biosignatures to distinguish between patients with or without bacterial infections (7). The applicability of such tools in the clinical practice of emergency departments remains debatable, both in terms of costs and availability.

Although platelets have been traditionally evaluated for their central role in the hemostatic process, several studies have supported their involvement in the acute phase response, in which IL-6 production underlies the increase in thrombopoietin levels (8). Moreover, the identification of toll-like receptors on platelet surface and their ability to release antibacterial molecules has suggested thrombocytes involvement in the response to infectious pathogens (9). This highlights the potential role of platelet indices (platelet count, mean platelet volume, platelet distribution width) as biomarkers of inflammatory conditions and even of bacterial infections, especially in the emergency setting, where blood count is rapidly and routinely evaluated.

Since their clinical significance remains uncertain and given the absence of comparative analyses in this regard, the aim of our study was to evaluate the efficacy of platelet indices in discriminating between the bacterial or viral etiology of an infectious disease in infants younger than 12 months. Furthermore, we aimed to characterize their diagnostic accuracy in differentiating between upper and lower urinary tract infections and between bacterial and viral pneumonias.

MATERIALS AND METHODS

We performed a retrospective observational study evaluating 236 patients younger than 12 months admitted to our Pediatric Emergency Department with a diagnosis of urinary tract infection (UTI), bronchiolitis, pneumonia or gastroenteritis. Such age range corresponds to the population group whose clinical presentation is more non-specific and which, at the same time, is at a higher risk of invasive forms. Platelet indices were extracted from medical charts, specifically referring to the blood sample collected at admission. Platelet count and volume can be altered by an inadequate blood sample collection (e.g., haemolysis). Being ours a retrospective analysis, it was not possible to certify the quality of the pre-analytical phase; however, patients whose laboratory tests displayed signs of haemolysis and/or extremely altered platelet counts (PLT <50000/µl or >1000000/µl) were excluded by the study. Additional exclusion criteria were prematurity (gestational age <37 weeks) and comorbidities (chronic diseases, syndromes, respiratory and/or urinary malformations, congenital heart diseases).

Infants with UTIs (single bacterial species >100.000 CFU/ml in urine culture) (10), have been divided into two subgroups: lower (cystitis, urethritis) and upper UTIs (pyelonephritis). Upper UTIs were defined in presence of fever (body temperature ≥37.5 °C) and a CRP value ≥median +1 quartile (5.58 mg/dl in our statistic).

In children with respiratory illnesses, nasopharyngeal secretions were collected through a nasal tube after

the injection of 3 ml of isotonic saline solution into each nostril. A panel of either reverse transcriptase PCR or nested PCR assays allowed to detect 14 respiratory viruses (RSV, RV, Influenza A and B, Adenovirus, Coronavirus OC43-229E, NL63 and HKUI, Parainfluenza 1-3, MPV and BoV) (11). *M. pneumoniae* and common bacteria DNA were detected by Real-Time PCR reactions on samples extracted from throat swab (12). An additional blood sample was collected to evaluate *M. pneumoniae* and *C. pneumoniae* serologies.

Bronchiolitis was defined as the first episode of lower respiratory tract infection in previously healthy infants with spread crackles on chest auscultation (13).

Pneumonia diagnosis was established when fever was associated with clinical or radiological evidence of a new pulmonary consolidation. Further criteria differentiated two subgroups:

– bacterial pneumonias: defined by the presence of all the following: lobar consolidation at chest X-ray; elevated white blood cells count; elevated CRP values;
– viral pneumonias: defined by the presence of all the following: radiological evidence of perihilar peribronchial thickening, interstitial infiltrates or non-lobar pulmonary consolidation; detection of a virus in the nasopharyngeal aspirate; absence of *M. pneumoniae* and common bacteria in throat swab; negativity of *M. pneumoniae* and *C. pneumoniae* serologies.

Gastroenteritis diagnosis was made in the presence of fever, diarrhea and/or vomiting, thence a stool sample was collected to perform a coproculture and to detect viral antigens. Children with documented presence of Rotavirus and/or Adenovirus antigens in stools and a negative coproculture were included in the study. To carry out a comparative analysis, we grouped enrolled patients in two categories as follows: bacterial diseases (UTIs and bacterial pneumonias) and viral diseases (bronchiolitis, viral pneumonias and gastroenteritis).

Statistics

Data statistical analysis was performed using SPSS software (version 25.9; SPSS Inc., Chicago, Illinois, USA). Qualitative variables were expressed as absolute values and percentages, and then compared with Chi-squared test. Normally distributed quantitative variables (PLT, PLT/MPV) were expressed considering average and standard deviation and Student t-test was used for their comparison. Quantitative variables with no-normal distribution (MPV) were expressed using median and the relative range (minimum and maximum value), then compared by Mann-Whitney U test. Concerning PLT, MPV and PLT/MPV ratio, the normality of their distribution curve was established using the Kolmogorov-Smirnov test. A p-value ≤0.05 was considered as statistically significant. The statistical correlation between quantitative variables was evaluated using Pearson's correlation coefficient. A Receiver Operating Characteristic (ROC) curve was constructed to evaluate the diagnostic accuracy of platelet indices and to compare it to the diagnostic value of white blood cell (WBC), neutrophil percentage (NP), lymphocyte percentage (LP) and CRP.

RESULTS

We performed a retrospective observational study involving 236 infants. The median age was 3.0 months (age range: 0.3-11.9 months), and 124 infants (52.5%) were males. The sample was grouped as follows: 145 patients (61%) with bronchiolitis; 41 (17%) with urinary tract infection, 28 of whom were lower UTIs; 29 (13%) with pneumonia, 18 of whom were bacterial; 21 (9%) with gastroenteritis. We divided patients based on the microbial etiology: 59 children with bacterial infections (31 males) and 177 with viral infections (93 males). We documented a non-significant slightly lower value of PLT and PLT/MPV ratio in bacterial diseases, while MPV values were completely overlapping (**Table 1**).

Table 1. *PLT indices: comparison between bacterial and viral infections.*

	Bacterial infections (n = 59)	Viral infections (n = 177)	p-value
PLT	451084 ± 137807	454192 ± 138701	0.88
MPV	7.9 (6.1-10.9)	7.9 (6.4-10.2)	0.93
PLT/MPV	57291 ± 18909	58087 ± 19453	0.78

Normally distributed quantitative variables (PLT, PLT/MPV) are expressed as average ± standard deviation. Quantitative variables with no-normal distribution (MPV) are expressed as median (range). Abbreviations: PLT Platelets; MPV Mean Platelet Volume.

Table 2. *ROC analysis of traditional markers and platelet indices.*

	AUC	Standard Error	Lower Bound	Upper Bound
WBC	0.767	0.034	0.700	0.834
NP	0.832	0.027	0.779	0.886
LP	0.197	0.030	0.137	0.256
CRP	0.871	0.025	0.822	0.920
PLT	0.479	0.041	0.399	0.559
MPV	0.499	0.043	0.414	0.584
PLT/MPV	0.481	0.040	0.402	0.559

Abbreviations: AUC Area Under the Curve; WBC White Blood Cell; NP Neutrophil Percentage; LP Lymphocyte percentage; CRP C-Reactive Protein; PLT Platelets; MPV Mean Platelet Volume.

We used ROC curves to evaluate the diagnostic accuracy of platelet profile. The Area Under the Curve (AUC) of PLT, MPV e PLT/MPV demonstrates that platelet indices do not differentiate between viral and bacterial infections, unlike already validated markers (WBC, NP, LP, and CRP), whose AUC indicates proper accuracy (**Table 2** and **Figure 1**).

Urinary infections were subgrouped into lower (cystitis, urethritis) and upper (pyelonephritis) tract infections. PLT, MPV and PLT/MPV did not differ between the groups (**Table 3**).

Considering bacterial and viral pneumonias, we found slightly lower PLT, MPV and PLT/MPV in bacterial pneumonias, albeit statistically non-significant (**Table 4**).

We documented a positive correlation between white blood cells (WBC) and PLT (r = 0,198; p <0,05) as well as WBC and PLT/MPV (r = 0,176; p <0,05). The absolute neutrophil count (ANC) positively correlates with PLT (r = 0,238; p <0,05) and PLT/MPV (r = 0,239; p <0,05). Conversely, we found no statistical association between CRP values and platelet indices (PLT, MPV, PLT/MPV) (**Table 5**).

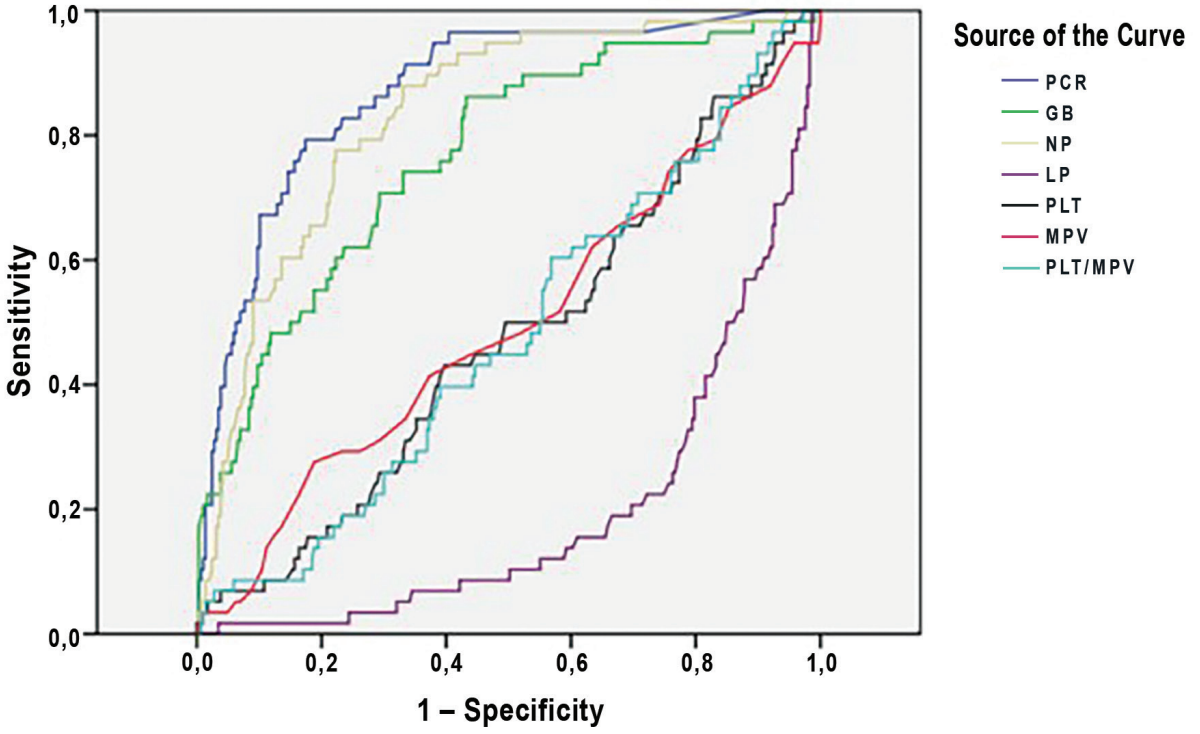

Figure 1. *ROC curves of traditional markers and platelet indices.*

Table 3. *PLT indices: comparison between upper and lower UTIs.*

	Lower UTIs (n = 28)	Upper UTIs (n = 13)	p-value
PLT	437607 ± 127260	422000 ± 109982	0.71
MPV	7.9 (6.1-10.9)	8 (6.4-10.3)	0.81
PLT/MPV	55556 ± 17155	54789 ± 19451	0.90

Normally distributed quantitative variables (PLT, PLT/MPV) are expressed as average ± standard deviation. Quantitative variables with no-normal distribution (MPV) are expressed as median (range).
Abbreviations: PLT Platelets; MPV Mean Platelet Volume.

Table 4. *PLT indices: comparison between bacterial and viral pneumonias.*

	Bacterial pneumonias (n = 18)	Viral pneumonias (n = 11)	p-value
PLT	493055 ± 166495	540000 ± 178266	0.48
MPV	7.8 (6.8-9.9)	8.0 (7.1-9.8)	0.41
PLT/ MPV	61797 ± 21311	65535 ± 21347	0.65

Normally distributed quantitative variables (PLT, PLT/MPV) are expressed as average ± standard deviation. Quantitative variables with no-normal distribution (MPV) are expressed as median (range).
Abbreviations: PLT Platelets; MPV Mean Platelet Volume.

DISCUSSION

In this retrospective observational study involving 236 infants younger than 12 months, we aimed to evaluate the efficacy of platelet indices in discriminating the bacterial or viral etiology of infectious diseases.

The involvement of thrombocytes in bacterial infections has been evidenced by the correlation between platelet indices and procalcitonin, a well-known bacterial biomarker (14). Significantly higher MPV values were demonstrated in sepsis patients, the emblematic paradigm of a bacterial disease (15, 16). The physiopathological rationale for this increase would lie in the release of larger newly formed platelets, aimed at the replacement of the thrombocytes destroyed by peripheral consumption. Tamelyte *et al.* pointed out that the increase of the PLT/MPV ratio in children presenting to the emergency department resulted more effective than leukocytosis, neutrophilia and CRP in detecting sepsis or bacteriemia (17).

Conversely, MPV reduction under inflammatory conditions has been interpreted as consequence of the seizure of larger platelets inside the mesenteric district during acute appendicitis as well as in rotavirus gastroenteritis, resulting in a lower mean platelet volume (18, 19). Analogous mechanisms have been hypothesized to explain the MPV decrease in infants suffering from acute bronchiolitis (20). As far as most recent findings are concerned, a reduction in MPV has also been documented in influenza and COVID-19 patients, the latter showing significantly lower values (21).

In the present study, none of platelet indices has proved effective in discriminating bacterial from viral infections (non-significant differences between the two groups; smaller AUC than WBC, NP, LP, and CRP). The slightly positive association that correlates WBC and ANC to PLT and PLT/MPV does not allow to draw definitive conclusions concerning platelet indices' ability to detect bacterial infections.

Our findings are in contrast with results emerging from the literature and several reasons might underlie such discrepancy. Most studies involve adults or a wide age range of pediatric patients, resulting in their sample being unavoidably heterogeneous. Furthermore, they take into consideration a specific infectious disease and, above all, the control group is

Table 5. *Pearson's correlation coefficient.*

	WBC		ANC		CRP	
PLT	0.19815	*p <0.05*	0.23814	*p <0.05*	0.00026	p = 0.99
MPV	0.00496	p = 0.93	-0.08395	p = 0.12	-0.03932	p = 0.47
PLT/MPV	0.17568	*p <0.05*	0.23923	*p <0.05*	0.01102	p = 0.84

Abbreviations: WBC White Blood Cells; ANC Absolute Neutrophil Count; CRP C-Reactive protein; PLT Platelets; MPV Mean Platelet Volume.

generally composed of healthy subjects. To the best of our knowledge, ours is the first study that evaluated platelet indices accuracy comparing a pool of bacterial diseases with one of viral infections, regardless of their specific etiology and without a healthy control group. For this purpose, the results obtained document their limited usefulness. Therefore, platelet indices cannot be generalized as markers of bacterial disease; this does not exclude that they may vary significantly from healthy controls, as the latest available evidence shows.

