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RespDoc: A new Clinical Decision Support System for Childhood Asthma Management based on Fraction of Exhaled Nitric Oxide (FeNO) Measurements

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Abstract— **The use of Fraction of Exhaled Nitric Oxide (FeNO) for measurement of inflammation in the respiratory system is a good way to assess the level of asthma in children. In this paper we present a new Clinical Decision Support System (CDSS) for Childhood Asthma Management based on FeNO, which is named RespDoc. The core of RespDoc is a decision making algorithm and a patient's monitoring process that are extensively analyzed in the paper. The performance of RespDoc is tested through the process and assessment of archived patients' data.**

I. INTRODUCTION

Asthma is one of the most prevalent chronic childhood diseases. It may adversely affect the child's everyday life as it can cause deterioration of lung function and bothersome symptoms. Asthma exacerbations often become so severe that the child must be transferred to the emergency department or requires hospitalization [1]. As a result, a multitude of studies have focused on the management of childhood asthma and many propose the creation of Clinical Decision Support Systems (CDSS) that are designed to aid in the decision process by evaluating each patient's condition in real time [2].

In [3], the authors have presented a CDSS with a modular structure for use by the doctor, the school nurse and the parents. The work in [4] introduces a decision support tool to encourage guideline adherence in a primary care setting by measures' collection, automatic severity assessment and treatment proposal. The authors of [5] propose a CDSS aimed to promote pediatric asthma exacerbations' management at the emergency department. The system described in [6] was also developed for asthma management in an emergency department and incorporated the guidelines of the National Heart, Lung and Blood Institute of the USA.

All the CDSSs mentioned above took into consideration one or more of the following factors: symptoms, lung function measurements (spirometry, peak flow measurements), oxygen saturation, medication and allergenic factors. However, they do not take into account the degree of airway inflammation, which is particular to asthma and constitutes the pathophysiological basis of the disease but cannot be defined by the measurement of airway mechanics [7]. In this paper, we present a novel CDSS for childhood asthma management, which is designed according to the guidelines in [8]. The system, termed RespDoc, is based on the measurement of the Fraction of Exhaled Nitric Oxide (FeNO), which reliably reflects the activity of asthmatic inflammation. RespDoc can be used in real world conditions, either in a clinical setting or at home.

This paper is organized as follows: In Section II the means of FeNO assessment of asthmatic inflammation is presented. In Section III the decision making process for defining the asthmatic inflammation and proper medication administration is described. In Section IV we present the proposed patient monitoring process, while in Section V the RespDoc architecture is analyzed. Finally, Section VI includes the discussion and the conclusion.

II. FRACTION OF EXHALED NITRIC OXIDE (FENO) METHOD

In order for a pulmonologist to diagnose a patient with asthma they need to take into account the symptoms, the clinical history and the results of functional tests (spirometry or peak flow measurements) of the patient. However, inflammation of the airways is also an important constituent and in fact the pathogenetic basis of asthma (asthmatic inflammation). Consequently, diagnostic techniques that measure the level of asthmatic inflammation are being utilized in order to assess the severity of the patient's condition and to choose the optimal therapy [9].

FeNO in exhaled air has been recognized as a biomarker of asthma during the last decade and it has been proven to objectively reflect the degree of asthmatic inflammation. The level of Nitric Oxide (NO) in the exhaled air is measured in parts per billion (ppb) in a noninvasive, simple and safe manner. The patient needs simply to exhale with a constant flow for a few seconds in a portable device, the NO analyzer [8]. Patients with pulmonary diseases can easily familiarize themselves with such a maneuver, which, in fact, resembles but is much easier than spirometry.

It is important to note that FeNO measurements represent more accurately the state of asthmatic inflammation at the early stages of the disease. Thus, it is an objective and sensitive marker of childhood asthma [9].

For those children whose symptoms are suggestive of asthma, but the doctor cannot ensure his suspicion, FeNO measurement may confirm the diagnosis [10]. Moreover, it

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has been proven that the values of FeNO increase during acute asthma exacerbations. Therefore, FeNO measurements can aid the early identification of patients who are at risk of an exacerbation [11]. Finally, prescription of inhaled corticosteroids (ICS) and/or leukotriene receptor antagonists (LTRA), the typical medications used in childhood asthma, leads to the decrease of the FeNO value, while, conversely, a reduction of ICS medication can result in the rise of FeNO in case of a poorly controlled asthmatic inflammation [10]. Periodic monitoring of the FeNO values can help guide the pulmonologist adapting the medication to the individual needs of each patient and aid in the avoidance of unnecessary use of ICS [7].

