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Adrenal suppression in bronchiectasis and the impact of inhaled corticosteroids

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ABSTRACT: The present study identified three patients with bronchiectasis receiving inhaled corticosteroids (ICSs) who had symptomatic adrenal suppression secondary to ICS. The prevalence of adrenal suppression is unknown in bronchiectasis. The frequency of adrenal suppression and the impact of ICS use in bronchiectasis patients were examined.

In total, 50 outpatients (33 receiving ICSs) underwent a short Synacthen test and completed a St George's Respiratory Questionnaire (SGRQ). Symptoms of adrenal suppression, steroid use and lung function were compared between subjects who were suppressed and those who were not.

Adrenal suppression was evident in 23.5% of subjects who did not receive ICSs and 48.5% of those who did. Basal cortisol and the increments by which cortisol increased 30 min after Synacthen were lower in suppressed than in nonsuppressed subjects. The incremental cortisol rise was negatively correlated with SGRQ impacts and total score, suggesting a worse quality of life in those who had an impaired adrenal response. The greatest frequency of generalised symptoms was seen in the suppressed group.

A significant proportion of subjects with bronchiectasis have evidence of adrenal suppression, and this is increased when inhaled corticosteroids are also used. Impairment of the cortisol response to stimulation is associated with poorer health status.

KEYWORDS: Adrenal insufficiency, bronchiectasism, glucocorticoids, inhaled corticosteroid, short synacthen test

Patients with bronchiectasis often describe nonspecific symptoms, including tiredness and lack of energy, which are usually attributed to their underlying inflammatory disease. These symptoms become worse during an exacerbation and are believed to relate to an increased inflammatory burden, such as that in chronic obstructive pulmonary disease (COPD) [1].

However, the current authors have identified three patients with bronchiectasis taking long-term inhaled corticosteroids (ICSs) who presented with generalised symptoms (lethargy, malaise, depression, arthralgia, nausea, vomiting, weight loss, falls, light-headedness and postural hypotension) that became worse during periods labelled as exacerbations of lung disease. Following investigation, they were found to have adrenal suppression (table 1). Unfortunately, adrenocorticotropic hormone (ACTH) was only measured in one patient and was found to be undetectable. In all cases, there was no history of excessive or recent oral steroid use and no other reasons for adrenal insufficiency were identified, thus ICSs were considered to be the cause. The symptoms and short Synacthen test (SST) continued to improve for 2 yrs after commencing hydrocortisone replacement and changing inhaled fluticasone to ciclesonide, but was not yet within the normal range in one case (basal cortisol in abnormal case: 181 nmol·L^{-1}; post-stimulation cortisol: 344 nmol·L^{-1}).

Several studies have demonstrated that ICS treatment is associated with a rapid dose-dependent fall in serum cortisol, implying that systemic absorption occurs, leading to suppression of the hypothalamo–pituitary–adrenal (HPA) axis [2]. Subsequently, safety studies, many of which were generated by the pharmaceutical industry, have generally used static measures of serum cortisol, which show small reductions in circulating cortisol that are considered to be clinically insignificant [3]. Importantly, these studies are in large cohorts and individual patients show great variability in response; therefore, a small average fall in serum cortisol in subjects treated with ICSs does not exclude a large fall in some patients. Another common misconception is that cortisol secretion must be greatly suppressed before the adrenal glands become resistant to stimulation. In reality there is a poor relationship between basal levels of

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TABLE 1 Clinical features of three patients with chronic lung disease with adrenal suppression attributed to prolonged inhaled corticosteroid therapy

Case	Sex	Age yrs	Diagnosis	Daily maintenance treatment	Extra steroid treatment	Symptoms and signs	Basal cortisol nmol·L^{-1}	Post-Synacthen cortisol nmol·L^{-1}
1	Female	27	Bronchiectasis Asthma	1 mg fluticasone	2–3 short courses oral prednisolone per yr	Fatigue, lethargy, malaise, depression, nausea, vomiting, hypotension especially with exacerbation	<20	32
2	Female	63	COPD Bronchiectasis	1 mg fluticasone	2 short courses prednisolone per yr Occasional nasal steroid	Fatigue, falls, postural hypotension	80	253
3	Female	81	Bronchiectasis	1 mg fluticasone	4–5 short courses prednisolone per yr	Arthralgia, malaise, fatigue	175	397

COPD: chronic obstructive pulmonary disease.

cortisol and the increase in cortisol secretion during intercurrent illness [4]. Clearly, in an illness such as bronchiectasis, which is characterised by recurrent episodes of acute infection, the ability of the HPA axis to respond appropriately to stress is fundamentally important. Therefore, the use of a dynamic test of adrenal function, such as the SST, is warranted.