The secondary aim of the present study was to define the ability of platelet indices to distinguish between infections of the upper and lower urinary tract and between bacterial and viral pneumonias. Similarly to Gökçe's *et al.* analysis (22), none of the PLT parameters evaluated in our study showed statistically significant differences between the two subgroups of UTIs. This is in contrast with the hypothesis that the increase in MPV is higher in pyelonephritis, more susceptible to complications (such as bacteremia) (23). To our knowledge, no study has ever assessed platelet indices modifications in pneumonias, far less in the pediatric population. Although our results documented lower PLT, MPV and PLT/MPV values in patients with bacterial pneumonias, no statistically significant differences were found compared to viral forms.

Recent studies have evaluated platelet indices' alterations in pediatric bacterial infections, comparing them to healthy controls. A significant novelty and main strength of the present study is being the first to investigate variations in platelet indices among febrile infants, comparing bacterial to viral diseases. Nevertheless, several limitations should be addressed. Due to its retrospective nature, a prognostic evaluation could not be performed. Furthermore, bacterial and viral pneumonias were differentiated according to laboratory parameters (leukocytes, CRP, serology) and thoracic imaging, without isolating the specific etiological agent. Although the disproportion in the sample size of the two comparison groups is considerable (59 bacterial, 177 viral), it reflects the distribution of admissions in our emergency department. Moreover, the homogeneity of the recruited sample, limited to the first year of life, prevents us from generalizing our conclusions to the entire pediatric population.

CONCLUSIONS

Our results demonstrate the substantial inefficacy and inaccuracy of platelet indices in discriminating the microbiological etiology of an infectious process during the first year of life. It seems more useful and pragmatic, especially in the emergency setting, to use widely validated markers, such as leukocytosis, neutrophilia and CRP, integrating them with the clinical picture, which always represents the cornerstone of the most appropriate clinical practice.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The authors have no conflicts of interest relevant to this article to disclose.

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Authorship

We observed the credit criteria.

Author contributions

The authors confirm contribution to the paper as follows. Study conception and design: FV and FM; data collection: FV and GDM; analysis and interpretation of results: FV and EB; draft manuscript preparation: FV and LM; critical revision: RN and LP; supervision: FM. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the research and ethics committee of the Policlinico Umberto I Hospital (n. 2377/2012).

Human studies and subjects

The study followed the ethical standards established in the Declaration of Helsinki.

Animal studies

N/A.

Data sharing and data accessibility

The major dataset will be available when requested.

Publication ethics

Plagiarism

All original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

Manipulation of images

All images are original.

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RESEARCH ARTICLE

Outcomes of severe meconium aspiration syndrome in a resource restricted hospital, South Africa

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ABSTRACT

Meconium aspiration syndrome (MAS) is defined as respiratory distress in a neonate born through meconium-stained liquor (MSAL) whose symptoms cannot be otherwise explained. Mortality and morbidities vary in different resourced health settings. This retrospective study aimed to describe the management strategies, short-term (in-hospital) outcomes and mortality of neonates with severe MAS (defined as those requiring invasive ventilation) at a resource restricted hospital in Cape Town, South Africa.

Ninety-two neonates with suspected MAS were included, of which only 47 were included based on the radiological findings (patchy infiltrates and hyperinflation). The mean gestational age was 39.7 ± 1.4 weeks and mean birth weight was 3246 ± 522g. Most neonates were outborn. High frequency ventilation was the most common initial mode of ventilation (55%). The median duration of invasive ventilation was 3 (IQR 2-4.5) days and total duration of respiratory support was 9 (IQR 4-16) days. Surfactant was administered in 70% of neonates. Pulmonary hypertension (PPHN) developed in 53% and 88% received inhaled nitric oxide. Inotropes were administered to 45% of neonates and steroids were administered in 64%. Pneumothorax was present in 9%. Neonates were discharged from NICU after a median age of 5 (IQR 3-7) days and had a hospital stay of 12 (IQR 6-21) days. Overall mortality was 8.5% (n = 4).

Mortality was low and complications (PPHN and sepsis) were high, remaining higher than in high resource countries. Management of PPHN and hypotension, as well as steroid administration were variable. A protocolized management strategy should be adopted, according to resource availability.

HIGHLIGHTS BOX

What is already known about this topic? Meconium aspiration syndrome is associated with a variety of complications. Management is varied, mostly supportive and differs depending on health care resources. **What does this article add to our knowledge?** With a combination of therapies, morbidities remain high but mortality decreases, in a resource restricted institution but remains higher than in high resource institutions. **How does this study impact current management guidelines?** Therapies – high frequency ventilation, surfactant, inotropes and inhaled nitric oxide – should be combined to improve outcomes, especially in resource restricted institutions.

KEY WORDS
Meconium aspiration syndrome; surfactant; mortality; pulmonary hypertension.

INTRODUCTION

Meconium aspiration syndrome (MAS) is defined as respiratory distress in a neonate born through meconium-stained liquor (MSL) whose symptoms cannot be otherwise explained (1). There is no clear classification for the severity of meconium aspiration, with some studies defining severe MAS (sMAS) as a neonate requiring respiratory support (continuous positive airway pressure and/ or mechanical ventilation) (2), or a neonate requiring mechanical ventilation for more than 7 days, high frequency ventilation or extracorporeal membrane oxygenation (ECMO) (3). Grading may be also based on FiO2 and management requirements: mild MAS – requiring FiO2 <0.4 for less than 48 hours; moderate MAS – requiring FiO2 >0.4 for more than 48 hours but with no air leaks and severe MAS – requiring assisted ventilation for more than 48 hours and associated with persistent pulmonary hypertension (PPHN) (1).

Eight to 19% of neonates are born through MSL, of which 5-33% develop MAS, and 30-50% of those develop sMAS (4). Studies in high resource countries have shown a 4-fold decrease in the incidence of MAS with a decrease in mortality (1, 5, 6). However, in low resource countries, the incidence has not decreased, and mortality remains high (7, 8). A United States population-based study has shown that neonates born through MSL, with symptoms, have a two-fold increase in length of hospitalization, three-fold increase in hospitalization costs, four-fold increase in risk of mortality, three-fold higher risk of PPHN and a five-fold increase in the risk for hypoxic ischemic encephalopathy (HIE) compared to neonates born through MSL without symptoms (9).

MAS is associated with a variety of complications. These include hypoxic respiratory failure, PPHN, air leak syndromes and asphyxia. Although these are reported as low in high resource countries (1, 5, 6), their incidence remains high or unknown in low resource countries (10, 11). The clinical and complications of MAS differs between developing and developed countries and affects management techniques (12).

The management of MAS is mainly supportive and includes maintaining thermoregulation, adequate oxygenation, maintenance of an adequate blood pressure and correction of acidosis and other metabolic or electrolyte disorders. Respiratory support includes surfactant administration (13), ventilatory support (14), management of PPHN (15) and steroid administration (16). However, in most cases, a wide variety of practices occur, with varying success of treatment, especially in resource-restricted environments (12).

This study aimed to describe the mortality, complications, and management strategies of neonates with severe MAS admitted to a resource restricted hospital in Cape Town, South Africa.

MATERIALS AND METHODS

A retrospective, descriptive study was performed at a tertiary, academic, public health hospital, Cape Town, South Africa between 1st January 2016 and 31st December 2018. All neonates admitted to the neonatal intensive care unit (NICU) requiring invasive ventilation for a presumptive diagnosis of MAS were eligible for inclusion. Neonates were excluded if they required ventilation for other reasons or were diagnosed with chromosomal or congenital abnormalities.

Maternal and neonatal demographic data were collected. Prevalence and management data were collected for specific MAS-complications. Severe meconium aspiration (sMAS) was defined as neonates born through MSL who developed respiratory distress with characteristic radiological findings (hyperinflation and patchy opacity) and requiring invasive mechanical ventilation (2). Persistent pulmonary hypertension of the neonate (PPHN) was defined by echocardiography or the need for iNO and/or sildenafil. Hypoxic ischemic encephalopathy (HIE) was defined by the need for therapeutic hypothermia (institutional protocol was in line with the TOBY protocol). (17). Sepsis was defined as early (<72 hours of age) or late (≥72 hours of age) onset sepsis and a positive blood culture and/or C-reactive protein (CRP) more than 10nmol/l (18).

Chest XRs (CXR), as performed at admission, were reviewed by a neonatologist and a pediatric pulmonologist, separately, for signs consistent with MAS (hyperinflation and bilateral patchy infiltrates) and air leaks. The pediatric pulmonologist was blinded to the diagnosis.

Statistical analysis

Data were presented as means and standard deviation, or median and interquartile range, depending on

normality of data. Categorical data were reported as numbers and percentage. Correlation between investigators was calculated for agreement for diagnosis of MAS on CXR. Data were analyzed using STATA IC15 (Stata Corp, 2017, College Station, TX, USA).

Ethical approval

A waiver of informed consent was approved by Stellenbosch University Health Research Ethics Committee (S20/06/141). Research was performed in accordance with the ethical standards established in the Declaration of Helsinki of 1946.

RESULTS

Ninety-two neonates were admitted with a presumptive diagnosis of sMAS during the study period. Forty-five (49%) neonates were excluded from the study. Four neonates admitted to NICU with a diagnosis of MAS did not require invasive ventilation and a further 41 neonates were excluded as the CXR's did not meet the study definition of MAS. The final study population was 47 neonates. (**Figure 1**)

Maternal demographics are described in **Table 1**. The majority of neonates with sMAS were born via cesarian delivery. Meconium-stained liquor (MSL) grading was poorly reported (31/47(66%)) with most cases reported as grade 3 (**Table 1**).

The majority (89%) of neonates with sMAS were outborn. One-third of the included neonates with sMAS required IPPV during resuscitation at delivery and one-quarter required intubation at delivery (**Table 1**).

Radiological diagnosis of MAS

Agreement between a neonatologist and pediatric pulmonologist was high (78%) regarding the radiological diagnosis of MAS. Agreement was high for both evaluated radiological components of MAS (bilateral infiltrates and hyperinflation) as well as for air leaks (**Table 2**).

Alternative CXR diagnoses included normal lungs, diffuse alveolar disease, congenital pneumonia, and

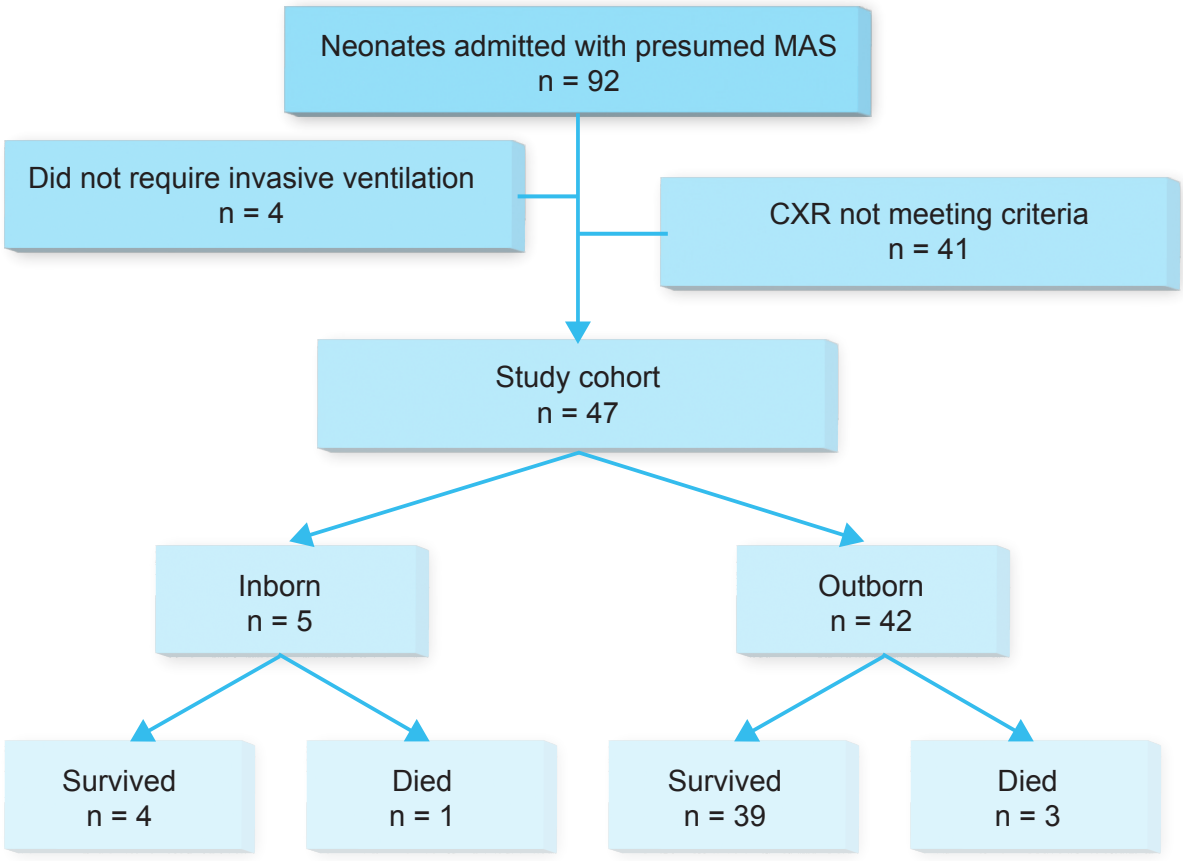

Figure 1. *Flow diagram of patients included in study.*

Table 1. *Study population demographics.*

Variable		Data N = 47
Maternal Demographics		
Cesarian section, n (%)		32 (68)
Normal delivery, n (%)		15 (32)
Pre-eclampsia, n (%)		5 (11)
Chorioamnionitis, n (%)		1 (2)
Liquor, n (%)	Clear	1 (3)
	MSL 1	2 (6)
	MSL 2	7 (23)
	MSL 3	21 (68)
Neonatal Demographics		
Gestational age, weeks, mean ± SD		39.7 ± 1.4
Birth weight, grams, mean ± SD		3246 ± 522
IUGR (<10th centile)		8 (17)
Inborn n (%)		5 (11)
Resuscitation at delivery, n (%)	No resuscitation	6 (13)
	CPAP	11 (23)
	IPPV via T-piece	14 (30)
	Intubation	13 (28)
	Adrenaline	3 (6)
Apgar 10-min, median (IQR)		8 (7-9)

CPAP-continuous positive airway pressure; IPPV-Intermittent positive pressure ventilation; IUGR-intra-uterine growth restriction; IQR interquartile range-; MSL-Meconium-stained Liquor; MSL 1-Meconium-Stained Liquor Grade 1, MSL 2-Meconium-stained Liquor Grade 2, MSL 3-Meconium-stained Liquor Grade 3; SD-standard deviation.

transient tachypnoea of the newborn. The correlation of alternative diagnoses between the 2 clinicians was low (r = 0.115).