Therefore, we consider that the integration of FeNO values into the factors handled by CDSSs provides essential benefits for the assessment/diagnosis of childhood asthma.

III. Fundamentals of the Decision Making Algorithm based on FeNO measurements

Figure 1 depicts the integrated decision making algorithm that includes the yielded patient's asthmatic inflammation status and the proposed medication plan, according to the conducted FeNO measurements. The algorithm is based on the rules of the official guidelines of The American Thoracic Society [8].

At the first stage of the algorithm, it is examined whether the child has been previously diagnosed with asthma. If there has been no previous diagnosis of asthma, but the symptoms (cough, wheeze, shortness of breath, chest tightness) are present, the algorithm categorizes the state of inflammation and proposes, if necessary, an initial treatment plan, based on the FeNO value:

- If the FeNO value is less than 20 ppb, an asthmatic inflammation is unlikely and treatment is not needed.
- If the FeNO value is between 20 and 35 ppb, the state of asthmatic inflammation cannot be yet defined, so further monitoring at a next appointment is necessary.
- If the FeNO value is greater than 35 ppb, there is an asthmatic inflammation so prescription of ICS and/or LTRA, based on the severity of the symptoms, is mandatory.

On the other hand, if the child has been previously diagnosed with asthma, the algorithm proceeds to a second categorization, based on the presence of symptoms.

If there are no symptoms present, the FeNO value offers the following alternatives:

- If the FeNO value is less than 20 ppb, the asthmatic inflammation is under control. In addition, if the current value of FeNO is smaller than the previous value of FeNO (measured during the previous appointment) by more than 10 ppb, the ICS dose may be reduced by 25%.
- If the FeNO value is between 20 and 35 ppb, asthmatic inflammation is under control and the ICS dose should be maintained at the same level.
- If the FeNO value is greater than 35 ppb, the state of inflammation is severe. If poor adherence or inhaler technique is not the issue, the dose of ICS should be doubled in the following cases: if the current value of FeNO is less than 50 ppb and it is also greater than the previous one (measured during the previous appointment) by more than 10 ppb, or if the current value of FeNO is more than 50 ppb and is also greater than the previous one by 20%.

Finally, if the child has been previously diagnosed with asthma and the symptoms are present, the algorithm proceeds as follows:

- If the FeNO value is less than 20 ppb, asthmatic inflammation is considered to be under control and the dose of ICS remains the same. However, the symptoms should continue to be monitored.
- If the value of FeNO is greater than 20 ppb the state of airway inflammation is severe. In addition, if the value of FeNO is greater than 35 ppb the child is also at risk of exacerbation. The ICS dose must be doubled in the following cases: if the current value of FeNO is less than 50 ppb and is also greater than the previous one (measured during the previous appointment) by more than 10 ppb, or if the current value of FeNO is more than 50 ppb and is greater than the last one by 20%.

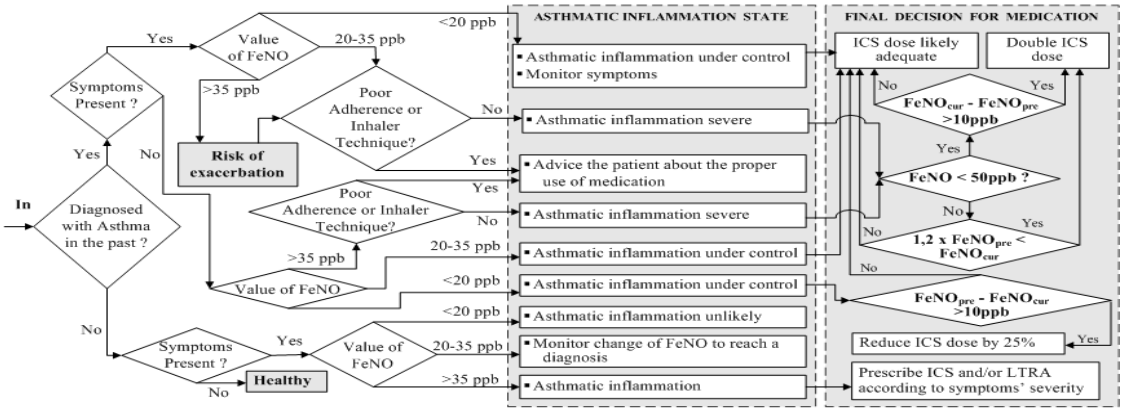

Figure 1. Flowchart of the decision making algorithm for asthmatic inflammation state and medication definition

However, before increasing the ICS dose, poor adherence or inhaler technique should be taken into consideration.