Stimulatory studies have been performed in order to examine the ability of the adrenal gland to respond to stress, but these have usually been restricted to patients treated with steroids for a short duration (<12 weeks), or there have been confounding factors (including the concomitant use of cytochrome P450 inhibitors), thus the quoted risks of adrenal impairment may be misleading [5–9].

Therefore, it was hypothesised that adrenal suppression in subjects with bronchiectasis receiving ICSs may be more common than widely believed and may contribute to symptoms. In the current study, the HPA axis in a group of patients with bronchiectasis was studied and its relationship with the severity and impact of their respiratory disease was examined.

METHODS

Sequential patients who attended a tertiary referral bronchiectasis clinic, were eligible for the study and willing to give informed consent were included, up to a total of 50 patients. In total, 33 were on regular ICSs (for >1 yr) whilst the remaining 17 had not received ICSs over the previous year. Patients who had taken more than three courses of oral steroids over the previous year, received oral steroid over the previous 6 weeks and those on long-term nebulised steroids were excluded from the study. All subjects attended following an overnight fast, having discontinued inhaled steroids 24 h previously. Blood was taken at 08:00 h for basal cortisol, ACTH and glucose. Synthetic $ACTH_{1–24}$ 250 μg (Alliance Pharma Plc, Chippenham, UK) was administered intramuscularly and blood was taken 30 min later for cortisol. Subjects completed a St George's Respiratory Questionnaire (SGRQ) and blood pressure was measured while supine, and at 1 and 3 min after standing.

TABLE 2 Demographic data and short Synacthen test (SST) results for study subjects divided according to the use of inhaled corticosteroids (ICSs)

	No ICS	ICS	p-value
Subjects n	17	33	
Females	14 (82.4)	22 (66.7)	0.33
Males	3 (17.6)	11 (33.3)	
Age yrs	62±2	64±2	0.66
FEV_1 % pred	56.2±4.9	54.3±3.5	0.76
FEV_1/FVC	61.7±2.3	56.5±2.8	0.15
***K*CO % pred**	105.4±6.2	103.4±5.2	0.90
Taken oral steroid in previous 3 months	1 (6)	5 (15)	0.65
Basal cortisol nmol·L^{-1}	412±26	400±20	0.71
Cortisol post-Synacthen nmol·L^{-1}	609±27	565±20	0.20
ACTH ng·L^{-1}	24.3±2.8	31.5±3.6	0.12
Cortisol increment nmol·L^{-1}	197±24	165±17	0.29
SST test failures	4 (23.5)	16 (48.5)	0.04

Data are presented as n (%) or mean±SEM, unless otherwise stated. FEV_1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; *K*CO: transfer coefficient of the lung for carbon monoxide; ACTH: adrenocorticotropic hormone.

