The success rate and safety of induced sputum is better than you think: give it a try!

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To the Editor:

Induced sputum is an easy, non-invasive, reproducible and inexpensive tool to collect cells from airways. It has been used for monitoring airway inflammation and to successfully guide treatment in the context of asthma for years, and is now recognised as a gold standard in the management of severe asthma patients by the Global Initiative for Asthma (GINA) guidelines (https://ginasthma.org).

However, induced sputum is challenging, and a certain expertise is needed for the immune cell count after sputum processing, as the cells can be in different states of degradation and the slides can be contaminated with debris, mucus, and squamous cells from the mouth.

This observational study aims to share our experience in induced sputum technique and demystify the feasibility of the whole process. We introduced this technique more than 20 years ago in our asthma clinic and we decided to outline our results regarding the success rate and causes of failure of induced sputum over the past 20 years. The complete induction and processing procedures were detailed in a previous publication [1] and followed the European Respiratory Society recommendations that were summarised 10 years ago [2]. Since 2004, we have been adding salbutamol to the inhaled solution to avoid bronchoconstriction during the induction step [3]. This study was approved by the ethics committee of CHU Liege, Belgium and all subjects gave written informed consent for participation.

Between January 2004 and January 2024, we performed 5419 sputum inductions in our asthma clinic. Inclusion criteria included all sputum induction performed at our centre in the follow-up of patients diagnosed with asthma, at the pneumologist's discretion according to the GINA guidelines. The GINA stage distribution of the patients was as follows: GINA 1: 25% of patients; GINA 2–3: 10%; GINA 4: 9%; and GINA 5: 56%. Patients were also classified in severe asthma according to the European Respiratory Society/American Thoracic Society criteria [4].

551 patients (10.2%) were not able to produce an expectoration. Then, at the laboratory processing step, when observed at magnification 400× under the light microscope on the haemocytometer, 103 (1.9%) appeared to contain no cells or only a few cells, and were thus not further processed.

An excessive amount of large squamous cells from the mouth (>80%) was noticed in 246 samples (4.5%) and those slides were not used for further immune cell count, because the presence of a high number of squamous cells reflects poor sample quality and does not allow for an accurate count. It was not possible to count 500 immune cells in 155 samples (2.9%), mainly due to the deterioration of the cells, rendering them unrecognisable. All causes of failure are summarised in figure 1a.

Finally, 4356 sputum samples were interpretable, which represents 80.4% success. The success rate evolution of our centre over the years is shown in figure 1b and on average equals 84%. This is higher than the success rate of 70% reported by D'Silva *et al.* [5]. They were able to perform a differential cell count in 86% of the samples successfully obtained, which represent 81% of the total number of inductions (n=4232 inductions, of which 37% were from asthma patients). An explanation for our higher success rate could be that we used salbutamol in the inhalation solution, which is bronchoprotective and limits the

Shareable abstract (@ERSpublications)
This letter aims to summarise 20 years of experience of the induced sputum technique and the causes of failure. For 5419 sputum inductions, the procedure was well tolerated, and the success rate was close to 80% after processing. https://bit.ly/4haU6Yx

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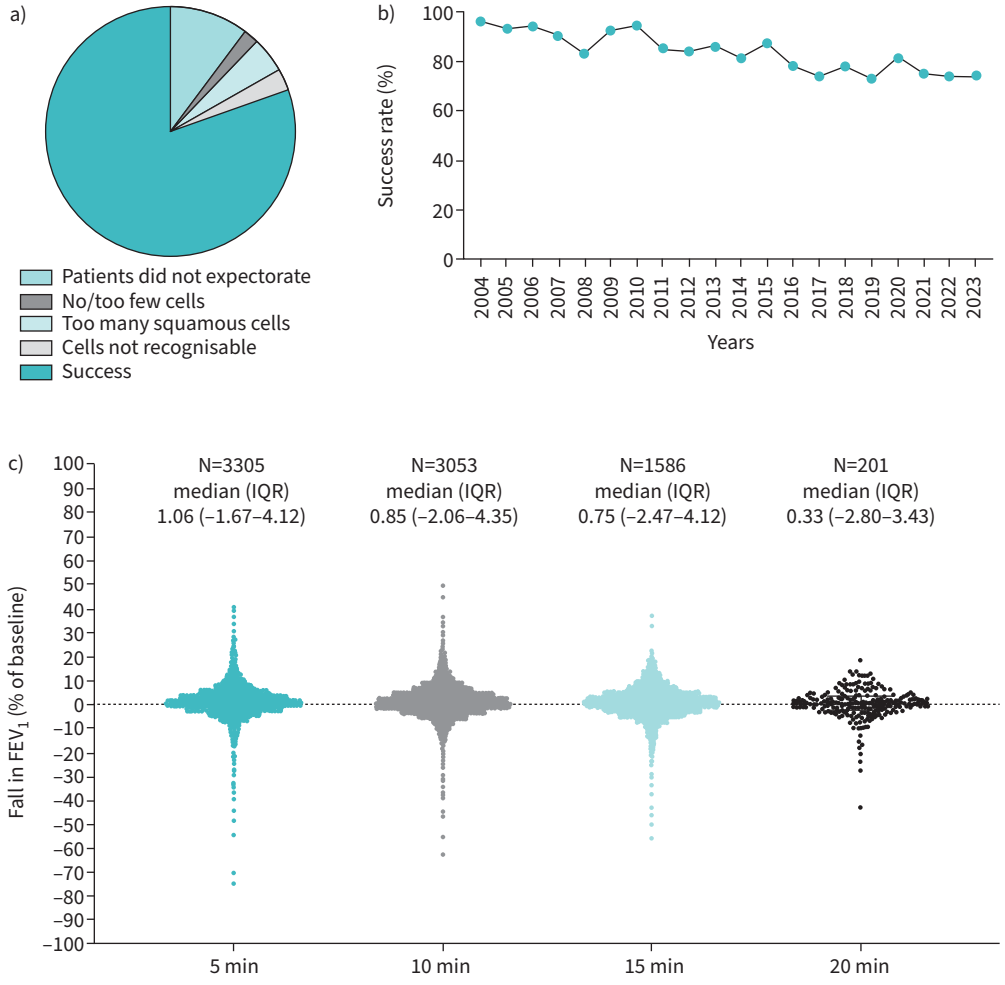

