Bronchiectasis in primary Sjögren's syndrome: prevalence and clinical significance

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Abstract

Objectives

To analyse the prevalence and clinical significance of bronchiectasis in a large series of patients with primary Sjögren's syndrome (SS) and evaluate its impact on disease expression and outcomes.

Methods

The study cohort included 507 patients with primary SS. Bronchiectasis were diagnosed according to pulmonary computed tomography (CT). As a control group, we included 37 consecutive SS patients evaluated by pulmonary CT during the same study period without pulmonary involvement.

Results

Fifty primary SS patients had bronchiectasis according to the pulmonary CT. Nine patients were excluded due to non-autoimmune processes and 41 were classified as bronchiectasis associated with primary SS (40 women, mean age of 64 years). All cases of bronchiectasis were of the cylindrical type and were located in the inferior lobes in 29 cases (71%). Patients with bronchiectasis were older at diagnosis of SS (60.39 vs. 52.54 years, p=0.022) and had a higher frequency of hiatus hernia (41% vs. 16%, p=0.024) in comparison with controls. Immunologically, patients with bronchiectasis had a lower frequency of anti-Ro/SS-A antibodies (27% vs. 54%, p=0.022) but a higher frequency of anti-smooth muscle – SMA-antibodies (82% vs. 60%, p=0.043). During follow-up, patients with bronchiectasis had a higher frequency of respiratory infections (56% vs. 3%, p<0.001) and pneumonia (29% vs. 3%, p=0.002) in comparison with those without.

Conclusions

Patients with primary SS and bronchiectasis are characterised by an older age, a high frequency of hiatus hernia, a specific immunologic pattern (low frequency of anti-Ro/SS-A and high frequency of anti-SMA) and during follow-up a much higher frequency of respiratory infections and pneumonia.

Key words

Sjögren's syndrome, pulmonary involvement, bronchiectasis

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Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease that presents with sicca symptomatology of the main mucosal surfaces (1). The histological hallmark is a focal lymphocytic infiltration of the exocrine glands, determined by a biopsy of the minor labial salivary glands (2). The spectrum of the disease extends from sicca syndrome to systemic involvement (3). When sicca symptoms appear in a previously healthy person, the syndrome is classified as primary SS, but when they are found in association with another systemic autoimmune disease, most commonly rheumatoid arthritis, systemic sclerosis or systemic lupus erythematosus, it is classified as associated SS.

Insterstitial lung disease has traditionally been considered the most frequent type of pulmonary involvement in primary SS (4). However, some recent studies in small series of patients have found predominantly bronchial/bronchiolar involvement rather than interstitial involvement. Papiris *et al*. (5) described small airway disease as the main functional disorder of patients with primary SS and pulmonary involvement, Taouli *et al*. (6) found that large/small airway disease was the predominant computed tomography (CT) scan pattern in more than 50% of their patients and Franquet *et al*. (7) described bronchiolar abnormalities in one third of their patients. In contrast, other studies have described a ground-glass pattern (suggestive of interstitial involvement) as the predominant CT scan pattern (8), coexisting in some cases with bronchiectasis (8, 9). No study has specifically analysed bronchiectasis in patients with primary SS.

The aim of this study was to analyse the prevalence and clinical significance of bronchiectasis in a large series of patients with primary SS and to evaluate its impact on disease expression and outcomes.

Patients and methods

Study cohort and observation time

The study cohort included 507 patients fulfilling the 1993 classification criteria (10) for primary SS consecutively evaluated in our unit between 1984 and 2008. All patients were considered to have well-established primary SS defined as fulfillment of at least four of the six 1993 SS classification criteria (including positive autoantibodies as mandatory criteria), the exclusion of other processes that may cause sicca syndrome (infiltrative processes, infections or neoplasia) and the absence of other systemic autoimmune diseases (11). Of the 507 patients, 286 (56%) fulfilled the 2002 classification criteria; in the remaining patients (all Ro/La negative), the criteria could not be applied since salivary gland biopsy was not performed.

Extraglandular involvement in primary SS was evaluated according to the clinical guidelines of the Spanish Society of Internal Medicine (SEMI) for the management of primary SS (12). The following manifestations present at diagnosis or developing during the follow-up were defined as systemic features of primary SS: arthritis, Raynaud's phenomenon, renal involvement (interstitial nephritis or glomerulonephritis), vasculitis, pancreatitis, peripheral neuropathy (axonal polyneuropathy, multineuritis multiplex or neuronopathy), cranial neuropathy and central nervous system – CNS involvement (demyelinating disease, myelitis or meningitis).