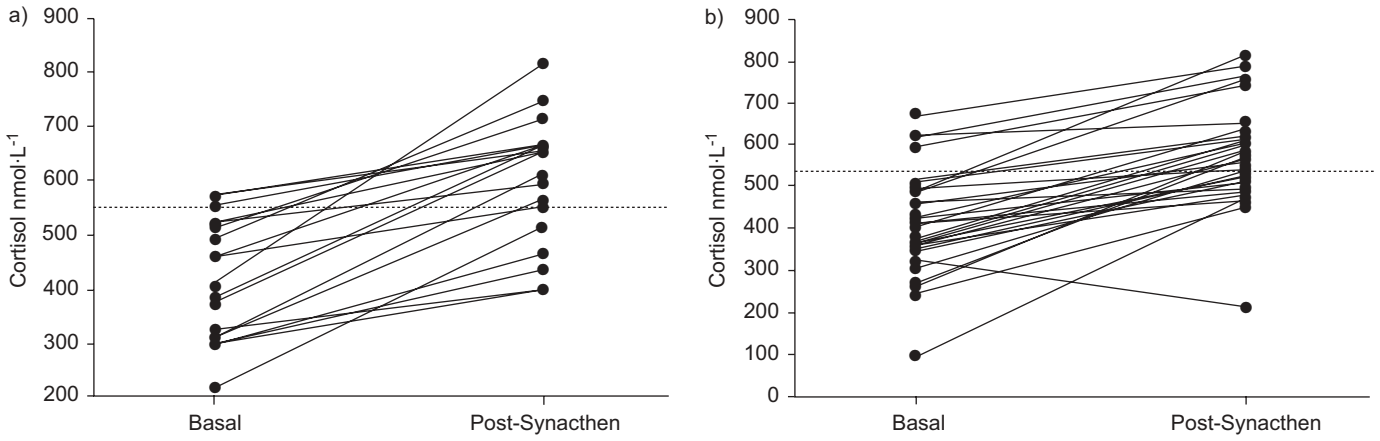

FIGURE 1. Basal and 30 min post-stimulation serum cortisol levels (nmol·L^{-1}) for subjects who a) did not receive inhaled corticosteroid and b) did receive regular inhaled corticosteroid. ·····: abnormal 30 min cortisol values.

Postural hypotension was defined as a fall in systolic blood pressure of >20 mmHg and a fall in diastolic blood pressure of >10 mmHg upon standing [10]. Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and transfer factor corrected for alveolar volume (K_{CO}) were assessed using Vitalograph Wedge Bellows (Vitalograph, Maids Moreton, UK) and Benchmark TT501 (Morgan Medical, Gillingham, UK), and expressed as % predicted [11].

Serum cortisol was analysed using a chemiluminescent immunoassay (Advia Centaur; Siemans Medical Solutions, Newbury, UK). Plasma ACTH was analysed by a chemiluminometric assay (Immulite 2000; Siemans Medical Solutions, Llanberis, UK); and glucose was analysed using a ROCHE Modular (ROCHE Diagnostics, Indianapolis, IN, USA). Adrenal insufficiency was defined as a cortisol concentration <550 nmol·L^{-1} 30 min after Synacthen administration, as previously reported [12].

For tests of significant differences, the Chi-squared test was performed for categorical data, the unpaired t-test was used for normally distributed continuous variables and the Mann–Whitney test was used for nonparametric continuous data. Pearson's correlations were used to compare two continuous parametric variables, and Spearman's correlations were used for nonparametric variables. Data are presented as mean±SEM, unless otherwise stated, and $p<0.05$ was regarded as significant.

The study was approved by the South Birmingham Research Ethics Committee (Birmingham, UK).

RESULTS

In total, 50 patients with bronchiectasis were enrolled. There was no significant difference in sex, age, FEV_1 % pred, FEV_1/FVC ratio, K_{CO} % pred, the number of patients with bronchodilator reversibility (>200 mL and 12% pred value [13]) or the number who had taken oral steroids over the previous 3 months, between those who received ICSs and those who did not (table 2).

In total, 48.5% (16 out of 33) of patients on ICSs and 23.5% (four out of 17) of the subjects who did not receive ICSs had evidence of adrenal impairment ($p=0.043$ for ICS *versus* no ICS; fig. 1).

Basal cortisol levels were significantly lower in subjects with adrenal suppression compared with those who responded adequately (mean±SEM 335±19 *versus* 450±9 nmol·L^{-1}; $p<0.001$). In addition, the incremental cortisol response (30-min cortisol minus basal cortisol) was lower in suppressed patients compared with those who were not suppressed (141±23 *versus* 199±90 nmol·L^{-1}; $p=0.05$). No differences were observed between groups for ACTH or fasting serum glucose levels (table 3).

There were no differences in age, sex, lung function, ICS drug preparation and dose (corrected for bioequivalence), mouth rinsing after ICS, and spacer use, between those who were suppressed and those who were not. Furthermore, the number of courses and total dose of oral steroids over the preceding 3 months and 1 yr, the use of nasal and topical steroids and co-administration of drugs known to inhibit cytochrome P450 3A4 were not different between those patients with adrenal suppression and those without (data not shown).