Admission parameters

Upon admission, most neonates with sMAS were acidotic and hypoxic: respiratory acidosis (49%), metabolic acidosis (36%) with admission peripheral saturation of 89 ± 9% requiring a fractional inspired oxygen of 0.69 ± 0.27.

Pulmonary indices (OI, PF ratio and OSI), calculated on the first blood gas, are shown in **Table 3**.

Management

High frequency ventilation (HFV) and conventional ventilation (CV) (time cycled, pressure limited assist control (TCPL) mode) were used. HFV was the most common initial mode of ventilation. The primary and sole mode of ventilation was HFV in 15 (32%) and CV in 19 (40%) neonates. Two neonates (4%) were initially started on CPAP but required escalation to HFV within 4 hours of admission. In 5 (10%) neonates CV was escalated to HFV and in 8 (17%) HFV was de-escalated to CV (**Table 3**).

For neonates placed on CV, the mean PIP was 20.9 ± 3.5 cmH2O and PEEP was 4.9 ± 0.8 cmH2O on day 1 of admission. For neonates on HFV, the mean MAP was 16.6 ± 4.3 cmH2O. The mean MAP for the whole study cohort was 13.2 ± 4.3 cmH2O at time of admission.

The majority of infants received intratracheal surfactant-administered as a bolus (**Table 3**).

Non-invasive modes of ventilation, CPAP, and high flow nasal cannula were used as step down respiratory support modes for varying lengths of time (**Table 3**).

Complications and management

Air leaks were found in 11% of the study population on the CXR, with pneumothorax being the most common type (**Table 4**).

PPHN was the most common complication involving more than half of the cohort, mostly diagnosed by echocardiography. iNO was started within 4 hours of admission life, with the cohort receiving a maximum dose of 20ppm, as per institutional protocol. Sildenafil was used in a third of infants (**Table 4**). The mean

Table 2. *Agreement statistics of CXR for MAS.*

Parameter	Agreement (%)	Kappa	p-value
Overall CXR diagnosis of MAS	77.5	0.542	<0.001
Bilateral infiltrates	76.4	0.459	<0.001
Hyperinflation	82.0	0.444	<0.001
Pneumothorax	96.6	0.557	<0.001
Pneumomediastinum	96.6	0.709	<0.001

CXR-chest x-ray; MAS meconium aspiration syndrome.

Table 3. *Respiratory support modalities.*

Parameters		Results
Admission FiO_2, mean ± SD		69 ± 27
Admission OI#, median (IQR)		6.3 (4.1-16.7)
Admission PF ratio#, median (IQR)		94.5 (45.7-167.5)
Admission OSI ratio, median (IQR)		9.0 (5.6-16.3)
Conventional ventilation	Total, n (%)	34 (72)
	Duration, days, median (IQR)	2 (1-4)
HFV	Total, n (%)	28 (61)
	Duration, days, median (IQR)	3 (2-4.2)
CPAP	Total, n (%)	40 (85)
	PNA started, day, median (IQR)	3.5 (2-5)
	Duration, days, median (IQR)	2 (1-3)
High flow nasal cannula	Total, n (%)	16 (34)
	PNA started, days, median (IQR)	6.9 (5-15.5)
	Duration, days, median (IQR)	2 (1-6.5)
NPO_2	Total, n (%)	36 (77)
	PNA started, days, median (IQR)	8 (7-17)
	Duration, days, median (IQR)	2 (1-6.5)
Total duration invasive ventilation, days, median (IQR)		3 (2-4.5)
Total duration non-invasive ventilation, days, median (IQR)		2 (1-5)
Total duration all respiratory support, days, median (IQR)		9 (4-16)
Surfactant administration, n (%)	Any surfactant	38 (81)
	1 dose	33 (70)
	2 doses	4 (9)
	3 doses	1 (2)

CPAP-Continuous positive pressure ventilation; HFV-High frequency ventilation; IQR-interquartile range; NICU-Neonatal intensive care unit; NPO_2-nasal prongs oxygen; OI-oxygenation index; OSI-oxygenation saturation index; PF-partial pressure of oxygen: fraction of inspired oxygen ratio; PNA-postnatal age. #Calculated in 38 neonates who had arterial line.

dose was 1.4 ± 0.75mg/kg/dose. In 12% (3/25) of neonates, sildenafil was administered primarily due to the unavailability of iNO.

One fifth of neonates were also diagnosed with hypoxic ischemic encephalopathy (HIE) and underwent therapeutic hypothermia (TH) (**Table 4**).

Of the 12 neonates (25%) with sepsis, early onset sepsis occurred in 5 (25%). Late onset sepsis microorganisms included Serratia Marcescens (n = 3), Pseudomonas Aeruginosa (n = 1), coagulase negative staphylococci (n = 1) and Klebsiella Pneumonia (n = 2). No neonate had more than one episode of sepsis.

Steroids, mostly dexamethasone, were administered for: weaning of ventilation (13/25(52%)); catecholamine-resistant hypotension (8/25(32%)); hypoglycemia (4/25(16%)), post-extubation stridor (1/25 (4%)) and for management of convulsions (1/25 (4%)). One neonate received a mixture of dexamethasone and hydrocortisone (**Table 4**).

Most neonates required an NICU stay of less than 1 week (median 5 days (IQR 3-7)) and were hospitalized for less than 2 weeks (median 12days (IQR 6-21)). The survival rate was 92% (43/47) with most neonates (77%) being discharged home. Of the 4 neonates that died, 1 (25%) neonate was inborn and 3 (75%) were born outside the hospital. Due to the low mortality, multivariate regression and odds ratio for mortality were not able to be performed as planned.

DISCUSSION

This is the first study performed at our institution, a resource-restricted academic public health hospital,

Table 4. *Complications and treatment of complications.*

Parameters			Results N = 49
Air leak syndrome	Pneumothorax, n (%)		4 (9)
	Pneumomediastinum, n (%)		1 (2)
Systemic hypotension	Any inotrope, n (%)		21 (45)
	Duration, days, median (IQR)		2 (1-3)
	Initial drug, n (%)	Dobutamine	13 (62)
		Dopamine	8 (38)
	2nd line, n (%)	Milrinone	5 (45)
		Dopamine	3 (27)
		Dobutamine	2 (18)
		Adrenaline	1 (9)
	3rd line, n (%)	Milrinone	2 (100)
PPHN	Total, n (%)		25 (53)
	Echocardiography diagnosis, n (%)		15 (52)
	iNO	administered (%)	22 (88)
		Duration, days, mean ± SD	4.2 ± 2.4
	Sildenafil	Total, n (%)	13 (28)
		PNA at start, median (IQR)	1 (0-1)
		Duration, days, median (IQR)	12 (6-22)
HIE received therapeutic hypothermia, n (%)			10 (20)
Culture positive sepsis	Total, n (%)		12 (25)
	PNA at onset, days, median (IQR)		6.5 (0-8)
Steroids	Total, n (%)		25 (64)
	PNA at start, age, median (IQR)		1 (0-3)
	Duration, days, median (IQR)		2 (2-3)
	Type	Dexamethasone, n (%)	16 (64)
		Hydrocortisone, n (%)	8 (36)

HIE-hypoxic ischemic encephalopathy; iNO-inhaled nitric oxide, IQR-interquartile range; PNA-postnatal age; PPHN-persistent pulmonary hypertension of the newborn; SD-standard deviation.

in the Western Cape, South Africa, to determine the morbidity, management and short-term outcomes of severe meconium aspiration syndrome (sMAS). sMAS was defined as the need for intubation and invasive mechanical ventilation for neonates with radiological signs of MAS (hyperinflation and coarse infiltrates). Mortality was low but morbidities (PPHN, sepsis, HIE) were high.

MAS is traditionally defined as respiratory distress in a neonate born through MSL with characteristic radiological signs whose symptoms cannot be otherwise explained (1). This study's cohort was comprised only of neonates with severe MAS requiring invasive mechanical ventilation. The cohort also met the requirements of various other study's definitions of sMAS, with most neonates, requiring more than 40% oxygen upon admission, more than half of the cohort diagnosed with PPHN and more than half requiring HFV (1-3).

MSL and respiratory symptoms are often assumed to equate to MAS, and alternative diagnoses may only be found after radiological imaging (19). Despite a clinical diagnosis of sMAS, nearly 50% of study neonates were excluded based on radiological findings. Abnormal radiological findings are only apparent in 59.9% of neonates born through MSL (20). Hospital discharge coding data have been shown to be inaccurate (21). The retrospective nature of the current

study, using hospital admission codes and retrospectively reviewed CXR, may have contributed to the high exclusion rate.

The current study showed most neonates were admitted with acidosis, similar to other studies that indicated a pH below 7.25 was associated with sMAS (22, 23). Metabolic acidosis and respiratory failure, both present in this cohort, have been shown to predict mortality (24).

Admission FiO2 in this study was high, similar to another study (23). An FiO_2 >0.3 at 1 hour after admission has been shown to be associated with prolonged hospitalization (25).In the current study the admission FiO_2 was much higher than 0.3 but no 1-hour values were available. An FiO_2 >0.35 and a pH <7.22 have been shown to predict sMAS (23), as also seen in most of this study cohort. Survivors of sMAS had been shown to have a significantly lower FiO_2 with higher mean PaO_2 and SpO_2 at 6,12 and 24 hours as compared to non-survivors (26). Survivors and non-survivors unable to be compared due to the low mortality rate in this study.

Ventilation

Ventilation in neonates with sMAS is challenging due to airway obstruction with areas of atelectasis and hyperinflation, ventilation-perfusion mismatch, airway compromise, surfactant dysfunction, and is often complicated by PPHN and air leaks (4).

More than half the current study required HFV as primary or step-up mode of ventilation, compared to only one-third in a similar cohort in a previous South African study (2008) (11), with the reason stated as being due to resource constraints at that time. The mean duration of conventional and high frequency ventilation in the current study (2 and 3 days, respectively) was similar to other studies (3 and 5 days, respectively, with duration increasing in those requiring iNO or surfactant) (6).

The most appropriate mode of ventilation for infants with MAS is unknown as there are no comparative studies of high frequency ventilation (HFV) and conventional modes of ventilation. No difference in mortality, need for ventilation, pneumothorax or length of hospitalization has been shown with the use of CPAP compared to mechanical ventilation (27). In the current study, neonates who required CPAP only, for possible MAS, were not included. CPAP, in conjunction with surfactant, may be an alternative respiratory support strategy to avoid mechanical ventilation, especially in resource-restricted environments (28).

Oxygenation index (OI) has been used to determine the need for extracorporeal membrane oxygenation (ECMO) in neonates with hypoxic respiratory failure (HRF), including MAS, unresponsive to standard management. OI criteria for HRF are: OI <15 mild HRF, 16-25 moderate HRF, 26-40, severe HRF and >40 very severe HRF (29). OI in this study showed mild HRF, similar to other MAS studies (30). This may be due to the administration of surfactant (31).

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) have been defined using various pulmonary indices: ALI: P/F ratio ≤300, OI 5.3-8.1 and OSI 6.5-7.8. and ARDS: P/F ratio ≤200, OI >8.1 and OSI >7.8 (32). Our study showed that most neonates had a low PF ratio and a high OSI, indicating ARDS. A P/F ratio ≤200 has been associated with poor outcomes and predict mortality in neonates with MAS (26). In the current study, most neonates met these criteria, but mortality was low despite significant morbidities. This may be due to the combined management with HFV, surfactant and iNO. OSI, that does not require an arterial line, has been correlated with OI in neonates with HRF (29). This may offer an alternative to OI calculation in resource restricted environments and requires further research.

Surfactant

In the current study, more than three-quarter of neonates received at least one dose of surfactant (beractant), which may have contributed to the low mortality rate. This is in contrast to the previous South African study (2008) where only 14% of MAS neonates received surfactant, due to resource constraints (11). This study's surfactant administration rate was similar to a Spanish study (73%) (23) but higher than that used in a Swedish study (53%) (33).

MAS inactivates surfactant (34) and surfactant replacement therapy may decrease the incidence of respiratory failure (35). Beractant, due to its availability, was used during this study. Although both beractant and poractant alpha have been used in clinical trials, no direct comparison studies are available (36). Surfactant was administered as a bolus in the current

study. No clear clinical differences have been shown to exist between outcomes after bolus vs surfactant lavage (13, 36, 37).

HFV plus surfactant, as compared to conventional ventilation plus surfactant, has been shown to significantly improve respiratory indices and shortened the duration of ventilation and oxygen use (38). We were unable to perform a similar comparison due to crossover of ventilation modes in most neonates.

The European Society of Pediatric and Neonatal Intensive Care expert consensus, 2021 supports the use of surfactant in a variety of pediatric and neonatal acute respiratory distress disorders, including MAS (39). Surfactant could be beneficial in decreasing mortality, air leaks, duration of ventilation, oxygen therapy and hospitalization (40), which may be beneficial in low resource settings (41).

Persistent pulmonary hypertension (PPHN)

PPHN is a leading cause of death in neonates with sMAS (42). In the current study, more than half of the cohort developed PPHN, lower than in the previous South African study (57%) (11) but significantly higher than a Jamaican (5%) (10) and Indian study (17%) (8). PPHN has been shown to prolong hospitalization (25). iNO is the standard therapy for PPHN whilst phosphodiesterase inhibitors (sildenafil and milrinone) may be used as adjuncts (43). iNO was used in most of the PPHN cases in this cohort with sildenafil as an additional medication, representing the possible one-third of infants that do not respond to iNO (44). All modalities were used in the current study. HFV combined with iNO may be more successful in treating MAS with PPHN, as compared to ventilation only (45). The cost of iNO in resource restricted countries may be prohibitive. Sildenafil may be an alternative and should be investigated as a first-line drug with determination of appropriate dosing (46).

Sepsis

All study neonates received first line antibiotics (ampicillin and gentamicin) upon admission. Two-thirds had a raised CRP whereas only one quarter had a positive blood culture. This is similar to a Spanish study (23). Sepsis has been shown to be an independent risk factor for mortality in neonates with MAS (24). Despite this, the mortality in this study was low.

Meconium is a known irritant and causes pulmonary inflammation. Abundant neutrophils and macrophages, with subsequent release of inflammatory cytokines TNF a, IL 1b and IL 8, are present in alveoli within hours (1). Despite this, MAS has not been shown to increase the incidence of sepsis (47), despite prophylactic antibiotics (48). A raised CRP, possibly due a systemic inflammatory response, is common (49). Prophylactic antibiotics are therefore not recommended unless there are septic risk factors present (50, 51).