IV. Fundamentals of the Proposed Patient's monitoring process based on FeNO measurements

The proposed decision making algorithm for monitoring repetition based on FeNO measurements is presented in Figure 2 and was created according to the rules of the official guidelines of the American Academy of Allergy, Asthma and Immunology [1]. Depending on the presence of a previous diagnosis of asthma, the presence of symptoms and the value of FeNO measurements, the algorithm deduces the correct time interval until the next appointment for asthma monitoring.

Specifically, if the child has not been previously diagnosed with asthma and the symptoms are present (cough, wheeze, shortness of breath, chest tightness) the algorithm proposes the next appointment to be scheduled in six months, if the FeNO value is less than 20 ppb. Also, if the value of FeNO is between 20 ppb and 35 ppb, the next appointment should be scheduled in a month, and if the value of FeNO is greater than 35 ppb, the next monitoring session should be conducted in two weeks.

Furthermore, if the child has been diagnosed with asthma in the past, but does not suffer from any symptoms, the next appointment for monitoring should be scheduled as follows: if the value of FeNO is less than 20 ppb, it should be conducted in three months, if the value of FeNO is between 20 ppb and 35 ppb, it should be conducted in a month, or if the value of FeNO is more than 35 ppb, the next appointment should be scheduled in the next two weeks.

Lastly, if the child has been diagnosed with asthma and suffers from symptoms but has a low FeNO value (less than 20 ppb) the next monitoring session should be planned in one month. Otherwise, if the value of FeNO is greater than 20 ppb we recommend the use of a monitoring system at home for two months, based on FeNO measurements with the portable device.

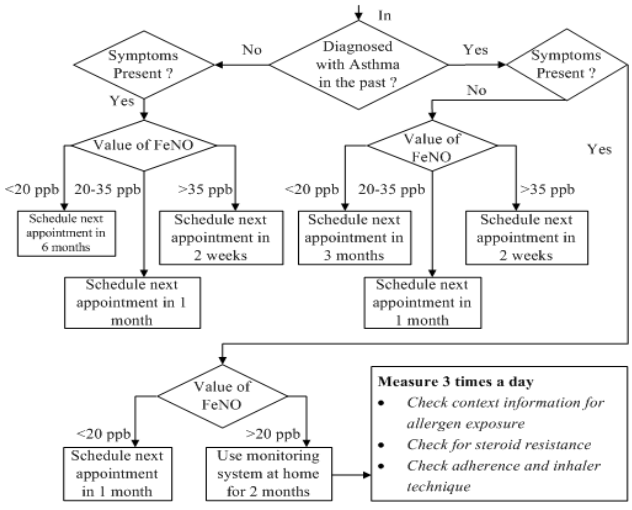

Figure 2: Flowchart of the decision making algorithm for monitoring repetition

V. The Proposed Architecture Of The Decision Support System

Both the algorithms described above were created in order to be integrated in the core of a CDSS for childhood asthma, namely RespDoc. RespDoc is being developed through the close collaboration of engineers and pediatric pulmonologists.

Our primary goal was to create a monitoring system that will be used by pediatricians not specialized in pulmonology, in their infirmary. RespDoc can also be used in small medical centers where there might be no pediatrician at all.

RespDoc is aimed to guide the doctor through the whole examination process.

However, during our collaboration with the pulmonologists, we reached the conclusion that, in the most severe cases, daily monitoring of the symptoms and FeNO values for a relatively short period of time (two months) would optimize the diagnosis and medication for each patient. The doctors proposed providing the parents of the child with a portable NO analyzer and we decided to expand the capabilities of RespDoc with a web service.