Although there were no significant differences between average health status in the suppressed and nonsuppressed group, the incremental cortisol response was related to respiratory health. Cortisol increment across the SST inversely correlated with the impact domain ($r= -0.338$, $p=0.016$), and the total SGRQ score ($r= -0.328$, $p=0.020$; fig. 2), suggesting that poor incremental cortisol response is associated with reduced quality of life. However, there was no correlation with the symptoms and activity variables of the SGRQ ($r=0.020$, $p=0.245$, and $r=0.018$, $p=0.110$, respectively).

Of the subjects receiving ICSs, a greater proportion of suppressed subjects described tiredness (100%), nausea (50%) and vomiting (25%), compared with those with no suppression (82.4%, 29.4% and 5.9%, respectively). The proportion of suppressed patients with postural hypotension at 1 min (50%), 3 min (75%) or at any time (75%) was higher compared with nonsuppressed patients (30.8, 38.5 and 53.8%, respectively). When analysed as a complete cohort, tiredness,

TABLE 3 Demographic data and short Synacthen test results for study subjects divided according to evidence of adrenal suppression

	Not suppressed	Suppressed	p-value
Subjects n	30	20	
Males	9 (64.3)	5 (35.7)	0.70
Females	21 (58.3)	15 (41.7)	
Age yrs	62±2	64±3	0.661
Number receiving ICS	17	16	0.043
FEV_1 % pred	55.3±3.9	56.9±4.7	0.790
FEV_1/FVC	58.1± 2.5	61.7±3.5	0.407
***K*CO % pred**	103.8±4.0	110.7±4.7	0.272
Basal cortisol nmol·L^{-1}	450±9	335±19	<0.001
Incremental cortisol response nmol·L^{-1}	199±90	141±23	0.05
ACTH ng·L^{-1}	28.5± 3.4	29.8±4.0	0.804
Fasting glucose mmol·L^{-1}	4.9±0.1	5.1±0.4	0.575
Systolic blood pressure mmHg	145±4.2	145±5.5	1.0
Diastolic blood pressure mmHg	83±2.3	82±1.9	0.807
Postural hypotension			
1 min	8 (26.7)	7 (35)	0.53
3 min	12 (40)	6 (30)	0.47
Anytime	14 (46.7)	9 (45)	0.91
Tiredness	27 (90)	20 (100)	0.27
Generalised weakness	19 (63.3)	13 (65)	0.90
Lack of energy	25 (83.3)	18 (90)	0.69
Weight loss	10 (33.3)	8 (40)	0.69
Nausea	9 (30)	10 (50)	0.15
Vomiting	2 (6.6)	5 (25)	0.42
SGRQ			
Symptoms domain	47.6±1.9	42.9±2.3	0.125
Activity domain	66.8±3.5	61.6±5.8	0.450
Impact domain	35.5±3.0	40.5±5.0	0.404
Total	47.0±2.5	47.3±4.4	0.962

Data are presented as n (%) or mean± SEM, unless otherwise stated. ICS: inhaled corticosteroid; FEV_1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; *K*CO: transfer coefficient of the lung for carbon monoxide; ACTH: adrenocorticotropic hormone; SGRQ: St George's Respiratory Questionnaire.

generalised weakness, lack of energy, weight loss, nausea and vomiting were all more common amongst individuals with suppression of the HPA axis (table 3). However, owing to the relatively small number of individuals within the present study, none of these observations reached statistical significance. There were no abnormalities of serum electrolytes (sodium or potassium) and no differences between those with evidence of suppression and those without.

DISCUSSION

The present data, from a cross-sectional study of patients with bronchiectasis, have clearly shown that the prevalence of adrenal suppression is two-fold higher in patients receiving ICSs compared with those who are not. Importantly, a poor incremental cortisol response to SST was associated with a poor respiratory quality of life as measured by SGRQ. With the exception of the use of ICSs, no specific factors that were associated with adrenal insufficiency could be identified.