Air Leaks

The current study had a slightly lower incidence of air leaks as compared to international literature (9% vs 10-24% (6, 11, 52). This may be due to the higher use of HFV use in the study, due to HFV's reduction of local lung overexpansion and repeated alveolar opening and closing (53).

Steroids

Steroids were administered to half of the study cohort to decrease ventilation requirements. Intravenous methylprednisolone and nebulized budesonide may shorten the duration of respiratory distress and oxygen requirement, shorten hospital stay but has shown no effect on mortality in MAS (54) . The early use of steroids, as part of a protocolized management strategy, should be considered and further evaluated.

Hypoxic ischemic encephalopathy

Nearly one fifth of study neonates had HIE meeting criteria for therapeutic hypothermia (TH), similar to Portuguese and Indian studies (30%) (25, 55) but higher than in a Jamaican study (6%) (10). HIE has also been shown to predict prolonged hospitalizations (25).

TH is an accepted therapy for HIE in most developed countries with contradictory evidence in low resource countries (56). There may be an additive effect of TH and surfactant therapy for neonates with MAS, when other respiratory therapies have been optimized (57). TH for MAS has shown improved oxygenation, less mechanical ventilation, shorter ICU, and total hospital stay (57, 58). More research is required to determine if TH would be advantageous for sMAS in low resource environments.

Mortality

MAS-associated mortality is low in high resource countries (2.5-4%) (6, 22), whilst low resource countries have reported high mortality rates (13-26%) (7, 8). A previous South African study (2004-2006) of neonates requiring mechanical ventilation for MAS reported 33% mortality (11), attributed to infection, PPHN and the low usage of respiratory adjuncts related to various resource constraints (11). The use of surfactant, HFV and iNO, was 6-9%, 21-45% and 3-6%, respectively, during the study period (11), much lower than in the current study. Despite being a resource restricted NICU, our study's mortality was 8%, which is slightly higher than in high resource countries but lower than other low resource countries. This may be due to the combined use of surfactant, HFV, iNO and sildenafil, representing higher resource availability more than a decade after the previous South African study. A Spanish study, with a similar cohort and similar management strategy, showed a mortality of 6.6% (23).

In a Taiwanese study, MAS was managed according to a standard protocol (CPAP and conventional mechanical ventilation with surfactant (lavage or bolus), HFV and iNO for hypoxic respiratory failure, and dexamethasone for unresponsive hypotension). This protocolized management showed a decrease in morbidity and mortality (59). Larger studies utilizing a protocolized approach to the management of neonates with severe MAS should be performed.

This study has several limitations. Due to the retrospective nature, not all data were available. Neonates with non-severe MAS (not requiring intubation and invasive ventilation) were not included as this diagnosis was not consistently documented. Many neonates admitted with a suspected diagnosis of sMAS were excluded based on radiological images and were not further investigated.

CONCLUSIONS

Despite relative resource limitations, our study found that mortality was low despite a high incidence of morbidities (PPHN, HIE and culture-positive sepsis). This may be due to combined use of high frequency ventilation, surfactant and pulmonary vasodilators. Standardized, combined therapies should be investigated for MAS in resource restricted centers.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The authors declare no conflict of interest

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Authorship

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Author contributions

Research question, study design, ethics submission: JB, LW and PG; literature review and data collection: JB; data interpretation: LW and PG; data analysis: LW; report: JB; supervision, literature review, data collection review, report review and auditing: LW and PG. All authors reviewed and approved the final manuscript.

Ethical approval

A waiver of informed consent was approved by Stellenbosch University Health Research Ethics Committee (S20/06/141). Research was performed in accordance with the ethical standards established in the Declaration of Helsinki of 1946.

Human studies and subjects

An informed waiver of informed consent was granted by Stellenbosch University Health Research Ethics Committee.

Animal studies

N/A.

Data sharing and data accessibility

Data is available from the corresponding author upon reasonable request and upon approval by the local Ethics Committee.

Publication ethics

Plagiarism

All original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

Manipulation of images

All images are original.

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REVIEW

Exposome and pharmacogenomics: towards precision medicine in childhood asthma

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ABSTRACT

Asthma is a complex and heterogeneous disease that requires individualized management. In childhood, poor asthma control can irreversibly compromise the children's lung function. Beyond asthma phenotypes, considering disease endotypes has been assumed a crucial issue in developing tailored therapies. The interaction between genome and exposome determines the emergence of several cellular and molecular mechanisms that contribute to different asthma endotypes and clinical phenotypes. The exposome concept was introduced as an innovative approach for simultaneously assessing environmental risk factors and their impact on human health, thus encompassing the totality of the environmental exposures occurring over a lifetime. Given that different types of environmental exposures occurring throughout life have a major impact on asthma, an exposome-based approach appears to be particularly suggested, as it provides a risk profile rather than individual predictors. Pharmacogenomics refers to the genome-wide study of variants in the deoxyribonucleic acid, which evaluates the effect of genetic variants on the individual's response to treatment. Though many genetic variants have been shown to influence response to asthma treatment, results are still inconsistent and/or effect sizes are small. Furthermore, it should be considered that epigenetic changes, gene-gene and gene-environment interactions could affect pharmacogenomic associations. Sustainability and large-scale population-based studies are needed in order to improve research in exposome and pharmacogenomics. This review aims to discuss the latest developments related to childhood asthma in the fields of exposome and pharmacogenomics as well as challenges in integrating these innovative approaches into clinical practice and opportunities for future research.

IMPACT STATEMENT: Advances in the fields of exposome and pharmacogenomics research pave the way to precision medicine in pediatric asthma.

KEY WORDS
Asthma; children; exposome; pharmacogenomics; precision medicine.

INTRODUCTION

Asthma is a chronic respiratory disease of the airways affecting about 9% of children in the US and 15% of school-aged children in Europe (1), remaining a significant global health burden worldwide (2). The term "asthma" encompasses subgroups of patients characterized by considerable clinical variability, with some having persistent and some only transient or intermittent symptoms, some having eosinophilia and some not, some showing reduced and some normal lung function, some responding well to prescribed treatments and others with

severe forms of therapy-resistant disease (3). Despite advances in understanding the mechanisms underlying the disease, the general principles of therapy have remained the same over time, being based on an approach calibrated on severity and exacerbations (4). Indeed, asthma guidelines have traditionally advocated a stepwise approach to treatment, in which uncontrolled patients are treated with higher doses or combinations of drugs. However, it is well recognized that patients with heterogeneous diseases comprising multiple phenotypes do not respond equally to the same treatment and have different prognoses. Therefore, such a traditional approach to asthma therapy may result in overtreating some patients, exposing them to adverse side effects from potentially harmful drugs, and undertreating others, putting them at risk of acute exacerbations. This suggests that patients with asthma need a more personalized and precise treatment approach (5).

The term “precision medicine” has been recently proposed to indicate “treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations” (6). Hence, this concept refers to the probability of responding (or not) to a certain therapeutic intervention and/or of suffering (or not) adverse effects, and can be adopted as an innovative strategy to guide asthma treatment (7). The challenge in achieving the concept of precision medicine is defining disease endotypes, that is identifying specific subtypes of a disease based on underlying molecular mechanisms, rather than on clinical features. Indeed, characterization of the endotype is crucial to ensure an optimal response to treatment (8).

It has been recently proposed that the interaction between the genetic background (genome) and the cumulative environmental exposures over a lifetime (exposome), through complex biological networks, determines the emergence of several cellular and molecular mechanisms that contribute to endotypes and clinical phenotypes (7).

Herein, the latest developments related to childhood asthma in the fields of exposome and pharmacogenomics are reviewed, describing their contribution to our current understanding of disease endotypes with regard to treatment response, and discussing challenges in integrating these innovative approaches into clinical practice as well as opportunities for future research.

The Exposome: an innovative approach for assessing environmental determinants in childhood asthma

Starting from the recognition that the genome alone explains only a small part of the variance observed in patients with chronic diseases, the exposome concept was introduced about 15 years ago as an innovative approach for providing a deep comprehension of the role that environmental risk factors have in disease etiology and pathophysiology, thus encompassing the totality of the environmental exposures occurring over a lifetime (9-11). Indeed, the exposome aims to cover the time frame of lifelong exposure history, providing an accurate assessment of the impact of environmental factors on human health, capturing the fluctuating dynamics of environmental exposures, the diversity in their sources, and their interactions and also considering that body responses against these exposures can mediate the influence of these exposures on individual health (12).

The exposome encompasses three different domains interacting closely with each other: the general external exposome, which includes the urban-rural environment, climate, socio-economic and psychological factors; the specific external exposome, which includes exposures from chemical (including environmental pollutants), biological (infectious organisms, diet), physical (radiation, noise) and lifestyle factors; the internal exposome, including internal biological factors, such as metabolic factors, gut microbiota, inflammation, oxidative stress and aging (**Figure 1**) (13).

More recent definitions of the exposome have been formulated to include the application of omics sciences that can better characterize exposures and the molecular changes associated with exposures, introducing the concept of “precision exposomics” within the context of precision medicine (14).

Given that different types of environmental exposures occurring throughout life have a major impact on asthma, an exposome-based approach appears to be particularly indicated, as it provides a risk profile rather than individual predictors (15). The first study investigating

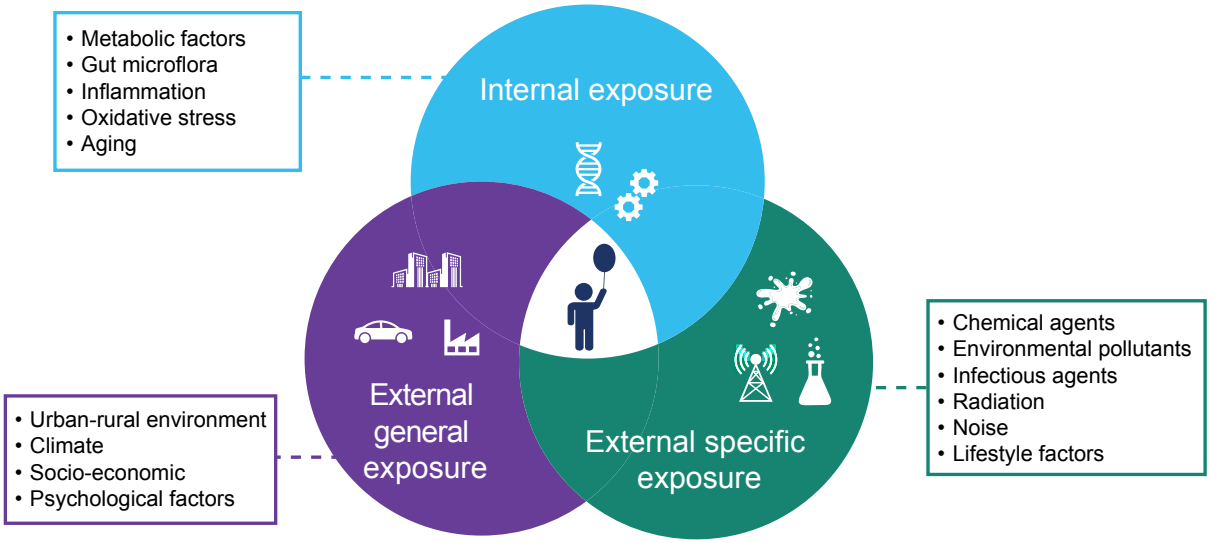

Figure 1. *The three exposome domains: general external, specific external and internal.*

childhood respiratory health through an exposome approach has been based on the Kingston Allergy Birth Cohort, a prenatally recruited cohort characterized by a wide variety in environmental exposures.

Data about respiratory symptoms of 235 children at 2 years of age were obtained by parents. All the three exposome domains showed effects on the respiratory health of the study population. In particular, significant associations were observed between wheeze or cough without a cold and prenatal tobacco smoke exposure, mold/dampness in the house, and the use of air fresheners in the home environment. On the contrary, breastfeeding, older siblings, and increased gestational age were associated with decreased respiratory symptoms (16).

In the past years, some initiatives have been launched with the aim of expanding the current knowledge on the exposome approach in pediatric environmental health. In 2014, the "Health and Environment-wide Associations based on Large population Surveys" (HEALS) project (FP7-ENV- 2013- 603946 http://www.heals-eu.eu/) was funded by the European Commission with the aim to describe in a series of about 335,000 individuals the internal exposome by integrating omics and biomonitoring data through population studies taking into account different levels of environmental exposure, age-specific windows of exposure, and genetic variability (17-19). Notably, the HELIX project (https://www.projecthelix.eu/), involving six birth cohorts, has been already launched to investigate, with the aid of omics markers, the relationships between the early childhood exposome and health in 32,000 mother-infant pairs, as well as measure growth, development and children's health, including asthma and lung function (20, 21). In this context, the association between 85 prenatal and 125 postnatal environmental exposures and lung function has been investigated in 1,033 children aged 6-12 years. The authors reported that lower values of FEV_1 were associated with prenatal perfluorononanoate and perfluorooctanoate exposures, as well as with 9 postnatal exposures (copper, ethyl-paraben, phthalate metabolites concentrations, house crowding, and facility density around schools), whereas the inverse distance to the nearest road during pregnancy was associated with a higher FEV_1 (22). More recently, the PROMESA cohort study protocol aims to characterize the external exposome (ambient and indoor exposures) and its contribution to clinical respiratory and early biological effects in children under five in tropical countries (23).

Though promising, the study of the exposome is challenging both in terms of measuring it and analyzing its relationship to health. Exposure assessment should be "holistic", with different assessment tools that are needed for different exposure domains. The exposome approach then involves the collection of cumulative measures of external and internal exposures since preconception. Measuring the "totality" of exposures also requires the use of wearable devices capable of

evaluating personal exposures in real time. Therefore, being able to increase the volume of exposures without affecting the measurement accuracy is a major challenge in exposome research (24).

According to this vision, the "European Environmental Exposure Assessment Network" (EIRENE) project (https://www.eirene-ri.eu/) was launched to support a comprehensive research on human health and the environment. Based on the Czech national research infrastructure RECETOX (https://www.recetox.muni.cz/en/services/recetox-ri), EIRENE connects 50 research institutions from 17 countries around the world, with the mission of studying the effects of long-term exposures to various types of environmental stressors on human health and the roles played by such exposures in the development of chronic diseases. In addition, within the context of the "European Long-term Study of Pregnancy and Childhood" (ELSPAC) (https://www.elspac.cz/index-en.php), a prospective study launched by the World Health Organization (WHO) in the early 1980s in six European countries, the CELSPAC platform (https://www.recetox.muni.cz/en/services/celspac-population-studies/celspac-study) is continuing to expand data collection, build large databases, and create new protocols for addressing the exposome concept in environmental health (25).

