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Precision medicine targeting groups of intervention in difficult-to-treat asthma

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ABSTRACT

Introduction:

Asthma is a chronic airway inflammatory disease, and its medical complexity essentially resides in the management of the difficult-to-treat and severe forms. Previous studies have focused essentially on severe asthma and endotypes. Using the concept of precision medicine, we addressed the less standardized management of difficult-to-treat asthma based upon clinical features solely.

Objectives:

The objective of this work was to identify possible reasons for adults and children for suffering from difficult-to-treat asthma, to propose the best therapeutical and diagnostic approach.

Material and methods:

We conducted a qualitative analysis of the medical records of 42 consecutive adult and pediatric patients suffering from difficult-to-treat asthma seen in a tertiary hospital and based on the French [62TD\$DIF] respiratory medicine society questionnaire for severe asthma. The study of all records was performed by two independent clinicians. In all cases, missing data were openly discussed among all [72TD\$DIF]coauthors until resolution was achieved.

Results:

Our findings show that, in a real-life setting, patients with difficult-to-treat asthma may be better approached if considering one or more of the [73TD\$DIF]nine following groups of [74TD\$DIF] co-intervention: metabolic comorbidities; ENT comorbidities; other comorbidities such as gastro-esophageal reflux; non-allergic environment; allergic environment linked to respiratory or food allergens; inappropriate behavior; error of diagnosis; insufficiently treated patients; and intrinsic resistance. When these groups are identified and targeted with the appropriate treatment in one patient, including their approach in the management of asthma allow reaching better control of symptoms.

Conclusions:

Behind each group of intervention, a specific pedagogic challenge is hidden on which physicians may implement their management strategy to optimize the treatment of their patients based on their own individual characteristics.

1. Introduction

Precision medicine consists of identifying which approaches/ treatment will be effective in specific patients, according to their biological, lifestyle and environmental characteristics [1]. Its application in asthma holds promises [2]. Asthma is a chronic airway inflammatory disease resulting from environmental, genetic and immunological factors; and defined by different recognizable phenotypes, sometimes underpinned by different endotypes with a unique and codified international therapeutic strategy (GINA) via a whole drug pharmacopoeia to be implemented through different stages [3]. The medical complexity of asthma essentially resides in the management of difficult to-treat asthma: uncontrolled despite prescribing of medium- or high dose inhaled corticosteroids (ICS) with a second controller or with maintenance oral corticosteroids (OCS), or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations [3–5]. Difficult-to-treat asthma is a frequent reason for consultations in respiratory medicine. Often unscheduled, unscheduled office or emergency room visits concern all patients suffering from asthma, including at least 20 [75TD\$DIF]% of patients treated with a GINA step 1 therapy and up to 50 [76TD\$DIF]% of the patients at GINA steps 4 and 5 [6]. Difficult-to-treat asthma comprises all uncontrolled asthma [1, 2]. Therefore, it does not necessarily correlate with severe asthma and many of these patients will not need a prescription of a monoclonal antibody; nevertheless, the cost of their disease is increased by the need of emergency consultations (at their doctor's office or at emergency rooms), of controller and reliever drugs, of the management of drug-related side effects, and of indirect costs affecting their quality of life, the risk of absenteeism and of presenteeism. With at least 85,000 severe uncontrolled asthmatics in France, primary care physicians (general practitioners, general pediatricians, emergency physicians) and specialists (pulmonologists, allergists) are particularly solicited. To guarantee a preserved quality of life for patients and to avoid their vital prognosis, good asthma control is essential [3]. While practitioners refer many cases of asthma to hospital experts, especially for severe asthma to evaluate the possibility of prescribing monoclonal antibodies, we wanted to address the issue of difficult-to-treat asthma, the management of which is less codified. In the era of personalized medicine, where monoclonal antibodies are more and more prescribed for severe asthma patients, based on their specific endotypes, shouldn't difficult-to-treat asthma be investigated with a personalized approach to optimize patients' management, before prescribing expensive and more invasive therapies? Indeed, the management of difficult-to-treat asthma should be focused on the individual patient, following national and international recommendations [3], on the expertise of each healthcare professional and on the lessons learned from real-life data and from quantitative and qualitative analyses of the medical complexity of these patients.