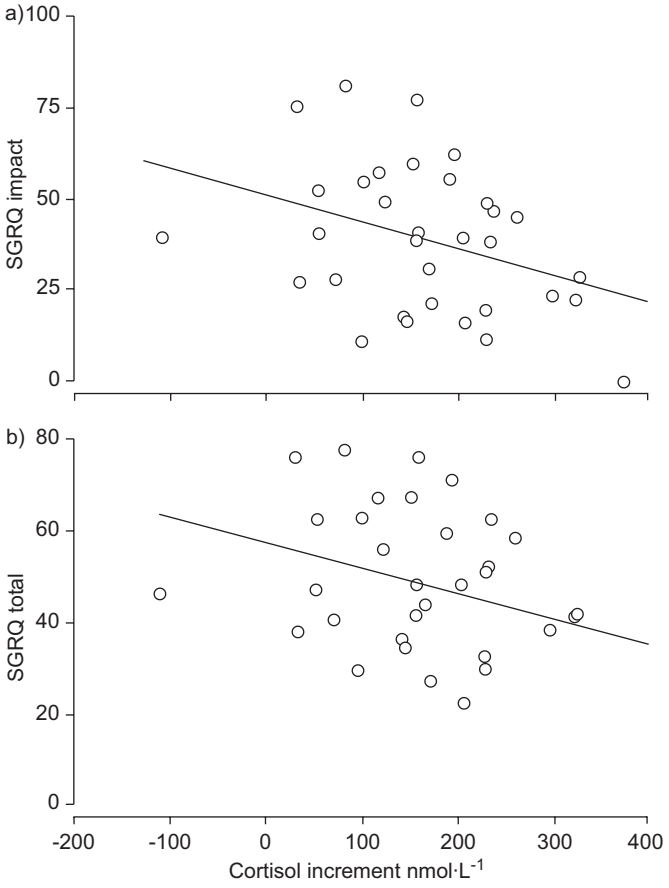

FIGURE 2. a) St George's Respiratory Questionnaire (SGRQ) impact domain score and b) SGRQ total score and the relationship to the cortisol increment following stimulation with synthetic adrenocorticotropic hormone. ○: a single patient.

Several studies have examined the dynamic adrenal function in healthy subjects and patients with asthma or COPD who have received ICSs, and many have yielded negative results. However, there are important differences in the methodology and patient characteristics when compared with the present study. Healthy volunteers or patients with asthma taking ICSs for <8 weeks were previously found to have no abnormality in the SST [5–8]. In the present cohort, all patients had been on ICSs for >1 yr. Studies in COPD patients from the Lung Health Study II also failed to demonstrate any abnormality using the SST after 3 yrs of ICS therapy [14]. However, these patients had mild disease and the inhaled triamcinolone was administered at a low dose. Although pre- and post-stimulation cortisol levels were lower in the group of patients on ICSs compared with the placebo group, they were not significantly different. As only mean values are given, it is possible that some individual patients did have adrenal insufficiency that was not reflected in the average value for the whole cohort. If the present data are analysed in a similar manner, there is no difference in the mean post-stimulation cortisol levels ($p=0.198$) nor the cortisol increment ($p=0.288$) between subjects who receive regular ICSs and those who do not. Therefore, this masks the important observation that a

significantly greater proportion of subjects who receive ICSs have adrenal suppression. In agreement with the present results, one small study of 12 asthmatic patients with no confounding factors reported adrenal insufficiency in 25% of patients who had taken beclomethasone (200–900 $\mu g \cdot day^{-1}$) for 12 weeks, suggesting that suppression may be more common than is currently believed [15].

The correlation of incremental cortisol response with SGRQ is an interesting observation and it is reasonable to speculate that at least some of the impact of their disease state in these patients may be attributed to ''occult'' adrenal insufficiency. Furthermore, the question arises as to whether, in some circumstances, hospital presentation may be related to adrenal insufficiency yet inappropriately labelled as an ''exacerbation'' of underlying lung disease due to nonspecific symptomatology. The administration of glucocorticoids in this setting will undoubtedly improve the clinical condition, but this does not assist in establishing the underlying diagnosis.

The use of the incremental cortisol response is not generally advocated in ''routine'' endocrine testing; however, in the context of chronic illness, or in the setting of intensive care [16], it would seem valid that the inability to mount an adequate cortisol response to stimulation may be an important marker of inadequate adrenal reserve. Studies in intensive care units suggest that functional adrenal impairment is present in ~50% of patients and is associated with a marked increase in mortality [17–19]. In these subjects, a rapid HPA response to stress would be appropriate, and it is possible that traditionally ''normal'' values of serum cortisol are actually physiologically deficient when the metabolic needs of these patients are taken into account.