These initiatives are expected to contribute to a better understanding of the relationships between environment and health through studies that will need to be continuously ongoing and systematically evaluated. Indeed, levels of environmental stressors usually vary during lifetime, and individual changes in lifestyle can result in increased or decreased exposures (26). Moreover, certain life stages are recognized to be more susceptible to environmental exposures with regard to specific health outcomes such as asthma (15). In this context, the use of prospective birth cohort studies has been advocated (11, 27). However, it should be pointed out that biomarkers of exposure might not be continuously recorded for a long time. Another issue to be considered is the risk of increasing exposure misclassification due to the increased number of time-varying exposures assessed (28). Additionally, other gaps in the research field of exposome need to be acknowledged, i.e. the ability to link exposome and genome data in order to investigate gene-environment interactions. Moreover, we lack validated criteria for selecting the best assay for assessing the chosen research question, as well as guidelines for sample collection, repositories and biobanks, data sharing and security (15). From a statistical point of view, methodologies combining omics and multiple exposures, mediators, confounders, and outcomes are needed, along with specific expertise to optimize the analyses of complex data and to facilitate transdisciplinary collaborations (29). Finally, exposome-based projects are highly expensive due to the large study sample sizes and to the use of innovative tools required to assess several exposome components, including environmental monitoring and omics technologies (30).

In summary, the main future research perspectives in the field of exposome include:

- to improve the identification of the target population according to the research question, the optimal study design, timing and duration of measurements;
- to establish standards for data collection and security, as well as for the use of emerging technologies for the exposome assessment;
- to develop advanced biostatistical approaches for linking a large number of exposures with biological and clinical outcomes.

Pharmacogenomics: an innovative approach for assessing response to treatment in childhood asthma

The term "pharmacogenomics" refers to a subfield of genomics, i.e., the genome-wide study of variants in the deoxyribonucleic acid (DNA), which evaluates the effect of genetic variants on the individual's response to treatment (31). The relevance of pharmacogenomics has been recognized even by the European Medicines Agency, that described pharmacogenomics as an "integral part of the development and post-authorization (marketing) phase for a number of medicines, with significant impact on the management of their benefits and risks in clinical use" (32, 33). Indeed, the degree of the genetically determined variability in response to pharmacological treatment can vary considerably, from 20 to 95% depending on the drug (34). Therefore, the availability of a pharmacogenomic test would dramatically influence the choices made by the prescriber, detecting a genetic predisposition to an adverse drug reaction, or differentiating between drug responders and drug non-responders, or indicat-

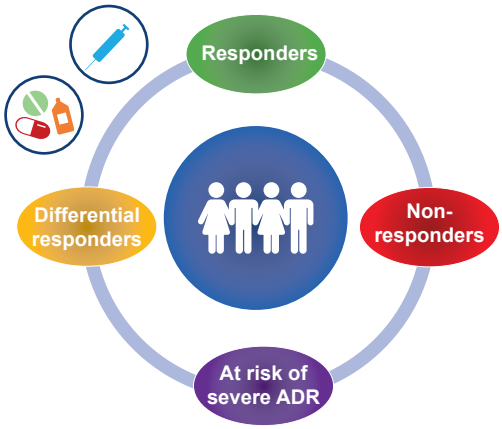

Figure 2. *Stratification of patient groups according to treatment response. ADR: adverse drug reaction.*

ing that a different dose of the drug - or in some cases a different class of drug - is needed (**Figure 2**) (35).

With regard to asthma, there is evidence that individuals from different populations and ethnic groups respond differently to pharmacological treatment, likely due to genetic variants inherited from a specific ancestry associated with disease severity or response to treatment (36). This suggests that the inter-individual variation in drug response in asthmatic patients could be partly genetically determined (37).

Despite the numerous genetic variants identified, the poor replication of the results obtained only partially explains the heterogeneity of the response to treatment in pediatric asthma. With regard to response to inhaled corticosteroids (ICS), the most consistent findings have been reported for DNA variants in chromosomes 5 (rs10044254), 6 (rs6924808), 11 (rs1353649) and 16 (rs2388639). Other genetic variants have been associated with response to ICS, though not reaching genome-wide significance. The most relevant results were reported for the FCER2 gene, encoding for a low-affinity IgE receptor (CD23). In particular, the DNA variant rs28364072 has been associated with asthma symptoms and poor lung function, and the largest effect was reported with the risk of exacerbations (hazard ratio: 3.95, 95% CI: 1.64-9.51) (38). Genetic variation has also been associated with response to long-acting β-2 agonists (LABA) in children. According to a recent systematic review including eight studies on children (n = 6051), the ADRB2 rs1042713 variant resulted more associated with LABA response in children than in adults. In particular, five studies and a meta-analysis reported an increased risk of exacerbations in children having one or two A alleles (OR: 1.52, 95% CI: 1.17-1.99), suggesting to investigate further the potential role of rs1042713 genotyping for personalized treatment in pediatric asthma (39).

Pharmacogenomic testing has recently become mainly available and less costly; however, challenges and evidence gaps have been associated with its use in childhood asthma research and practice (40). In addition, whereas the use of pharmacogenomics in pediatrics is currently limited to less common diseases, such as cystic fibrosis (41), international guidelines for asthma do not recommend it. In spite of this, a pilot prospective questionnaire-based study recently conducted in children and young people with asthma, their parents, and healthcare professionals at a secondary/tertiary children's hospital in the UK demonstrated that the use of genetic information to guide asthma management it is widely acceptable. In particular, 46% of participants were happy about sharing genetic data with healthcare providers, and 46% agreed to share solely to guide asthma management (42). A relevant issue to address in pharmacogenomics is the identification of genetic markers associated with treatment response in patients with different ethnicities to guide asthma treatment (43). Additionally, validation of the genes identified to date, as well as identification of the loci accounting for a large proportion of the variation in treatment response should be considered (40). International collaboration may be helpful in identifying genetic markers in large samples of well-phenotyped children with asthma. In this regard, the Pharmacogenomics in Childhood Asthma (PiCA) consortium was established as the first consortium focusing on pharmacogenomics in pediatric asthma. PiCA's main goals are developing a platform to discover new pharmacogenomic markers, replicating identified loci associated with treatment response, and ultimately establishing algorithms to guide asthma treatment (44).

Another potential limitation to the application of pharmacogenomics in the clinical management of asthma patients is the little functional evidence and the lack of experimental studies investigating the link between genetic markers identified and biological pathways (45).

Given the existence of many asthma pheno/endotypes, a promising approach in asthma pharmacogenomics is through applying phenome-wide association studies (PheWAS), which test for associations between genetic variants and a wide range of phenotypes in a given population (46). The application of pharmacogenomics in childhood asthma should also take into account the heterogeneous disease endotypes to improve the response to biological drugs (47). Genome-wide interaction studies (GWIS) might also provide novel insights into complex relationships between genetic background and the environment. Through this, Dahlin *et al*. have identified age-by-genotype interactions in several asthma candidate genes, suggesting that age-specific genetic mechanisms may be implicated in the response to ICS as measured by the occurrence of exacerbations. In particular, the top-ranked age-by-genotype association was found for the DNA variant rs34631960 in THSD4, a gene potentially involved in lung function, airway remodeling, and asthma severity, which could be protective against the risk of exacerbations in younger asthmatics on ICS treatment, or, conversely, may predict an increased risk of poor ICS response in older patients (48).

Actually, one of the main challenges for the implementation of pharmacogenomics in clinical practice is the lack of validated and useful biomarkers. High-throughput technologies approaching different-omics layers simultaneously, hold the promise of expanding our knowledge of molecular mechanisms underpinning asthma pathophysiology and may contribute to select and stratify targeted treatment strategies (49-51). Nevertheless, integrating multi-omics and clinical data needs large-scale databases, strong computational power, and close collaboration between clinicians and bioinformaticians (43). In this context, the Biobanking and BioMolecular resources (BBMRI-ERIC) infrastructure (https://www.bbmri-eric.eu/) (52), sustains the collection of biological samples that may be useful to detect new targets for therapy and may support drug discovery and development. In addition, the ELIXIR infrastructure (https://elixir-europe.org/) (53), which integrates and sustains bioinformatics resources across European life science organizations, may provide new insights from large data sets, particularly data from gene sequencers.

Finally, implementing a multidisciplinary team of healthcare professionals and stakeholders for the care of children with asthma will be a crucial aspect in the context of an innovative model of therapeutic management that also includes pharmacogenomics in the evaluation of response to treatment (35).

In summary, the main future research perspectives in the field of pharmacogenomics include:

- to investigate the associations between genetic variants and different asthma phenotypes;
- to study the interaction between the genetic background and the environment;
- to correlate endotype and response to treatment with biological drugs;
- to develop and validate genetic biomarkers that can help select and stratify personalized therapeutic strategies.

CONCLUSIONS

Asthma is a complex and heterogeneous disease that requires individualized management. Uncontrolled asthma is still an issue worldwide, particularly in low-resource settings (54). In childhood, poor asthma control can irreversibly compromise the children's lung function. Beyond asthma phenotypes, considering disease endotypes is considered a crucial issue in developing tailored therapies (55). Looking at the concept of precision medicine in childhood asthma, we need validated biomarkers to identify the main drivers of morbidity, allowing the provision of the right treatment, at the right time to the right patient.

It has been suggested that the interaction between genome and exposome determines the emergence of several cellular and molecular mechanisms that contribute to different asthma endotypes and clinical phenotypes (7). The latest developments related to childhood asthma in the fields of exposome and pharmacogenomics may contribute to identify disease endotypes with regard to treatment response. Indeed, an exposome-based approach is particularly suited to chronic diseases such as asthma as it provides a risk profile rather than individual predictors. On the other hand, advances in pharmacogenomics pave the way for investigating the association between treatment response and genetic variants. However, main challenges are associated with exposome and pharmacogenomics in childhood asthma research and practice (**Figure 3**).

Exposome	Pharmacogenomics
■ Heterogeneity of measurements ■ Lack of measurement standards	■ Studies underpowered with limited effects size ■ Heterogeneity in outcome measures and in study populations
■ Exposures rapidly change with individual locations and activities ■ Data have to be accumulated over long times and from multiple sources	■ Identification of genetic markers associated with treatment response in patients with different ethnic background ■ Link between genetic markers and biological pathways
■ Collecting several biosamples per subject may be logistically cumbersome ■ High-throughput «omics» technologies are expensive and still lack of standardized procedures	■ Cost-effectiveness ■ Difficulties in interpreting test results

Figure 3. *Main challenges associated with exposome and pharmacogenomics in childhood asthma research and practice.*

Though many genetic variants have been shown to influence response to asthma treatment, results are still inconsistent and/or effect sizes are small. Furthermore, it should be considered that epigenetic changes, gene-gene and gene-environment interactions could affect pharmacogenomic associations (37). In this regard, Perez-Garcia *et al*., report novel associations of epigenetic markers with bronchodilator drug response (BDR) in pediatric asthma identifying five differentially methylated regions and two CpGs in African Americans located in FGL2 (cg08241295, $p = 6.8x10^{-9}$) and DNASE2 (cg15341340, $p = 7.8x10^{-8}$), demonstrating that BDR influence DNA methylation (DNAm) and ultimately showing the applicability of pharmacoepigenetics in precision medicine of respiratory diseases (56).

Sustainability and large-scale population-based studies are needed in order to improve research in exposome and pharmacogenomics. In addition, huge efforts are required in terms of consortia building as well as development and validation of measurement devices and statistical tools. Furthermore, collaboration between experts from different fields (such as clinicians, pharmacologists, immunologists, and data scientists) is required to pave the way for more precise, personalized, and effective management of childhood asthma, and to identify endotypes/phenotypes that are predictive of therapy response. Integrating multi-omics and clinical data might improve the ability to predict treatment response in children with asthma and to build decision support tools potentially valuable for the selection of drugs, in particular emergent and expensive biologicals, and to predict adverse events as well as exacerbations and decline in lung function (40).

COMPLIANCE WITH ETHICAL STANDARDS

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Author contributions

Conceptualization and writing original draft: GF; writing review, editing and supervision: GP and SLG. All authors contributed to the article and approved the submitted version.

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N/A.

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Plagiarism

All original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

Manipulation of images

All images are original.

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BRIEF REPORT

Indications and outcomes of exercise challenge tests performed in children before and during COVID-19 pandemic

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ABSTRACT

COVID-19 pandemic has had a significant impact on general health. In fact, although barely affected by respiratory problems, children and adolescents undoubtedly suffered from the consequences of the pandemic, especially from a psychological standpoint. We aimed to evaluate whether the COVID-19 pandemic modified the indications and the results of Exercise Challenge Tests (ECTs) conducted in a pediatric pulmonology center. This was an observational retrospective monocenter study. We analyzed indications and results of all the ECTs performed between March 2021 and September 2022 (COVID-19 period) and, for comparison, those performed between September 2018 and March 2020 (pre-COVID-19 period). 62 ECTs were performed during the COVID-19 period and 64 during the pre-COVID-19 (proportion of positive test 19.3% and 18.7%, respectively). During the COVID-19 period there was a significant increase (18 vs 4) in the number of ECTs requested because of a mix of subjective respiratory symptoms and vague non-respiratory symptoms and all these tests resulted negative. During the pandemic era we observed an increased number of children and adolescents complaining mixed subjective exercise-related respiratory and non-respiratory symptoms. The ECTs conducted in these patients were all negative, suggesting a functional nature for the reported symptoms.

IMPACT STATEMENT: The COVID-19 pandemic has significantly influenced pediatric health, especially from a psychological standpont. We analyzed Exercise Challenge Tests (ECTs) performed before and during Covid-19 Pandemic. We demonstrated that during the COVID-19 period there was a significant increase in the number of ECTs requested because of a mix of subjective respiratory symptoms and vague non-respiratory symptoms and all these ECTs resulted negative.

KEY WORDS
Children; COVID-19; exercise challenge test; exercise-induced asthma; Sars-Cov2.

INTRODUCTION

Exercise challenge test (ECT) is a standardized test used to investigate exercise related respiratory symptoms allowing the differentiation between exercise-induced broncho-constriction (EIB) and other conditions (1, 2).

ECT, in fact, can trigger airway obstruction activating endogenous pathways involved in the pathophysiology of asthma (3). Moreover, the ECT can help differentiating EIB from other exercise related respiratory symptoms such as dysfunctional breathing or exercise-induced laryngeal obstruction (EILO), physical

deconditioning and subjective sensation of breathlessness when reaching the personal physical limit (4).

COVID-19 pandemic had a significant impact on general health of children and teenagers.