FIGURE 1 a) Success rate and causes of failure of the induced sputum technique in our centre. b) Evolution of the success rate of the technique over the past 20 years. c) Fall in forced expiratory volume in 1 s (FEV_1) during the sputum induction expressed as percentage from baseline value. IQR: interquartile range.

bronchospasms responsible for a reduction in expectorations. In addition, the Hamilton group selected mucus plugs from saliva at the beginning of the processing, while we have been using the whole sputum sample, which is less selective. Our success rate was also higher than the 76% obtained by Pin *et al.* [6], but lower than the 92% and 93% success rates reported in other studies [7, 8]. However, those results were based on a more limited number of patients and the cohorts were not similar as they included patients with respiratory diseases other than asthma. Moreover, the induction and processing procedures slightly differed from ours, which should elicit caution regarding strict comparisons. Indeed, these studies used increasing concentrations of saline of up to 5% for induction, while we used a constant concentration of 4.5% when forced expiratory volume in 1 s (FEV_1) was >65% predicted and 0.9% when FEV_1 was <65% pred prior starting the inhalation procedure.

Among our cohort, 2053 out of the 2660 patients classified as having severe asthma were able to produce an adequate sputum sample, which represents a success rate of 77%, slightly lower than across the whole cohort of patients, but still very satisfying.

The sputum induction should last 15–20 min in order to obtain all the desired airway cell fractions, as composition can change according to the induction duration [9, 10]. However, the procedure had to be stopped for some patients after 5–10 min because of discomfort, including cough and/or nausea. The median fall in FEV_1 predicted during the induction procedure is indicated in figure 1c and is globally close to zero, which confirms that this procedure is well-tolerated and safe. After 5 min, only 42 patients (1.3%) had a fall ⩾20% of the FEV_1 value that led to an interruption of the induction. After 10 min, 40 patients

(1.3%) displayed a fall ⩾20% of the basal FEV_1 value and after 15 min, only five patients (0.3%). A smaller fraction of our patients was asked to continue the saline inhalation for a whole time of 20 min in order to increase the amount of collected sample and be sure to have enough material for processing. Among these patients, none had a drop of FEV_1 ⩾20%.

Finally, we performed a univariate logistic regression analysis to highlight the predictors that could discriminate patients who were able to expectorate than those who were not. We found that being male (OR 1.237, 95% CI 1.032–1.487; p=0.0225), being a smoker or ex-smoker (*versus* nonsmoker: OR 1.987, 95% CI 1.451–2.782; p<0.0001; and OR 1.400, 95% CI 1.117–1.767; p=0.0040, respectively), having a higher FEV_1 and forced vital capacity expressed as predicted percentage (OR 1.007, 95% CI 1.002–1.011; p=0.0018; and OR 1.013, 95% CI 1.008–1.018; p<0.0001, respectively), having a higher blood eosinophil count (OR 2.594, 95% CI 1.637–4.290; p=0.0001) were all predictive of a production of a sputum sample as opposed to be classified as GINA stage 5, which was linked to patients not able to expectorate (OR 0.4505, 95% CI 0.3676–0.5494; p<0.0001).

In summary, our success rate for the induced sputum technique was close to 80% for the 5419 sputum inductions performed over the past 20 years. Only a minority of patients experimented a significant drop in FEV_1 leading to an interruption of sputum induction. This technique appeared safe, was well-tolerated by patients and should be implemented without apprehension in centres that manage severe asthma patients.

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Author contributions: C. Moermans participated in the study design, performed the research and data analysis and wrote the manuscript; S. Gerday, N. Bricmont, R. Bonhiver, S. Graff, S. Ziant, F. Regnier, A. Onssels, M-S. Njock, A. Rosu, M. Henket, C. Sanchez, V. Paulus and F. Guissard participated in the sputum induction and processing and patient data collection. F. Schleich and R. Louis designed the study and interpreted the data. All authors participated in the manuscript reviewing and gave final approval of the manuscript and ensured that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Conflict of interest: C. Moermans, S. Gerday, N. Bricmont, R. Bonhiver, S. Graff, S. Ziant, F. Regnier, A. Onssels, M-S. Njock, A. Rosu, M. Henket, C. Sanchez, V. Paulus and F. Guissard have no conflicts to declare. R. Louis and F. Schleich had educational and research grants from GSK, AstraZeneca and Chiesi, consulting fees from GSK and AstraZeneca (national and international advisory boards), and lecture fees from GSK, AstraZeneca and Chiesi.

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