The role of ICSs in bronchiectasis remains unclear, owing to a lack of specific research studies, although there are suggestions that lung function may improve in some patients [20]. Approximately 20% of patients with bronchiectasis have clear bronchodilator reversibility with β-agonists [21] and 45% have bronchial hyperreactivity, as defined by the methacholine challenge [22], suggesting they may benefit from ISCs as part of their ''asthma'' management.

However, there are also theoretical reasons for caution in prescribing inhaled steroids to patients with bronchiectasis. Systemic absorption is more likely from airways with damaged epithelium, and impaired ciliary function and may lead to retention of the steroid in the airway, further exacerbating the problem. The possibility of increased systemic absorption because of damage in the airway may explain why a larger proportion of the present study patients have adrenal insufficiency while receiving ICSs. However, 24% of subjects who did not receive ICSs were also found to have adrenal insufficiency, so other possible explanations need to be considered. Patients with other inflammatory conditions, such as rheumatoid arthritis, have been shown to have reduced unstimulated levels of serum cortisol along with increased interleukin (IL)-1β and IL-6 compared with patients with noninflammatory osteoarthritis [23]. In these patients, a defect at the level of hypothalamic corticotrophin-releasing hormone (CRH) production and release has been postulated, and this remains a possibility in the present cohort. In rodents, the pro-inflammatory cytokine, tumour necrosis factor (TNF)-α, can inhibit CRH-stimulated ACTH release, although unstimulated levels of ACTH are unaffected [24]. In addition, production of cortisol by fetal adrenal cells is also inhibited by TNF-α in adults [25]. However, there was no difference in the circulating TNF-α levels in the present study patients with and without impaired SST response (data not shown). Lewis rats are a rodent model that is susceptible to inducible inflammatory conditions [26]. These rodents also display impaired CRH secretion and, as a consequence, impaired cortisol response.

A further possible explanation for the high proportion of adrenal suppression in subjects with bronchiectasis could be that patients with this chronic disease have lower levels of cortisol binding globulin, which results in lower total cortisol concentrations even though serum-free cortisol may remain consistent with a normal adrenal response. However, cortisol binding globulin in stored serum from this study was subsequently measured, and no difference was found in the levels when suppressed and nonsuppressed subjects were compared.

The results of the present study have significant implications for the management of patients with bronchiectasis and may be generalised to other patients with chronic lung disease, including COPD and asthma. Given the low sensitivity of baseline cortisol in distinguishing between suppressed and nonsuppressed patients [27], the present authors would advocate the use of the SST to identify adrenal suppression in these patients. Owing to the lack of previous similar studies, the best clinical practice has not as yet been defined, yet there is an urgent clinical need bearing in mind the magnitude of the problem. Clearly there is a balance between preventing adrenal crisis and not contributing to total glucocorticoid load. In the present authors' practice, a combined respiratory and endocrinological approach has been pursued. Where possible, ICS doses have been reduced and, in some cases, ICS switched to ciclesonide (accepting that it is currently only licensed for asthma), which is only activated in lung cells [28], and is reported to cause less adrenal suppression. For patients with a 30 min cortisol $<400\ nmol \cdot L^{-1}$, the present authors would advocate low-dose hydrocortisone replacement (5–10 $mg \cdot day^{-1}$) with repeat SST after modification of ICS therapy in order to assess the return of HPA axis function. During intercurrent illness, increasing hydrocortisone replacement to 30 $mg \cdot day^{-1}$ is recommended by the present authors. For patients with mild suppression (30 min cortisol 400–550 $nmol \cdot L^{-1}$) the present authors would suggest hydrocortisone supplementation (30 $mg \cdot day^{-1}$) only at the time of intercurrent illness.

In conclusion, a significant and important clinical problem has been uncovered. Assessment of adrenal function by a dynamic test is safe and simple, and may identify adrenal insufficiency that could account for many of the symptoms currently attributed to chronic lung disease. Larger studies are now urgently needed to determine whether adrenal insufficiency contributes to morbidity and, potentially, to mortality, not only in patients with bronchiectasis but all patients on inhaled corticosteroids.

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