Although children and adolescents have been less affected than adults from a medical perspective, showing milder respiratory symptoms, lower mortality (0-0.2%) and a better prognosis, they have been heavily affected by the psychological consequences of drastic routine disruption and lack of social interaction due to lockdown, distance teaching and sport interruption (5-7). During the pandemic, an increased number of emergency visits was reported for somatoform disorders, including disturbed sleep as well as respiratory and gastrointestinal issues (8, 9). The most frequently reported respiratory symptoms were shortness of breath and chest pain (8, 9). Moreover, dysfunctional breathing complaints because of hyperventilation during protective face mask wearing (10). These manifestations can mimic common respiratory disorders, like asthma, leading to further investigations to exclude a possible underlying pathologic condition.

We aimed to evaluate whether the COVID-19 pandemic modified the indications and the results of ECTs conducted in a tertiary referral pediatric pulmonology center, having the ECTs conducted in the period before the pandemic as control.

METHODS

In this retrospective study we analyzed the indications and results of the ECTs performed at the Pediatric Allergology and Respiratory Medicine Unit of Women's and Children's Health Department of our Hospital.

Two different periods were considered: the first period, (pre-COVID-19 period) included the 18 months before the pandemic, from the 1st of September 2018 to the 1st of March 2020; the second period (COVID-19 period), coincided with the second part of the pandemic, from the 1st of March 2021 to the 1st of September 2022.

ECTs were scheduled in outpatients attending the Pediatric Allergy and Respiratory Medicine Unit who reported exercise related respiratory symptoms and who had a normal spirometry test at baseline and a negative bronchodilator reversibility test. ECTs were requested by the doctors who evaluated the patients. An independent pediatrician involved in the research project retrospectively analyzed all the ECT indications and classified them. ECTs were conducted according to American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines and interpreted as positive in case of a post-exercise FEV1 decline of 12% or higher (1, 2).

Fisher's exact test was used to compare proportions between groups, while the age was compared using t-Test for unpaired data. The study was approved by the Ethics Committee of our Hospital (328n/AO/23).

RESULTS

62 ECTs were performed during the COVID-19 period and 64 during the pre-COVID-19 period, with a similar proportion of positive tests (19.3% and 18.7%, respectively).

During the COVID-19 period, the 62 patients enrolled were 33 males and 29 females and had a mean age of 12.5 years (range 7.0-16.0) (see **Table 1**). During the pre-COVID-19 period, the 64 patients enrolled were 46 males and 18 females and had a mean age of 11.5 (range 7.4-19.5) (see **Table 1**).

16 (26%) patients tested during the COVID-19 period had a personal history of SARS-CoV2 infection before the ECT. In all these patients the disease presented with mild symptoms followed by complete recovery.

The proportion of positive ECT was similar in patients with and without a personal history of COVID-19 (18,7% vs 19,6%, p = 0.9).

According to ECT indications, patients of both periods were classified in the following 4 groups:

1. asthmatic patients who reported exercise-induced respiratory symptoms, despite regularly taking the maintenance therapy and having no symptoms apart from those related to physical activity;
2. patients with no previous diagnosis of asthma who reported respiratory symptoms only with exercise;
3. patients with no previous diagnosis of asthma who reported both exercise-related and at rest subjective respiratory symptoms;
4. patients with no previous diagnosis of asthma who reported exercise-related subjective respiratory symptoms (often described as short breath or inability to take a deep breath) together with vague non-respiratory symptoms (i.e. chest/abdominal pain, dizziness, hyperventilation with tremors, weakness and nausea).

Table 1. *Patient's demographic characteristics and group distribution according to exercise challenge test (ECT) indications and ECT results.*

	Pre-COVID-19 period		COVID-19 period		p value
Number of ECTs	64		62		
Males/Females	46/18		33/29		**0.04**
Age (mean, range)	11.5 (7.4-19.5)		12.5 (7.0-16.0)		0.21
Group 1	21 (33%)		11 (18%)		0.065
	Positive ECT 3 (14%)	*Negative ECT* 18 (86%)	*Positive ECT* 5 (45%)	*Negative ECT* 6 (55%)	
Group 2	36 (56%)		26 (42%)		0.11
	Positive ECT 8 (22%)	*Negative ECT* 28 (78%)	*Positive ECT* 7 (27%)	*Negative ECT* 19 (73%)	
Group 3	3 (5%)		7 (11%)		0.20
	Positive ECT 1 (33%)	*Negative ECT* 2 (67%)	*Positive ECT* 0 (0%)	*Negative ECT* 7 (100%)	
Group 4	4 (6%)		18 (29%)		**<0.001**
	Positive ECT 0 (0%)	*Negative ECT* 4 (100%)	*Positive ECT* 0 (0%)	*Negative ECT* 18 (100%)	

Patient's demographic characteristics, classification according to indication and ECT results are reported in **Table 1**.

The number of ECTs belonging to group 4 significantly increased during pandemic (p <0.001).

The distribution of positive and negative ECTs within each group in pre-COVID-19 and COVID-19 period is shown in **Figure 1**.

The number of positive ECTs in group 1 (asthmatic subjects with persistent exercise-related respiratory symp-

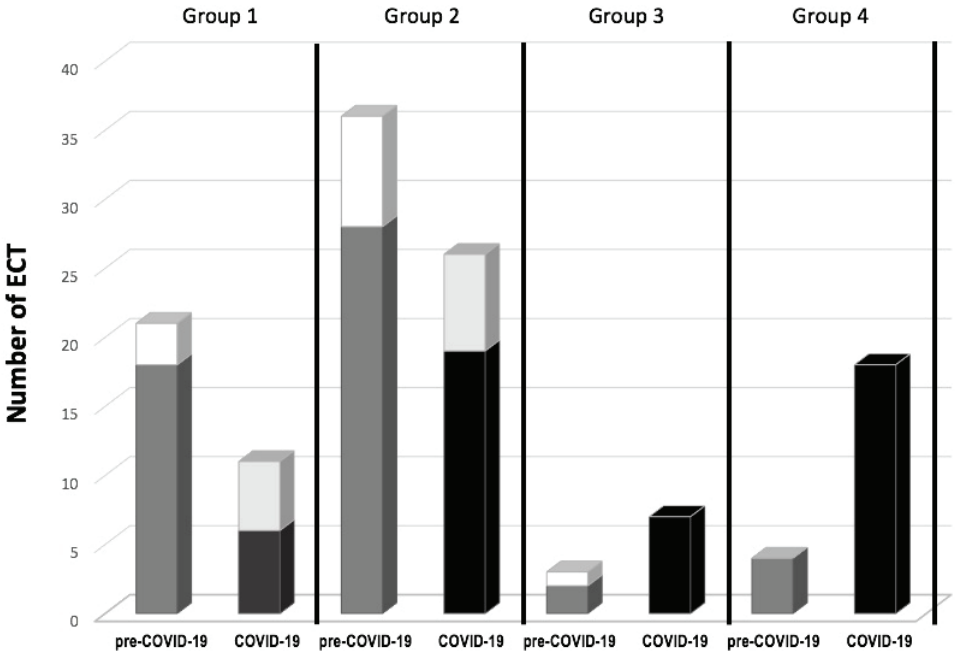

Figure 1. *Exercise challenge test (ECT) indications and results during pre-COVID-19 and COVID-19 period. For each group negative tests are represented in dark gray (pre-COVID-19 period) or black (COVID-19 period), while positive tests are represented in white and light gray respectively.*

toms) was similar in the two periods analyzed (3 vs 5 pre- and during COVID-19 respectively) although the proportion was higher in the COVID-19 period (45% vs 14%). Comparison of positive ECTs between the two periods resulted similar also in groups 2 (8 vs 7) and 3 (1 vs 0). No ECTs resulted positive in group 4 in both periods.
Patients with history of Sars-Cov2 infection (n = 16) were distributed among different groups as it follows: group 1 (n = 3), group 2 (n = 8) and group 4 (n = 5).

DISCUSSION

Our data show, during the COVID-19 pandemic, a significant increase in the number of patients who underwent an ECT because of mixed subjective exercise-related respiratory symptoms (often described as short breath or inability to take a deep breath) and vague non-respiratory symptoms (chest/abdominal pain, dizziness, hyperventilation with tremors, weakness and nausea) (group 4). The ECT was negative in all these patients and, therefore, the reported respiratory symptoms were interpreted as somatic.
These findings suggest that, in many cases, respiratory symptoms reported by children and adolescents during the COVID-19 pandemic had psychological roots. This hypothesis is in keeping with the increased anxiety, depression and psychological distress described by several papers in children and adolescents (11-14).
Factors contributing to the development of psychological issues in children and adolescents during the pandemic include concern of severe illness and fear of losing relatives, social isolation due to quarantine, routine life disturbance, exposure to parental stress and concern for family financial loss (5, 6, 15, 16). Pre-existing mental health problems has been described as a major risk factor (17). Also female gender has been reported as a risk factor, as girls seemed more exposed to COVID-19 psychological negative consequences (18, 19). Our data are in keeping with this, in fact we observed a significant increase in the request of ECTs in girls during pandemic ($p = 0.04$).
Children's vulnerability to the pandemic negative psychological effects has been highlighted by various cross-sectional studies and systematic reviews, which indeed focused especially on anxiety symptoms, while somatoform disorders have been less explored (8, 12, 16, 20). Somatization is a common phenomenon encountered in pediatrics, characterized by presentation of symptoms that are inconsistent with history, physical examination, and investigative findings (21). When symptoms cause distress and affect patient's everyday functioning, somatization becomes a medical illness, defined by DMS-5 "somatic symptom disorder" (SSD) (15).
Children's most frequent somatization include pain manifestations such as abdominal pain and headache, and respiratory issues (e.g. dysfunctional breathing, hyperventilation, sighing dyspnea, psychogenic cough) (22).
R. Turco *et al*. recently reported, in children, a significant increase in emergency department admission rate because of somatic symptom disorder during pandemic compared to pre-pandemic year (8). In this retrospective study, the symptoms reported more frequently in pandemic compared to pre-pandemic era were chest pain, trouble breathing, anxiety, insomnia, general discomfort, anorexia, dysphagia and tachycardia, with children under 12 being apparently more affected than adolescents (8).
In a cross-sectional survey focused on behavioral consequences and coping strategies related to the COVID-19 pandemic, interviewed parents reported behavioral changes and somatoform disorders in 64.3% and 72.5% of children under 6 and 6-18 years, respectively (9). Somatization was the major behavioral change observed in the 6-18 years old group, being shortness of breath the most frequently reported symptom, while children under 6 years of age were mostly affected by behavioral changes (irritability and sleeping disorders, in particular) (9).
Interestingly, our study did not reveal an increased number of ECT-based asthma diagnosis during the pandemic. In fact, the number of positive ECTs (FEV1 fall higher than 12%) was the same in the two periods analyzed (n = 12 in each period), with almost all the children with a positive ECT belonging to group 1 (which included asthmatic children) and group 2 (which included children with respiratory symptoms only during physical activity).
Moreover, we found no significant association between the ECT result and the previous SARS CoV2 infection since the proportion of positive ECTs was similar in children with and without a personal history of COVID-19.

These data suggest, one more time, that the differences described between the pre-COVID-19 period and the COVID-19 period are not ascribable to a lung dysfunction induced by the viral infection but they are likely due to the psychological distress suffered during pandemic by children and adolescents.

We acknowledge that our results have to be interpreted with caution considering study limitations. Being a retrospective study, we might have missed useful information regarding, first of all, psychological background, that could provide a better characterization of somatic aspects in our patients.

Furthermore, it could be argued that for children and adolescents belonging to group 4 the medical history and the type of symptoms reported were already indicative of a possible functional disorder. Indeed, it is difficult to exclude an underlying respiratory condition by considering only the medical history. In addition, proving that the exercise test causes no significant symptoms nor airway obstruction can reassure the patient (and family), making the child or adolescent confident in going back to his/her regular activities, including sport training.

In conclusion, during the pandemic era we observed an increased number of children and adolescents complaining mixed subjective respiratory and non-respiratory symptoms. The ECTs conducted in these patients were all negative, demonstrating no exercise-induced bronchial obstruction or respiratory symptoms. Our findings suggest a functional nature for these symptoms and are in line with the pandemic-related increase in somatoform disorders in children and adolescents previously described by other authors.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have no conflicts of interest to declare.

Financial support

The authors have no relevant financial or non-financial interests to disclose.

Authorship

All the authors critically revised the manuscript and approved its final version.

Author contributions

Study conception: SC and SZ; clinical data: GDB and VF; data analysis: SC; first draft of the manuscript: GDB. All the authors critically revised the manuscript and approved its final version.

Ethical approval

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and it was approved by the Ethics Committee for Clinical Research of Padova (Comitato Etico per la Sperimentazione Clinica della provincia di Padova) (328n/AO/23).

Human studies and subjects

N/A.

Animal studies

N/A.

Data sharing and data accessibility

Data are available in the text of the article.

Publication ethics

Plagiarism

All original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

Manipulation of images

All images are original.

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BRIEF REPORT

Telemonitoring in Cystic Fibrosis: a single centre experience in a Tertiary Paediatric Hospital

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ABSTRACT

Telemedicine during Covid-19 pandemic became a necessity to reach and follow up patients with chronic diseases. During this emergency period patients with cystic fibrosis required a follow-up reorganization to stay safe and to prevent cross-infections. The aim of this study was to explore the adherence to a telemonitoring program, patients' clinical status and to measure the rate of satisfaction related to our telemedicine program thought for patients with cystic fibrosis enrolled in a tertiary paediatric hospital.

Fifty patients (M 29 age mean 35,6 y) were enrolled in a study period from 2020 to 2022 with a rate of transmission data of twice a week; 30 of them were monitored also for lung function with the MIR Spirobank (spirometer).

The majority of data sent was during the Covid-19 pandemic with 1605 records forwarded; adherence was better particularly in females, and patients who lived farther away from our center. The FEV_1 mean value was 74.8%, 74.2% and 74.0% in 2020, 2021 and 2022 respectively. Average response rate about satisfaction and utility of the offered telemedicine service was respectively 4,03 and 4,5 on a 5-point Likert scale.

Thanks to transmission of spirometric values in 30 patients, we have intercepted indirectly 14 potential bronchopulmonary exacerbations, studying the delta variation between spirometries executed along the pandemic period and the previous consecutive values, preventing the use of unnecessary antibiotics.

Telemedicine could be a useful tool to be included in the follow-up of CF patients that could help families lowering the costs for frequent travels and containing the burden of healthcare management. Future efforts in chronic disease management should improve the use of telemedicine.

IMPACT STATEMENT: This brief report has the aim to underline the role of telemedicine in cystic Fibrosis not only during Covid-19 pandemic period.

KEY WORDS
Telemonitoring; Cystic fibrosis; Covid-19; telemonitoring; telemedicine; sensor technology.