The main objective of this work was to identify the profiles of patients referred for difficult-to-treat asthma to a tertiary hospital to then target individual characteristics or subgroups on which therapeutic actions could be implemented for patients and educational programs could be proposed for doctors.

2. Material and methods

Two independent clinicians retrospectively and anonymously collected data from 42 consecutive patients followed at the [7TD\$DIF]university hospital of Montpellier in the

outpatient clinic of the respiratory diseases department and referred for difficult asthma, by November 30th, 2020. Main inclusion criterion was a diagnosis of asthma reached either by a specialist in respiratory allergy or by an allergist. Also, asthma had to be defined as difficult-to-treat, as per current guidelines [3–5]. Patients suffering from chronic obstructive pulmonary disease (COPD) or other respiratory obstructive diseases were excluded; patients suffering from asthma-COPD overlap syndrome were excluded as well, if main clinical features were associated with COPD, as judged by specialists.

An electronic case report form was created, based on the items of the severe asthma questionnaire proposed by the interest group on [78TD\$DIF]asthma and allergies (G2A) of the French [79TD\$DIF]language pneumology society (Société de pneumologie de langue française, SPLF) [7]. This group, created more than 10 years ago with the aim of "identifying perfectly characterized asthma subpopulations (. . .)", develops practical tools for managing severe asthma patients. The questionnaire we used includes a list of items that should be investigated to better understand the disease and to propose the most appropriate treatment and follow-up [7]. Therefore, even though this questionnaire was developed for patients suffering from severe asthma, we deployed in our population since provided information are essential to fully understand the clinical picture in all asthmatic patients, including those presenting with difficult-to-treat symptoms.

Data were collected from patients' clinical records, extracted from the computerized patient record (DXCare1, Dedalus France) of the hospital. Qualitative analysis was performed for each patient with emphasis on specific individual characteristics. Each record was then assigned to one or more "groups of intervention", possibly explaining, according to the authors expertise, the difficulty for controlling asthma symptoms. The allocation of a patient to one or more specific group was decided after collegial discussion between allergists and respiratory medicine specialists. When trying to add 20 more patients to our analysis, we could not identify any other possible group of intervention as the data were already qualitatively saturated. This study was approved by the IRB (Institutional [80TD\$DIF] review board) of the university hospital of Montpellier (IRBMTP_2021_12_202100995) and registered on ClinicalTrials.org (NCT05185375).

3. Results

3.1. Characteristics of the patients

A total of 42 patients were selected for analysis including 25 adults and 17 children. 57.1 [81TD\$DIF]% of the patients were females. Mean age was 32.7+/-22.1 years (minimum 3 years; maximum 72 years). Asthma had been diagnosed in adults for an average of 18.6 years +/- 20.7 years (standard deviation). In children, the duration of asthma was 5.5 years +/-2.2 years. Detailed characteristics of included patients are shown in [Table 1](#).

3.2. Comorbidities in patients

As for comorbidities, they were present in 92 [82TD\$DIF]% of adults and 29 % of children: 16 % of adults presented with cardiovascular comorbidities (arterial hypertension, stroke) and/or diabetes and 55 [83TD\$DIF]% were overweight or obese. 24 [84TD\$DIF]% of adults

and 11.8 % of children presented with concomitant gastroesophageal reflux disease. ENT pathology (nasal polyposis or chronic [85TD\$DIF]rhinosinusitis) was present in 60 [86TD\$DIF] % of adults. Two patients had a psychiatric disorder (attention deficit hyperactivity disorder, bipolar disorder) and two patients had scoliosis. As for tobacco smoke exposure, 20 [75TD\$DIF] % of adults were active smokers, 16 [87TD\$DIF] % had withdrawn smoking. Almost 30 [8TD\$DIF] % of the children were exposed to passive smoking. Atopy was present in 32 [89TD\$DIF] % of adults and 65 % of children. Missing data concerned 43 [90TD\$DIF] % of patients for the item “overweight or obesity”, 24 [91TD\$DIF] % for “tobacco smoke exposure”, 26 [92TD\$DIF] % for “atopy”.

Table 1
Study on difficult-to-treat asthma: Main characteristics of the included patients.