Pulmonary tests

Of the 507 patients, 120 (24%) with a clinical suspicion of pulmonary involvement (presenting with respiratory symptoms such as chronic cough, haemoptysis and/or dyspnea) underwent pulmonary CT. Of these, patients with bronchiectasis diagnosed according to standard CT criteria (13) were included in the study. The presence and extent of bronchiectasis in each pulmonary lobe was graded using a scale from 0 to 3 where 0=no bronchiectasis, 1=involvement of one segment, 2=involvement of more than one segment, and 3=gross cystic bronchiectasis involving the entire lobe. Since the lingula was considered an independent lobe, the maximum possible number of points was 18. The final score (HRCT) was calculated as the total number of points divided by the maximum possible points multiplied by 100 (14).

The following data collected at diagnosis of bronchiectasis were retrospectively analysed: age, history of smoking, pulmonary tuberculosis, head/neck irradiation, respiratory symptoms (chronic cough, expectoration, haemoptysis, dyspnea), pulmonary function tests – PFT (total lung capacity, FVC and FEV1 indexes, FEV1/FVC ratio and carbon monoxide diffusing capacity – DLCO), bronchoscopy results and treatment. After diagnosis, all patients were followed-up until the last hospital visit, transfer out or death. The following outcomes were studied: functional status at the last visit, hospital admissions due to respiratory infections, repeated pulmonary tests (pulmonary CT, PFT) and mortality attributable to pulmonary disease. The study design conformed to current Spanish ethical standards. Due to the anonymous nature of the study, informed patient consent was not required.

The following control groups were included:

a) Group 1 (SS patients without bronchiectasis) consisted of 37 consecutive primary SS patients without symptoms and signs suggesting lung involvement, in whom pulmonary CT was carried out during the study period due to other causes and which discarded bronchiectasis or other pulmonary pathologies.
b) Group 2 (patients with bronchiectasis without SS) consisted of 77 consecutive patients with a similar mean age with bronchiectasis of any etiology (except SS) diagnosed by the Pneumology Department of our hospital (14).

Statistical analysis

Categorical data were compared using the χ^2 and Fisher's exact tests. Continuous variables were analysed with the Student's *t*-test in large samples of similar variance and with the nonparametric Mann-Whitney *U*-test for small samples, with results indicated as mean ± standard error of the mean (SEM). A two-tailed value of $p<0.05$ was taken to indicate statistical significance. A multiple logistic regression analysis adjusted for age, sex, length of follow-up and the variables which were statistically significant ($p<0.05$) in the univariate analysis was performed. The statistical analysis was performed with the SPSS program (SPSS, Chicago, IL).

Results

Fifty primary SS patients had bronchiectasis according to the pulmonary CT. Nine patients were excluded due to pulmonary tuberculosis or interstitial lung disease occurring before the diagnosis of bronchiectasis. The remaining 41 patients were classified as bronchiectasis associated with primary SS. There were 40 (98%) women, with a mean age at fulfillment of the SS classification criteria of 60.39 years (SEM 1.86) and a mean follow-up of 118.68 months (SEM 10.95) (Table I).

Clinical characterisation

The mean age at the diagnosis of bronchiectasis was 63.90 years (SEM 1.80, range 35–82). Only 3 patients were ex-smokers. The main respiratory symptoms included chronic cough in 34 (83%) patients, dyspnea in 29 (71%) and increased sputum production in 8 (19%).

Table I. Clinical characterisation of 41 patients with primay SS and bronchiectasis.

	n = 41
Females	40 (98%)
Mean age at SS diagnosis (years)	60.39 ± 1.86
Mean age at diagnosis of bronchiectasis (years)	63.90 ± 1.80
Mean follow-up (months)	64.61 ± 6.21
Respiratory symptoms	
- Chronic cough	34 (83%)
- Dyspnea	29 (71%)
- Increased sputum production	8 (19%)
Location of bronchiectasis	
- Inferior lobes	29 (71%)
- Middle lobe	10 (24%)
- Diffuse	10 (24%)
Other CT findings	
- Parenchymal micronodules	7 (17%)
- Bronchial wall thickening	7 (17%)
- Peribronchial ground-glass pattern	5 (12%)
- Atelectasis	3 (7%)
- Tree-in-bud pattern	2 (5%)
- Bullae	1 (2%)
Pulmonary functional tests at diagnosis	
- Normal PFT	10/26 (38%)
- Restrictive pattern	8/26 (31%)
- Obstructive pattern	8/26 (31%)
- Positive bronchodilation test	4/26 (15%)
- Reduced DLCO values	15/25 (75%)
Outcomes	
- Severe respiratory infections	23 (56%)
- Pneumonia	11 (27%)
- Death	1 (2%)

All cases of bronchiectasis were of the cylindrical type and were located predominantly in the inferior lobes (71%). Twenty-two (54%) patients had other CT findings, including parenchymal micronodules in 7 cases, bronchial wall thickening in 7, peribronchial areas of ground-glass attenuation in 5, atelectasis in 3, tree-in-bud pattern in 2 and bullae in one patient.