BACKGROUND

Cystic fibrosis (CF) is the most common autosomal recessive genetic pathology of the Caucasian race and it affects nearly 100,000 people worldwide (many have not been diagnosed) and, in Italy, we count around 6000 patients (1). Functional failure of CF leads to multisystemic dysfunction, such as lungs, gastrointesti-

nal tract, liver and pancreatic gland. Impaired mucociliary clearance and dense secretions primarily result in chronic pulmonary inflammation and infections, irreversible lung architecture modification, respiratory failure and death (2). Most people with CF will require lifelong treatment involving frequent hospital visits and admissions and rigorous daily therapy regimens (oral treatment, aerosol therapy, airway cleaning, and also physical activity rehabilitation) (3). Since many of these treatments necessitate frequent and continuous hospital visits for assessment and ongoing management, telemedicine and telemonitoring may be useful. Telemedicine is defined as a direct, synchronous, or remote communication between a physician and a patient (4). Telemedicine could potentially supply remote specialistic performance such as cardiological, pulmonary or rehabilitation service. In respiratory diseases, the telemonitoring was demonstrated to be able to identify early changes in patients' conditions; this is important to guarantee specific interventions and to avoid pulmonary exacerbations (5, 6). The role of remote telemonitoring had been of crucial importance during Covid-19 (7, 8, 9, 10, 11). The pandemic reality has underlined the extreme necessity of promoting remote monitoring for chronic conditions like cystic fibrosis, and it has shown how the use of telemedicine could prove to be extremely useful in this emergency (8, 9).

The primary objective was to compare the adherence to our telemedicine program during the whole study period, including the national pandemic of Covid-19. The secondary aims were to assess the clinical status of patients in relation to: lung function, number of hospitalizations for bronchopulmonary exacerbation and the need for extra visits or hospitalizations from 2020 to 2022, and in details during Covid-19 pandemic. Finally, we aimed to explore impression and satisfaction of patients related to our telemedicine program through a questionnaire distributed to patients.

MATERIALS AND METHODS

A longitudinal observational study was conducted at Bambino Gesù Children's Hospital during a period from 2020 to 2022.

Patients with Cystic Fibrosis (pwCF) were assisted by home tele-monitoring twice a week with remote transmissions of spirometric values and remote consultations with a specialized physician, respiratory physioterapist and research nurse. Demographic data entered by the user is used to calculate percent predicted values based on the Global Lung Function Initiative (GLI) (12).

Acceptable tests were compared to one another and were graded according to ATS guidelines (13).

The MIR Spirobank was used for telemonitoring in our patients, a portable spirometer that allows the transmission of data regarding the respiratory function to health specialists (nurses and physicians) and in some cases also tablet connected with Bluetooth and pulse oximeter. The program of remote telemonitoring includes two trasmissions per week and after each, the research nurse could call the patients or their parents to discuss the values of the spirometry executed.

RESULTS

Characteristics of 50 pwCF enrolled in the study are shown in **Table 1**. A total of 30/50 pwCF sent telemonitoring data regularly, also during Covid-19 pandemia.

In 2020, at the beginning of Covid-19 pandemic we recorded a peak of the number of telemedicine transmissions with a total of 1605 records submitted (**Figure 1**). On the contrary, during the last year of follow-up patients sent spirometries less frequently.

Looking at average trasmissions during and after the Covid-19 period (2020-2021) we found that the aver-

Table 1. *Patients characteristics.*

	Mean and/or N (%)
Patients characteristics	
Number of patients (M/F)	50 (39 M/21 F)
Age (years)	30,1
Staphylococcus colonization	36 (71%) 12 (24%)
Pseudomonas aeruginosa colonization	12 (24%)
Burkholderia Cepacia colonization	2 (5%)
Modulator	
Elexacaftor-Tezacaftor-Ivacaftor	27 (47%)
Compassionate use of Kaftrio	1 (3%)
Ivacaftor	8 (18%)
Without CFTR modulator	14 (28%)
Provenance	
Lazio region	34 (68%)
Other regions	16 (32%)

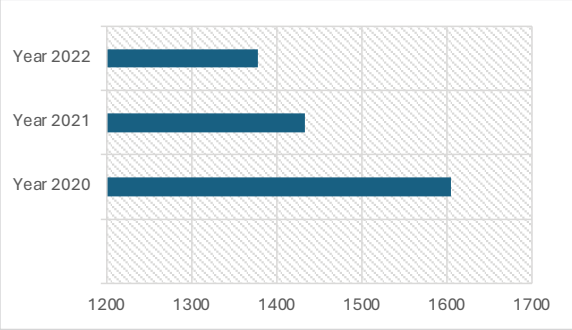

Figure 1. *Number of telemonitoring transmissions from 2020 to 2022.*

age of transmissions during the pandemia was 1,76 per week with a progressive decrease coming out from the pandemic period arriving at 0,86 (average of transmissions, data from 2022) (**Figure 2**).

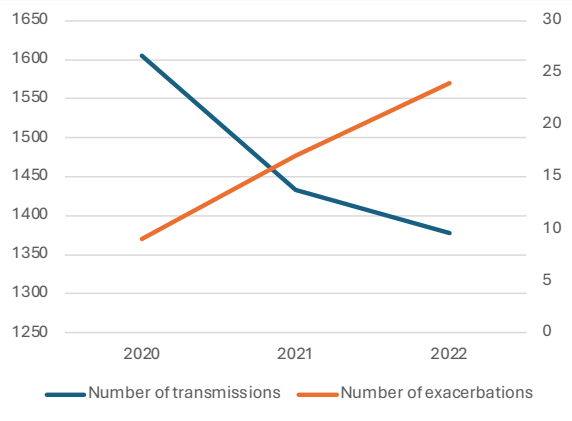

Figure 2*. Average number of transmissions and pulmonary exacerbations from 2020 to 2022.*

Adherence to trasmission was higher in females than males, 76% and 62,5% respectively. Patients living in other regions than Lazio had a higher average rate of transmission (1,54 transmission per week versus 1,21 transmission per week respectively).

Parents of paediatric patients sent transmissions more frequently than adolescents and adults. Patients living closer to the hospital (Lazio Region) progressively reduced the number of transmissions with a 25% reduction in particular after the period of Covid-19 pandemia).

The FEV_1 mean value was 74.8%, 74.2%, 74.0% and 76.9% respectively during 2020, 2021, 2022 and in the first 3 months of 2023.

Considering lung colonization, we recorded a lower FEV_1 in patients with *Pseudomonas aeruginosa* compared to patients with Staphylococcus aureus: FEV_1 mean 72,4 and 78%, respectively.

In 2021 we registered a decreased need for outpatients visits (-30%) comparing with 2022 year when there was a reduction of remote data transmission.

Thanks to the available spirometric values, we intercepted 9 pulmonary exacerbations during 2020, 17 during 2021 and finally 24 during 2022.

Regarding pwCF (30/50) who were in follow-up in telemedicine during Covid-19 period, a significant number (13,43%) was from other regions than Lazio (17,57%), and in particular from Calabria (3,10%), Molise (2,7%), Puglia (1,3%), Abruzzo (2,7%), Umbria (1,3%), and Campania (3,10%).

All those patients (30/30) could perform a home-spirometry, and 7 patients (23%) also had pulse oximeter and tablet for data transmission and to access to telemedicine platform; on the other hand 3 (10%) patients had only spirometer and tablet. 11/30 (36,6%) completed data trasmission twice a week, 12/30 (40%) patients once a week and only one patient (3%) sent spirometry every day. The rest of 6 patients (20%) preferred to send data after medical contact or for clinical need. Of these subgroups of 30 patients: 15 (50%) are in our telemedicine program from less than 3 years; 8 (26,7%) patients between 4 and 6 years, and 7 patients (23,3%) for over 6 years.

Those 30 patients were asked to answer to a specific questionnaire to explore their satisfaction and if they want to change something in telemedicine/telemonitoring service. 23/30 (76,6%) patients considered that telemonitoring service helped them to improve compliance to their daily therapy. Moreover, 26 patients (86,6%) reported that this program is helpful to intercept bronchopulmonary exacerbations.

18/30 (60%) would not want to change anything about the service, only 5 patients (16,6%) want to change the platform because considered it unclear and 7 patients (23,3%), instead, wanted to change both spirometer and platform. During the pandemic period the majority of patients (25, 83,3%) referred to feel more safe being part of the telemonitoring program which could them to prevent possible infections.

Finally, 24 patients (80%) reported that the telemedicine program improved their quality of life and that they felt more safe.

Average response rate about the satisfaction of the service was 4,03 on a 5-point Likert scale.
Average response rate about the utility of telemonitoring service was 4,5 always using the Likert scale.

DISCUSSION

The use of telemonitoring contributed to improve the quality of care during the pandemic period, and allowed our pwCF to reduce their need of hospital visits avoiding the risk of contracting the infection. As expected, number of patients admission after outbreak Covid-19 returned at the same level but during Covid-19 period telemedicine was a valid instrument to rationalize hospital access.
Telemonitoring could change the approach and management to chronic pulmonary diseases, and this seems valid also for pwCF. In fact, due to telemonitoring spirometric values, we intercepted 14 possible bronchopulmonary exacerbations, in particular considering a significant decrease of FEV_1 values between two consecutive spirometries. We could prevent the use of unnecessary antibiotics (intravenous or oral) in pwCF, stimuling patients to do respiratory physiotherapy and also underling the importance of physical activity increasing volume and number of training sessions (14). In particular these interventions could prevent a possible pulmonary damage. One important aspect about this tele-monitoring project is rationalization of hospital access, in fact patients decreased their hospital access, and in some cases, they transformed intravenous antibiotic treatment with outpatient access because the medical team stopped previously the possible exacerbations (15).
Probably the peak of adherence during the first year of pandemic underlines the priority for patients to stay safe and away from hospital, if their clinical conditions allowed it. The most important aspect was to intercept pulmonary exacerbations, in particular for patients with a severe lung damage. This is the most important result that underlines how this service can improve care for pwCF. In fact pulmonary exacerbations in CF are crucial events which progressively determine a loss of respiratory function, worsening of the quality of life and negatively impact overall survival. According to studies, lung function fails to return to baseline value in up to 25% of CF pulmonary exacerbations, despite a prompt antibiotic treatment (16, 17).
Patients thanks to telemonitoring have addressed more secure the pandemic years.
Telemedicine system could become a useful tool to monitor patients in a new CFTR modulator era where there are a reduced number of pulmonary flare ups and a new approach to disease with more number of outpatient controls (18). In particular, in Italy, Cystic Fibrosis centers are distributed mostly in large cities, and the use of telemedicine could cut the economic costs of patients travel and thus increase adherence to not postponeable checkups.
Despite the recommendation of physicians to transmit regularly, some patients were scared from the possible results obtained, infact FEV_1 deterioration in some patients brings a lot of psycological distress.
On the contrary, home monitoring might bear the risk of increased anxiety caused by increased awareness of deterioration in lung function in some patients (19). However, our experience showed that patients with CF considered our program to be useful to keep up with their daily treatment and let them feeling safer and more controlled.

CONCLUSION

In conclusion new forms of health care are to be evaluated for their impact on patients' health and also for their cost-effectiveness compared to traditional care, and telemedicine with tele-monitoring could be a passage essential to change the management of chronic diseases like Cystic Fibrosis. In summary, this experience offers the opportunity and consciousness to improve the use of telemedicine and to evaluate the use of telemedicine like a fundamental tool to manage pwCF in routine care, also reducing cost-effectiveness of medical treatments and high burden of health-care management.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors declare no conflict of interests.

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Authorship

Matteo De Marchis and Alessandra Federici.

Author contributions

Conceived the report: MDM, AF and SB; collected data: MDM and AF; wrote the manuscript: MDM, AB and NU; conceived and directed the work thanks to their knowledge of the subject matter: AGF and RC. All

Authors analyzed and interpreted patients' data read and approved the final manuscript.

Ethical approval

Human studies and subjects

Ethics approval for this study was obtained from Bambino Gesù Children's Hospital IRCCS, Rome, Italy.

Animal studies

N/A.

Data sharing and data accessibility

The data presented in this study are available on request from the Corresponding Author.

Publication ethics

Plagiarism

All original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

Manipulation of images

All images are original.

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CASE REPORT

Un unexpected pleural effusion in a pediatric patient in apparently good health

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ABSTRACT

Pleural effusion (PE) occurs when fluid collects between the parietal and visceral pleura. This condition is a complication of pneumonia and pleuritis and can occur in 5-40% of cases. In children, the main aetiological agents involved are S. pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae and Mycobacterium tuberculosis. However, in a few cases, it represents an epiphenomenon of a disease that can affect other organs different from the lungs, such as onco-haematological diseases. Herein, we described a pleural effusion due to an acute lymphoblastic leukaemia.

IMPACT STATEMENT: This case presents a singular experience manifested in a paediatric patient with ALL who initially presented with a large and unilateral pleural effusion with the aim to highlight the importance of never underestimating the possibility of an unusual underlying cause.

KEY WORDS
Case report; pleural effusion; bulky mass; differential diagnosis; children.

INTRODUCTION

Pleural effusion (PE) occurs when fluid collects between the parietal and visceral pleura The most common cause is infectious diseases; parapneumonic effusion complicates up to 13% of cases of pediatric community-acquired pneumonia, and sometimes hospitalization is required. The management of parapneumonic effusions remains disputed, and various therapeutic options are described (1). It is classified into two types: trasudative and exudative effusions; the former does not have any specific diagnostic procedures or follow-up, whereas the presence of exudate necessitates further study.

CASE REPORT

We are describing the case of a 9-year-old male child who was first admitted to the Emergency Room of another hospital due to hip pain, shortness of breath and loss of appetite, following a four-day-history of tachycardia associated with right hip pain and no fever. The biochemical analyses and the chest X-ray (performed in this hospital) showed increased phlogosis indexes C-reactive protein (CRP) 106.3 mg/L 21xN; lactate dehydrogenase (LDH) 373 U/L, white blood cells (WBC) 11800 mmc, neutrophils (N) 44%, lymphocytes (L) 51%, platelets (PLT) 297000 mmc; D-dimer 2.82 mg/L and lung consolidation with right pleural effusion (**Figure 1**).