Characteristics		All patients, n = 42 (100 %)	Adults, n = 25 (59.5 %)	Children, n = 17 (40.5 %)
General information	Mean age, years (SD)	32.7 (± 22.1)	48.0 (± 15.0)	10.3 (± 4.2)
	Males, n (%)	18 (42.9)	8 (32.0)	10 (58.8)
Asthma duration and severity	Mean age of asthma diagnosis, years (SD)	18.6 (± 20.7)	27.6 (± 23.2)	6.6 (± 4.5)
	GINA 2, n (%)	3 (7.1)	2 (8.0)	1 (5.9)
	GINA 3, n (%)	5 (11.9)	2 (8.0)	3 (17.6)
	GINA 4, n (%)	23 (54.8)	12 (60.0)	11 (64.7)
	GINA 5, n (%)	11 (26.2)	9 (36.0)	2 (11.8)
Main possible comorbidities	Cardiovascular comorbidity, n (%)	4 (9.5)	4 (16.0)	0
	Obesity, n (%)	8 (19.0)	8 (32.0)	0
	Tobacco smoke exposure, n (%)	16 (38.1)	11 (44.0)	5 (29.4)
	Firsthand smoking, n (%)	9 (21.4)	9 (36.0)	0
	Number of pack years, n (SD)	25.0 (± 21.5)	25.0 (± 21.5)	0
	Secondhand smoking, n (%)	7 (16.7)	2 (8.0)	5 (29.4)
	ENT comorbidity*, n (%)	13 (31.0)	12 (60.0)	1 (5.9)
	Gastroesophageal reflux, n (%)	8 (19.0)	6 (24.0)	2 (11.8)
	Atopy, n (%)	19 (45.2)	8 (32.0)	11 (64.7)
	Psychiatric disorders, n (%)	2 (4.8)	1 (4.0)	1 (5.9)
	Scoliosis, n (%)	2 (4.8)	1 (4.0)	1 (5.9)

SD: standard deviation; GINA: Global Initiative for Asthma guidelines.

* Asthma severity as per GINA guidelines.

* Nasal polyposis or chronic rhinitis/rhinosinusitis.

3.3. Identification of groups of intervention and educational challenges

Our qualitative analysis allowed us to differentiate [73TD\$DIF]nine groups of intervention, each corresponding to a specific issue that could be managed to reach a good, or at least a better control of asthma in our patients (Table 2, Fig. 1). Some patients could be associated to more than one group of intervention (Fig. 2). The analysis of the different groups led to a discussion of the working group that brought out [93TD\$DIF]seven points of improvement in the management of difficult-to-treat asthma (Table 3).

Table 2
Possible groups of intervention of difficult-to-treat asthma and interventions suggested for clinical practice.

Identified group	Example	Interventions suggested
1 Untreated or refractory metabolic comorbidity	Obesity or non-T2 inflammation	Dietary advice and discussion about pulmonary rehabilitation.
2 Untreated or refractory ENT comorbidity	Chronic rhinosinusitis, nasal polyposis, by T2 inflammation	Nasal corticosteroid ENT consultation
3 Other untreated or refractory comorbidity	Gastro-esophageal reflux, scoliosis	Proton pump inhibitors Physical rehabilitation
4 Uncontrolled non allergic respiratory environment	Smoking, occupational exposure	Smoking cessation with or without specific consultation
5 Uncontrolled allergic environment Respiratory Other	Hobbies, occupation, environment Food	Allergy consultation with or without allergen immunotherapy
6 Inappropriate behavior	Non-compliance with adolescence, psychiatric or isolated disorders	Therapeutic education A trial of extra fine fixed combination Psychiatric consultation
7 Diagnostic error	Other obstructive respiratory disease, or cardiac disease	CT scan Bronchoscopy Heart ultrasound
8 Untreated or undertreated patient	Patients whose diagnosis has not yet been established	Therapeutical trial Increase treatment
9 Intrinsic resistance	Failures of a first biotherapy	Diagnosis re-evaluation Treatment modification

4. Discussion

Studies from the past few years contributed a lot to the precision medicine approach in asthma, linked to phenotypes and endotypes [2]; clinical and physiologic features [8] or transcriptomic signatures [9]. Some study was based on patients' clinical features, but they focused on severe asthma only [10]. In our retrospective study, we wanted to have a strict clinical view and specially focused on the subgroup of difficult-to-treat asthma.