PFT were performed at diagnosis of bronchiectasis in 26 patients: 10 (38%) had normal results, 8 (31%) had a predominantly obstructive pattern and 8 (31%) had a restrictive pattern. Only 4/26 (15%) patients had a positive bronchodilation test. DLCO was measured in 20 patients: 15 (75%) had a DLCO <80 mmol/min/mmHg and two (10%) had <50 mmol/min/mmHg. Fibrobronchoscopy was carried out in 4 patients and showed no significant alterations: bronchioalveolar lavage disclosed a predominance of macrophages in one case and of neutrophils in another, and was normal in the other two cases.

Follow-up

All patients were followed up after diagnosis of bronchiectasis with regular visits at 6-12-month intervals, with a mean follow-up of 64.61 months (SEM 6.21, range 6–212). Treatment consisted of inhaled βadrenergics and corticosteroids in all cases, while 15 (37%) patients received at least one course of oral corticosteroids. Evaluation of pulmonary function status at the end of follow-up showed worsening in 7 (17%) patients. One patient died due to pulmonary aspergillosis.

Only four patients had a second PFT after a mean follow-up of 8 years: two patients showed no significant spirometric changes and two had worsened values. A second pulmonary CT was performed in 15 patients after a mean of 4 years without significant changes. Only two patients had minimal changes in associated inflammatory lesions (in one patient; there was spontane-

ous disappearance of the peribronchial ground-glass pattern, and in another micronodules appeared).

Twenty-three (56%) patients presented severe respiratory infections (defined as respiratory infection requiring hospital admission). Comparison of these patients with those without respiratory infections showed no significant differences in the main pulmonary features (characteristics of bronchiectasis, PFT) and SS features (clinical, haematological and immunological) except for a higher frequency of anaemia (61% *vs*. 22%, p=0.025), a poor clinical status at the end of the follow-up (30% *vs*. 0%, p=0.01) and a trend to a lesser use of antimalarials (13% *vs*. 33%, p=0.12).

Eleven (27%) patients developed pneumonia. Microorganisms were isolated in only four patients (*Pseudomonas aeruginosa* in 2, *Streptococcus pneumoniae* in one, *Aspergillus fumigatus* in one). Comparison of these patients with those without pneumonia showed no significant differences in the main pulmonary and SS features except for a higher frequency of bronchiectasis in sites other than the basal lobes (82% *vs*. 37%, p=0.015), raised ESR (55% *vs*. 17%, p=0.041) and hypocomplementemia (27% *vs*. 0%, p=0.017) in patients with pneumonia.

Comparison with control groups – Patients with primary SS without bronchiectasis

Epidemiologically, patients with bronchiectasis were older at diagnosis of SS (60.39 *vs*. 52.54 years, p=0.022) and had a longer mean follow-up (118.68 *vs*. 87.78 months, p=0.028) in comparison with patients without bronchiectasis (Table I). Clinically, no significant differences were found in the prevalence of the main SS clinical features, except for a higher frequency of hiatus hernia in patients with bronchiectasis (41% *vs*. 16%, p=0.024). Patients with bronchiectasis less frequently fulfilled the 2002 classification criteria (41% *vs*. 84%, p<0.001) and had a higher prevalence of respiratory infections (56% *vs*. 3%, p<0.001) and pneumonia (29% *vs*. 3%, p=0.002) in comparison with patients without bronchiectasis. The adjusted multivariate analysis identified age (p=0.04), fulfillment of 2002 criteria (p=0.027) and respiratory infections (p<0.001) as significant independent variables (Table II).

With respect to laboratory features, patients with bronchiectasis had a lower mean percentage of circulating gammaglobulins (17.9% *vs*. 21.9%, p=0.016), a lower frequency of anti-Ro/SS-A antibodies (27% *vs*. 54%, p=0.022) and a higher frequency of anti-smooth muscle antibodies (82%

Table II. Epidemiologic and clinical features of patients with bronchiectasis associated with primary SS in comparison with the control group.