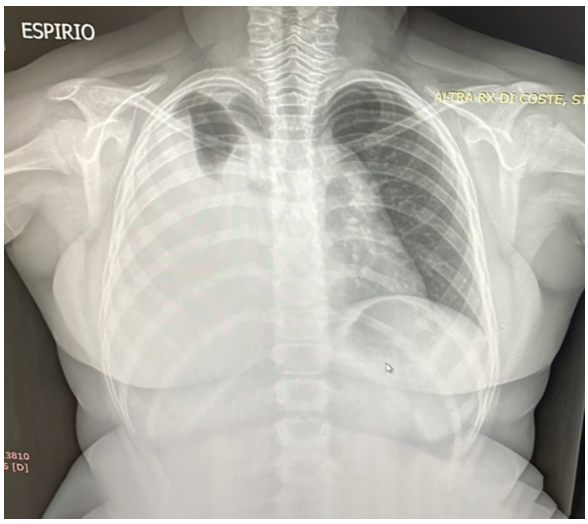

Figure 1. *Approximately complete opacity of the right hemithorax as massive amount of pleural effusion.*

The patient was therefore moved to our hospital for further study. At the time of admission, the child was eupneic. Although his condition was normal, the thoracic auscultation showed a respiratory silence in the right hemithorax. Moreover, laboratory tests confirmed the persistence of incremented phlogosis indexes (CRP 10.20 mg/Dl 21 x N, LDH 428 U/L, WBC 11780 mmc N50% L 45% PLT 288000 mmc); thus, an antibiotic therapy with amikacin and meropenem was started. The patient's past medical history was unremarkable. In consideration of his clinical presentation, we performed microbiological tests to exclude infectious diseases (serological tests for *Mycoplasma pneumoniae* and *Chlamydiapneumoniae*; Quantiferon-TB Gold test for *Mycobacterium tuberculosis*). The exams came out negative, with absence of significant microbiological evidence supporting the radiological findings. His clinical conditions worsened within the first 24 hours. The patient became tachypneic, so oxygen support was required. After performing a thoracic ultrasound which showed the presence of massive pleural effusion in the right pleura with right lung atelectasis, a thoracentesis was performed, and 1000 cc of serum-haematic pleural fluid was drained and sent to laboratory for cytologic, microbiologic and microbacterium testing. The cytological analysis of pleural effusions showed cells compatible with T-lymphoma; accordingly, a chest computed tomography (CT) was performed, showing a voluminous "bulky" mass in the anterior mediastinum (**Figure 2**), so a neoplastic aetiology was suspected. Finally, the bone marrow aspiration allowed us to diagnose T-cell acute lymphoblastic leukaemia (ALL).
Hence, according to the International Protocol for Children and Adolescents With Acute Lymphoblastic Leukemia, chemotherapy was started and the patient's symptoms significantly improved as he responded well to the treatment.

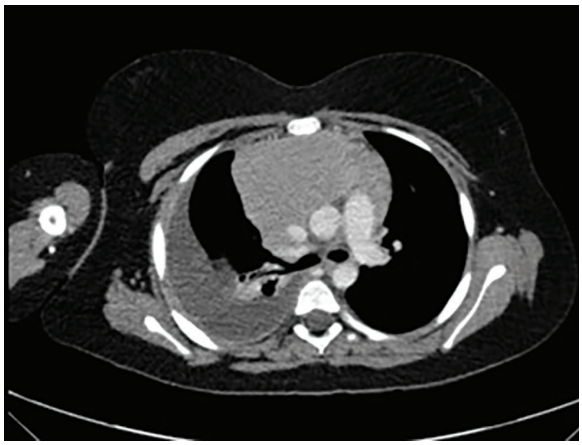

Figure 2. *A voluminous "bulky" mass in the anterior mediastinum, with hypodense structure, 9x7 cm. It coexists a copious right pleural effusion with passive atelettasia of the right lower lobe, part of medium and upper lobes. Moderate pericardic effusion.*

DISCUSSION

Infectious diseases, like pneumonia and pleuritis, can cause pleural effusion. It can be detected in 2% to 12% of children with community-acquired pneumonia (CAP) and up to 28% in case of hospitalization (3). In children with CAP, parapneumonic effusion may be suspected based on history and physical examination (4). Frequently, patients can be asymptomatic or refer to nonspecific symptoms like fever, malaise, loss of appetite, cough, dyspnea and chest pain, usually characterized by sudden and intense sharp, stabbing, or burning pain in the chest when inhaling and exhaling. The presence of prolonged fever, chest pain, and abdominal pain has been associated with parapneumonic effusion (4). Physical examination may show more specific clinical signs like dullness to percussion, decreased breath sounds, changes in the quality of breath sounds and transmitted speech over the effusion or respiratory silence to auscultation. Laboratory and radiologic findings, and also the appearance of the pleural effusion at drainage (**Table 1**), may help us to identify the underlying medical cause.

Table 1. *Pleural fluid appearence and causes of PE.*

Pleural fluid appearence	Causes of PE
Purulent fluid	Infection
Milky fluid	Chyle
Blood fluid	Trauma or malignancy

Chest radiography, including lateral decubitus views, should be used to confirm the presence of pleural fluid in children with CAP. If there is still a question of pleural fluid versus parenchymal opacification, thoracic ultrasounds (TUS) or CT scans are warranted. TUS are considered a safer imaging procedure than CT, owing to lack of ionizing radiation (4). Ultrasonography's (US) role in imaging the lung and extra cardiac mediastinum has evolved in the recent past. Although plain radiographs still remain the initial modality for paediatric chest imaging, there has been a significant increase in the clinical utility of thoracic ultrasounds in recent years. Ultrasounds are economical, easily available, portable and lack ionizing radiation. They can be performed after careful evaluation of the chest radiograph. Contrast administration and sedation are not required. The investigation can be performed at the bedside and allows real time visualization in various planes. In children presenting with breathlessness with or without fever where the chest radiograph reveals an opaque hemithorax, US helps in differentiating between pulmonary, pleural and mediastinal lesions and their morphological evaluation. Absence of air bronchograms on the chest radiograph is a clue to evaluating the child further with US (5).

TUS has recently become an extension of the physician's arm and has never been as important, both as a diagnostic tool, but also as a way to improve the safety of invasive procedures. It should be performed on every patient at their initial presentation and again whenever a pleural procedure is being performed. It will also provide information on the size and character of the effusion (6).

In fact, the role of US in confirming the presence of an effusion and differentiating it from pleural thickening is well established. The type of pleural effusion depends on the nature of the fluid collection. Serous fluid is usually a transudate and is a clear fluid or simple effusion. It may also be cloudy with or without swirling particles. An exudate or empyema is purulent fluid, also classified as a complicated effusion. This shows multiple septa within and is multiloculated. Multiple septa in the fluid favours infections like tuberculosis. Long standing haemothorax will also show multiple thick septa within it, however the child will have a history of a decrease in haemoglobin and haematocrit levels. Quantification of the fluid and marking a site for diagnostic and therapeutic aspiration are well-established indications to perform an US. Movement of the fluid with change in posture confirms amenability of the fluid to aspiration. The multiloculated nature of pleural fluid may be better appreciable on an US than on a CT.

Ultrasounds are also useful in detecting lung or pleural masses masked by a large pleural effusion (5).

The management of parapneumonic effusions remains a disputed matter, and various therapeutic options are available. Supportive care measures, including appropriate oxygen therapy, fluid and electrolyte and nutrition management are important management steps not to be overlooked (7).

A conservative treatment with antibiotics alone is a reasonable option for small parapneumonic effusions, turning to the evacuation of effusions in case of an enlarging effusion (>2 cm), compromising respiratory function and/or associated with loculations.

It is advisable to start an intravenous antibiotic therapy with amoxi/clav with the possibility to add clindamycin in selected cases (e.g. complex patient or delay ≥48 hours before chest drain insertion or suspected loculated pneumonia) and, after 48 hours of treatment, in case of clinical stability or improvement, it is useful to continue the intravenous treatment until the child is afebrile for almost 48 hours and, at a later time is possible to switch methods of administration using the oral route. In our case we choose amikacin and meropenem to guarantee a wide action spectrum against the most common bacteria causing pneumonia and pleural effusion.

The optimal duration of antibiotic treatment for parapneumonic effusion or empyema is dependent on the adequacy of the drainage procedure and may vary by pathogen, but it has not been determined through randomized controlled trials. Treatment for 2-4 weeks is commonly recommended; some experts treat the infection for approximately 10 days after resolution

of fever (7). In case of no clinical improvement, it is suitable to perform a thoracic ultrasound or X-ray, and to discuss with the surgical team the possibility of practising chest drainage or to consider adding clindamycin.

However, sometimes, it is necessary to perform the drainage from the beginning, such as in case of complete unilateral whiteout with mediastinal shift, when respiratory support is required and in case of sepsis (4).

As we know, corticosteroids inhibit the expression of many proinflammatory cytokines and it has been postulated that they may be a useful adjunctive therapy in children with CAP. A recent study by Thimmesch M and colleagues (2) showed that corticosteroids could represent a noninvasive therapeutic option when antibiotics and pleural drainage have failed; nonetheless their use in children with complicated pneumonia is a topic of debate and current evidence does not support the routine use of systemic corticosteroids in children with CAP (7). Corticosteroid pretreatment is common among patients with high-risk disease features. While the indications for corticosteroid pretreatment are not confirmed, a higher disease burden at presentation and more symptoms can prompt a misdiagnosis and treatment intervention before a diagnosis of ALL is recognized, as it has been shown that high doses of steroids can have significant effects on immune responses.

Intrapleural fibrinolysis is usually suggested for effusions of thick fluid with loculations or empyema; and surgery is recommended in case of failure of treatment by antibiotics, chest tube drainage, and/or fibrinolytics (2).

According to the treatment established by A. Kapur *et al.* (8), chest drainage should be performed only in a small percentage of cases, considering clinical signs and the effusion size. Drainage of a parapneumonic effusion may be required for several reasons. If there is doubt about the infectious aetiology of the effusion or if malignancy is suspected, thoracentesis may be performed for cytologic examination. Finally, the size of the effusion and the degree of respiratory compromise are important factors to be considered when determining the management plan. Small effusions (<10 mm rim of fluid on lateral decubitus or less than one-fourth of the hemithorax opacified on an upright chest radiograph) are likely to resolve on their own or often respond well to antibiotic therapy and usually require no further intervention. Moderate to large effusions are more likely to cause respiratory compromise, not resolve quickly, and benefit from drainage (4).

Thoracentesis (pleural aspiration) is a key intervention for both diagnostic and therapeutic purposes in the investigation and management of the patient with a unilateral pleural effusion. The use of thoracic ultrasound immediately prior to pleural intervention for suspected fluid has been strongly advocated for as a means of improving patient safety by reducing the frequency of iatrogenic complications and improving diagnostic yield (6).

In addition to infectious diseases, which are the most common causes of PE, also cardiovascular disease (e.g. congestive heart failure or constrictive pericarditis), lymphatic disorder (e.g. chylothorax or lymphangiectasia), intra-abdominal processes (e.g. pancreatitis or peritonitis), non-infectious lung diseases (e.g. pulmonary embolism or infarction) and cancer must be taken into account in the differential diagnosis of PE.

Particularly, pleural effusion may result from pleural invasion by the tumour, pneumonia, obstruction of lymphatic flow or atelectasis from an ab extrinsic compression.

Among the major malignant pathologies that can give rise to a pleural effusion there are lymphoma, leukaemia and carcinoma. Acute lymphoblastic leukaemia is a malignant proliferation of lymphoid cells blocked at an early stage of differentiation that can invade bone marrow, blood, and extramedullary sites (9).

It is the most common cancer in children and many studies demonstrate that it represents one of the most frequent causes of mediastinal mass, together with lymphoblastic leukaemia and Hodgkins lymphoma (10, 11).

The aetiology of ALL is unknown, but factors like ionizing radiation, infections, genetic factors, and chromosomal abnormalities play an essential role in the pathogenesis. ALL patients usually complain of symptoms reflecting bone marrow failure, including leukopenia, thrombocytopenia, and anemia, which present with bleeding, purpura, fatigue, malaise, and recurrent

infections. Although leukemia may manifest itself with extramedullary symptoms, it rarely causes malignant serous effusions, especially as the first manifestation (12). Pleural and pericardial effusions in patients with leukemia are more likely to be benign than malignant (13). Pleural effusion is a common finding in patients with Hodgkin and non-Hodgkin lymphomas, with a frequency of 20-30%, while leukemia rarely accompanies this manifestation (14).

In literature, pleural effusion in leukemia patients was often the result of underlying infections, secondary malignancy, or the toxicity of chemotherapy (14). Besides this, a study of 111 patients with acute leukemia or myelodysplastic syndrome who underwent pleural procedures showed the aetiology of the pleural effusion presented asinfection for nearly half (47%), followed by malignant disease (36%), and volume overload (13%).

Kendre and colleagues reported a case of T-ALL that presented with pleuropericardial effusion, and according to the literature, this was more frequently documented with T-ALL (16, 17).

The pleural effusion will be bloody or chylous, and the cytopathologic study with a documented presence of malignant cells will be diagnostic.

In our case, the patient sustained massive pleural effusion, leading to the diagnosis of T-ALL. Clinical findings and symptoms could be similar to those previously mentioned, with the possible presence of unexplained weight loss and lymphadenopathy.

Patients with ALL may also develop symptoms related to the infiltration of blasts in the bone marrow, lymphoid system, and extramedullary sites (including the central nervous system [CNS] and testicles). These symptoms may include fatigue or lethargy, constitutional symptoms (eg, fevers, night sweats, weight loss), dyspnea, dizziness, infections, and easy bruising or bleeding. Chin numbness or facial palsy may result from cranial nerve or CNS involvement. Among children, pain in the extremities or joints may be the only presenting symptom. The presence of lymphadenopathy, splenomegaly, and/or hepatomegaly on physical examination may be found in approximately 20% of patients. Abdominal masses from gastrointestinal involvement are more suggestive of mature B-cell ALL (Burkitt lymphoma) (18).

The treatment of the underlying malignancy often leads to an improvement in the effusion.

The first-line treatment for acute lymphoblastic leukaemia typically includes four phases over 2-3 years: induction, consolidation, intensification, and long-term maintenance. In addition, directed treatment is given to prevent CNS relapse. Allogeneic haemopoietic cell transplantation is reserved for patients with high-risk disease or persistent minimal residual disease. This intensive therapeutic approach has led to an estimated 5-year overall survival of 90% of patients with childhood acute lymphoblastic leukaemia (19).

To our knowledge, there are no reported cases of T-ALL in children that initially presented with massive pleural effusion like those in our patient. This leads us to consider malignant serous effusion in leukemia uncommon, rarely as the first manifestation.

This case aims to emphasize the importance of considering rare causes of serous effusion as it may also mirror underlying leukaemia. In conclusion, a large and unilateral pleural effusion must always make us suspicious and lead to suspicion of on-haematologic disease. The earlier we can make a diagnosis; the earlier we can administer the appropriate treatment.

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COMPLIANCE WITH ETHICAL STANDARDS

The manuscript was written according to Good Clinical Practice.

Conflict of interests

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Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. All authors read and approved the final manuscript.

Author contributions

Wrote the manuscript: SC and MV; contributed to the discussion: FM, FF and SFR; collected the references:

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Ethical approval

Human studies and subjects

The manuscript was written according to Good Clinical Practice and compliance with the Declaration of Helsinki with successive amendments.

Animal studies

N/A.

Data sharing and data accessibility

The data underlying this article can be shared just before a reasonable request to the Corresponding Author.

Publication ethics

Plagiarism

All original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

Manipulation of images

All images are original.

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