The present work with the in-depth individual analysis of each patient led to the characterization of multiple groups of intervention contributing to the lack of symptoms' control in asthmatics. To detect these groups and make them applicable in clinical settings, they have been translated into educational challenges for physicians. Identifying uncontrolled asthmatics is crucial. It could be the patient himself, the primary care doctor (general practitioner, pediatrician, emergency physician), the specialist (pulmonologist, allergist, other), another healthcare professional (nurse, pharmacist) and/or the society (through frequent unscheduled medical visits, absenteeism, presenteeism). The educational challenges identified in this work should then target these actors. As for physicians, the main challenge is to make sure that the clinical pathway for managing difficult-to-treat asthma is correctly respected, without any omission (i.e., confirming the diagnosis of asthma, assessing, and treating comorbidities, optimizing patients' understanding and compliance to the therapy, and adjusting the step of the treatment, following GINA guidelines). Even though not all patients presenting with difficult-to-treat asthma have severe asthma, we used the severe asthma questionnaire, designed by the [78TD\$DIF] asthma and allergies interest group of the SPLF, since it was validated by severe asthma experts in France, it is widely used since, and might help not only understand the complexity of the disease, but also indicate possible management solutions.

In addition, it is essential not to underestimate the toxicity of repeated therapies of OCS, and to avoid their use as much as possible, by assessing their risk/benefit ratio in each patient. Indeed, both the short-terms and even more the long-term side effects of systemic steroids no longer need to be demonstrated, especially the risk of infections, osteoporosis, diabetes or even psychiatric disorders [11–13]. The assessment of possible treatable traits is also a recently developed approach that should be considered, when dealing with asthmatic patients [14,15]. Defined in chronic respiratory diseases such as asthma and COPD, treatable traits relate to pulmonary conditions (e.g., eosinophilic or neutrophilic inflammation; repeated infections), extra-pulmonary ones (e.g., obesity, anemia, mood disorders) and behavioral/risk (e.g., smoking, using recreational drugs, including cocaine and cannabis). This innovative approach acts on the phenotypic and psychosocial characteristics of individuals and aims to be integrated into a precision medicine strategy which seems to demonstrate a significant benefit on quality-of-life scores, asthma control and risk of asthma exacerbations [16].

In the overall population, the three most common group of intervention include untreated or refractory comorbidities – besides metabolic and ENT ones – (26.2 [94TD\$DIF]% of patients), untreated or refractory ENT comorbidities (23.8 [95TD\$DIF]%) and under treatment (23.8 [96TD\$DIF]%). On the other hand, when considering the adult population only, the most common group included untreated or refractory metabolic comorbidities (36.0 [97TD\$DIF]%), followed by uncontrolled non allergic respiratory environment (28.0 [98TD\$DIF]%) and untreated or refractory comorbidities – besides metabolic and ENT ones – (24.0 [9TD\$DIF]%). Looking at the pediatric population, we found that under treatment was the main aspect to be considered (35.3 [10TD\$DIF] %), followed by untreated or

refractory comorbidities – besides metabolic and ENT ones – (29.4 [101TD\$DIF] %), and uncontrolled allergic environment (23.5 [102TD\$DIF] %). Also, we identified more than one possible group of intervention in almost a half of our patients (45.2 [103TD\$DIF] %), but especially in adults (56.9 [104TD\$DIF] % vs. 35.3% in children). The most common features highlighted as associated to other possible groups of intervention in our cohort were metabolic comorbidities (present in adults only), other comorbidities (besides metabolic and ENT ones) and under treatment.

First of all, these data underlines once again the difference in the management of asthma and on its clinical features between adults and children. They also confirm the importance of an holistic approach to the asthmatic patients, that goes beyond the prescription of the antiinflammatory therapy, but considers several different aspects of the patient's health and of its everyday life. In all asthmatic patients, and especially in children, the possibility of suffering from respiratory allergies should be ruled out and, if confirmed, preventive measures should be advised and adopted in the patients' personal and professional life. Indeed, sometimes the therapeutic obsession with asthma inflammation itself makes us to lose sight of the underlying pathophysiology of this asthma. In those patients suffering from allergic asthma, demonstrated by the positivity of skin prick tests and/or specific IgE to allergens exacerbating the clinical symptoms, an appropriate and specific anti-allergic treatment may modify the outcome of the disease [17]. It seems therefore wise to know when and how to refer the patient to the specialist, to first propose environmental and/or professional changes to avoid allergen exposure (e.g., by targeted allergenic evictions) and then to possibly prescribe allergen immunotherapy to treat the cause of the allergic disease. This approach should be particularly considered in certain populations such as preschool children or children with rhinitis (and therefore at risk of developing severe allergic asthma) or anyone treated with a significant therapeutic load and with proven respiratory allergies [18].