	Bronchiectasis n=41	Control group n=37	Two-sided p-value
Gender (female)	39 (95%)	35 (95%)	1.000
Age at criteria fulfillment – years (mean ± SEM)	60.39 ± 1.86	52.54 ± 2.86	0.022*
Time of follow-up – months (mean ± SEM)	118.68 ± 10.95	87.78 ± 8.03	0.028
Xerostomia[1]	40 (98%)	37 (100%)	1.000
Xerophthalmia[1]	41 (100%)	35 (95%)	0.222
Altered ocular tests[1]	37/37 (100%)	28/31 (90%)	0.090
Altered parotid scintigraphy[1]	31/32 (97%)	27/30 (90%)	0.346
Positive salivary gland biopsy[1]	12/18 (67%)	18/20 (90%)	0.117
Parotid enlargement	11 (27%)	9 (24%)	1.000
Arthritis	8 (20%)	8 (22%)	1.000
Arthralgias	25 (61%)	26 (70%)	0.477
Fever	7 (17%)	5 (13%)	0.759
Serositis	3 (7%)	1 (3%)	1.000
Raynaud phenomenon	8 (19%)	7 (19%)	1.000
Vasculitis	1 (2%)	3 (8%)	0.341
Hernia hiatus	17 (41%)	6 (16%)	0.024
Pancreatitis	0 (0%)	0 (0%)	1.000
Renal involvement	2 (5%)	1 (3%)	1.000
Peripheral neuropathy	4 (10%)	4 (11%)	1.000
CNS involvement	4 (10%)	4 (11%)	1.000
Fulfillment of the 2002 criteria	17 (41%)	31 (84%)	<0.001*
Respiratory infections	23 (56%)	1 (3%)	<0.001*
Pneumonia	12 (29%)	1 (3%)	0.002

[1]Defined according to the 1993/2002 classification criteria.
*Statistically significant in the adjusted multivariate model.

Table III. Laboratory and immunological abnormalities of patients with bronchiectasis associated with primary SS in comparison with the control group.

	Bronchiectasis n=41	Control group n=37	Two-sided p-value
ESR > 50 mm/h	11 (27%)	12/36 (33%)	0.621
Anemia (Hb <11 g/L)	18 (44%)	11/36 (31%)	0.249
Leukopenia (<4x 10^9/L)	8 (19%)	6/36 (17%)	0.777
Thrombocytopenia (<100x 10^9/L)	2 (5%)	1/36 (3%)	1.000
Serum gammaglobulins (mean %)	17.89 ± 0.95	21.94 ± 1.38	0.016
IgG levels –mg/L (mean ± SEM)	12.97 ± 0.88	15.29 ± 1.29	0.131
IgM levels –mg/L (mean ± SEM)	1.39 ± 0.15	1.32 ± 0.13	0.703
IgA levels –mg/L (mean ± SEM)	2.49 ± 0.25	3.09 ± 0.39	0.186
ANA	39/40 (97%)	32 (86%)	0.100
RF	18/40 (45%)	15 (40%)	0.818
Anti-smooth muscle antibodies	32/39 (82%)	21/35 (60%)	0.043*
Anti-parietal cell antibodies	5/39 (13%)	10/35 (29%)	0.147
Antimitochondrial antibodies	2/39 (5%)	2/35 (6%)	1.000
Antiphospholipid antibodies	4/28 (14%)	3/23 (13%)	1.000
Monoclonal band in serum	4/25 (16%)	4/22 (18%)	1.000
Anti-Ro/SS-A antibodies	11 (27%)	20 (54%)	0.022*
Anti-La/SS-B antibodies	9 (22%)	14 (38%)	0.213
Cryoglobulins	3/32 (9%)	1/30 (3%)	0.613
C3 levels <0.82 g/L	5/40 (12%)	6/36 (17%)	0.747
C4 levels <0.11 g/L	3/40 (7%)	5/36 (14%)	0.465
CH50 <34 U/L	6/40 (15%)	8/36 (22%)	0.556

Table IV. Main characteristics of primary SS patients with bronchiectasis in comparison with the control group without SS.