The architecture of the RespDoc is depicted in Figure 3. It comprises of the following modules:

- **Doctor Interface**, in order for the doctor to insert all the information acquired during the asthma examination process and to receive the results of the implementation of the abovementioned algorithms on the patient's data.
- **Parent Interface**, in order for the parents to daily report the evolution of their child's asthma through recording the presence and the severity of symptoms and the value of FeNO measurements conducted three times a day. The parents will also be asked to report any viral infections or other diseases that their child might suffer from and fill in questionnaires concerning context information. This context information will refer to the physical activity of the child at home and at school, to the state of the environment (temperature, humidity), to the presence of allergenic factors and to the use of medication.
- **Knowledge Base**, which contains the algorithms that represent the medical knowledge. The abovementioned algorithms will be held in the Knowledge Base.
- **Health Info Depository**, including any permanent (e.g. demographic information, medical history, previous diagnosis, allergies, symptoms, viral infections) or temporarily acquired information (e.g. clinical examination results, laboratory results, FeNO and spirometry measurements). This information concerns the patients' health status and it is entered into the Depository either directly by the FeNO device or through the Parent Interface. This way, an individualized profile is created for each patient that can be used in future examinations in order to monitor the progress of the disease and medication.

- **Context Info Depository**, where all the information concerning the patient's context is stored (physical activity of the child at home and at school, temperature, humidity, presence of allergenic factors).
- **Data Mining Algorithms**, which will be applied on the patient data of both Depositories, in order to determine which habits, or factors, influence the patient's asthmatic inflammation and asthma in general. Through these algorithms RespDoc is able to provide the doctor with analytical information on allergen exposure, steroid resistance, adherence to medication and inhaler technique. It will generate both new rules that will be stored in the Knowledge Base, and more results on the patient's condition, that will be stored in the Health Info depository.
- **Inference Engine**, where the algorithms from the Knowledge Base are applied on each patient's data, in order to reach the desired conclusions on the state of the asthmatic inflammation, medication and monitoring of the patient.
- **Explanatory Agent**, which will provide the doctor with specialized information on the results extracted from the patient data and explain the reasoning process, if asked.

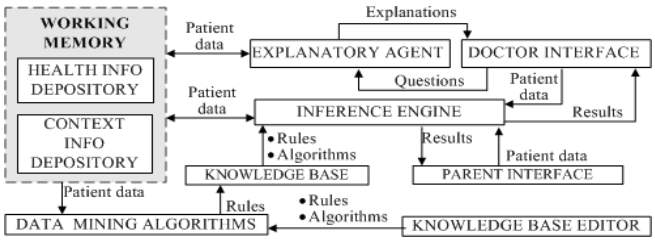

Figure 3. System architecture

It should finally be mentioned that the doctor will have a daily feedback, through the Doctor Interface, on the evolution of the disease for each patient. This daily feedback will also include recommendations on the treatment strategy, and reports on allergen exposure, steroid resistance, adherence to medication and inhaler technique. In addition, the system will alert the parents, through the Parent Interface, when the next appointment with the doctor should be planned, but, more importantly, when there is a risk of exacerbation. The parents will then be able to immediately contact the doctor and act appropriately in each case (rescue medication, visit to the emergency department).

VI. Discussion- Conclusion

RespDoc is still at the implementation stage. We intend to extend the Knowledge Base by incorporating more algorithms based on the results of spirometry, in order to further clarify each patient's asthma condition and customize the treatment plan.

The system is evaluated thoroughly in two stages. At the first stage, we have used 50 existing patient's files (archive data) in order to assess the accuracy of the decision making algorithms. Specifically, the abovementioned algorithms were applied to the data included in the research described in [12]. According to our team's doctors, one of whom is author both in this paper and in [12], the results were correct in 42 of the 50 cases. Therefore, the accuracy of the algorithms is 84%.

At the second stage, we will conduct our experiment by actually choosing an adequate number of patients to use the NO analyzer at home for two months, in combination with the RespDoc. We intend to evaluate the system's performance and effectiveness in terms of its impact on the patients' asthma (frequency of exacerbations, symptoms intensity and medication).

In this paper we introduced a new CDSS for childhood asthma management, the RespDoc. RespDoc is designed based on the objective FeNO measurement of asthmatic inflammation. The proposed system integrates two processes for definition of asthmatic inflammation state, medication and monitoring and is able to identify risk of exacerbation. RespDoc is comprised of a Doctor and a Parent Interface, a Knowledge Base, a Health Info and a Context Info Depository, Data Mining Algorithms, an Inference Engine and an Explanatory Agent. As future work, we intend to evaluate our system in a real world scenario.

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