This work raises several general questions such as how to strengthen patients' compliance in chronic airway diseases or how to manage patients who have more than one comorbidity. Indeed, in our cohort, for multiple reasons, some patients were involuntary or voluntary noncompliant. For example, patients needing to often change their residency found it difficult to have a regular follow-up with the same doctor, and this aspect worsened treatment adherence; we also reported the case of a lyric singer refusing to take inhaled corticosteroids because of their direct impact on her voice and therefore on her profession. The issue of noncompliance is of course not unique to asthma; it has significant consequences, and its approach is multiple and not always successful [19]. When focusing on compliance, it is important to consider adults and children population separately. Children's compliance will depend on parents giving them the treatment.

One of the skills of the doctor managing difficult-to-treat asthma will therefore be to seek the potential obstacles (and find related incentives) linked to the patient specific issues, habits and needs. Some of them may be considered as extrinsic, such as job-related factors (in those cases in exposure to an allergen/irritant at the workplace would diminish the therapeutic effect of the drugs); some as intrinsic, such as the patient's age (e.g., adolescent patients tend to revolt against any form of obligation or to rebel against what their caregivers ask them to do, including chronically taking a drug).

Finally, a crucial issue is to encourage healthcare professionals to communicate to their patients on how the different drugs work, and why they are prescribed, and what kind of

follow-up should be scheduled for a proper management of the disease; this educational process should also include possible biological drugs for asthma, by clarifying why one specific monoclonal antibody is initially chosen, and when it is possible to consider a switch to a different one. At any rate, communication and education make it possible for the patient to become more aware of his/ her condition, therefore more prone to be compliant, and a real actor in his/her disease.

The present study has certain limitations. First, we present the results of a qualitative study, and such an aspect might be considered as a weakness. Nevertheless, when we evaluated 20 additional patients, we found that data saturation was reached after the first 42. Also, by retrospectively analyzing medical records, we came across several missing data. This missing data possibly linked to non-reported data in medical files or simply non-mentioned because of its absence ([105TD\$DIF] such as obesity). A prospective study could have avoided this bias. During patients' consultation, their assessment was not necessarily based on the G2A questionnaire, that only concern patients labelled as suffering from severe asthma. The number of cases of difficult-to-treat asthma is therefore not easily assessed from the outset. However, the data is sufficient to meet our primary purpose. Finally, we presented results from a mono-centric study and such limit could be erased by replicating the analysis in other centers to verify data reproducibility.

5. Conclusion

With the advent of personalized medicine, asthma is now defined by clinical phenotypes and endotypes. In line with the concept of treatable traits, the present qualitative analysis on possible groups of intervention could make it possible to consider the patient in his/her individuality and to receive a treatment that is specific to him/her and thus contribute to the precision-based care in the future. Correlating our clinical groups of intervention with the well-known previously described asthma phenotypes could contribute to better manage patients' symptoms and therefore disease. An approach based on these possible interventions could also help specialist in their decision towards a possible prescription of monoclonal antibodies to treat asthma.

Thanks to the present work, both primary care physicians and specialists will be able to access all the educational challenges behind each group of intervention. Identifying the one or those corresponding to a specific patient will allow to reach good asthma control more easily, and in some cases to avoid the prescription of hazardous (e.g., systematic steroids) or more complex and costly therapies (such as biotherapies).

Finally, we suggest for physicians to use in routine clinical practice the questionnaire of the SPLF, even for difficult-to-treat asthma patients, regardless the severity of their disease. A prospective study could indeed prove its interest in the daily management of asthma and confirm the completeness of the groups of intervention proposed by our study.

Conflict of interest

The authors declare no potential conflict of interest for the present paper.

Declaration of [106TD\$DIF] generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors did not use any AI tool.

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