	SSp n=41	Controls n=77	*p*-value
Mean age (years) (SD)	60.4 (11.9)	58 (14)	0.353
Female (%)	40 (98%)	51 (66%)	*<0.001*
Chronic expectoration (%)	8 (19%)	49 (64%)	*<0.001*
Mean HRCT score (SD)	23 (10)	39 (21)	*<0.001*
Cylindrical bronchiectasis (%)	41 (100%)	56 (73%)	*<0.001*
Inflammatory infiltrates (HRTC)	12 (29%)	29 (38%)	0.360
PFT (mean, SD)			
FEV1 %	82 (23)	75 (23)	0.118
FVC %	80 (19)	82 (18)	0.574
FEV1/FVC %	96 (14)	67 (13)	*<0.001*

vs. 60%, p=0.043) in comparison with patients without bronchiectasis (Table III). The adjusted multivariate analysis identified anti-Ro/SS-A antibodies (p=0.029) and anti-smooth muscle antibodies (p=0.047) as significant independent variables (Table III).

– Patients without SS with bronchiectasis

Patients with SS-related bronchiectasis were more frequently female (98% *vs*. 66%, p<0.001), and had a lower frequency of chronic expectoration (19% *vs*. 64%, p<0.001), a lower mean HRCT score (23 *vs*. 39, p<0.001) and a higher frequency of cylindrical bronchiectasis (100% *vs*. 73%, p<0.001) and a higher mean FEV1/FVC% (96% *vs*. 67%, p<0.001) in comparison with patients without SS with bronchiectasis (Table IV).

Discussion

Pulmonary involvement is one of the most-frequent extraglandular manifestations in patients with primary SS (15), with a frequency ranging from 10% to 90%. This may be explained by the heterogeneity of the different studies, with significant differences in the criteria used for the diagnosis of pulmonary disease (histopathological, clinical, functional or radiological features), the study design (retrospective, prospective or longitudinal) and the inclusion of SS patients with other systemic or rheumatic diseases (16-20). Findings from studies including histopathological data vary widely. Strimlan *et al*. (16) described lung involvement in 13 out of 343 patients, including lymphocytic interstitial pneumonia, pseudolymphoma, pulmonary lymphoma, diffuse interstitial fibrosis and amyloidosis. Davidson *et al*. (21) found that although lung disease usually occurred early in the disease course of SS (predominantly in Ro+ patients), most of these patients did not develop progressive pulmonary disease.

Interstitial lung disease (ILD) has traditionally been considered the most-frequent type of pulmonary disease in patients with primary SS (5). However, since 2000, several studies have described a predominance of bronchial/bronchiolar involvement rather than interstitial disease (6-8, 22, 23). Bronchiectasis refers to the permanent abnormal dilation of the central and medium sized bronchi as a result of a vicious cycle of infection and inflammation (24). There are no data on the prevalence of bronchiectasis in the general population, although it seems to increase with age (25). Symptoms include chronic productive cough, wheezing and dyspnea. Infectious exacerbations are associated with worsening of respiratory symptoms and pneumonia (26). A study of 150 adults with bronchiectasis in the UK found that 53% were idiopathic and 29% were post-infectious (27).

No study has specifically investigated the presence of SS in adult patients with idiopathic bronchiectasis. The rationale for linking primary SS (often defined as "autoimmune epithelitis") (28) and bronchiectasis is based on increasing evidence that airway epithelium actively participates in the pathophysiological mechanisms of respiratory disease (29). We found that 41 (34%) out of the 120 patients with primary SS in whom CT was carried out had bronchiectasis, a prevalence similar to that of previous studies (23, 24). All cases were of the cylindrical type, more than 70% were located in the inferior lobes and, in 30% of cases, were associated with parenchymal micronodules or peribronchial ground-glass areas. PFT showed no predominance of a specific pattern (one third had normal results, one third an obstructive pattern and one third a restrictive pattern) and 75% of patients had a reduced DLCO, which was overwhelmingly low-moderate grade. Similar results have been reported in smaller series of patients with SS (24).

The three main clinical characteristics of our patients with primary SS and bronchiectasis were an older mean age and a higher frequency of hiatus hernia and respiratory infections in comparison with patients without bronchiectasis. The mean age of patients with bronchiectasis of any etiology ranges between 56 and 70 years (30,31) and most patients are female, an epidemiological profile very similar to that of primary SS. Unfortunately, there are no epidemiological studies of the prevalence of bronchiectasis according to gender and age in the general population, and therefore it is not possible to ascertain whether bronchiectasis are more frequent in primary SS than in the general population of the same gender and age. Nevertheless, in primary SS patients with suspected pulmonary involvement, bronchiectasis should be considered the most-probable diagnosis in patients aged >60 years.

Nearly half of our patients with bronchiectasis had hiatus hernia. Emerging data on the relationship between gastroesophageal reflux disease (GERD) and bronchiectasis (32) show that in 4% of unselected patients with bronchiectasis, the condition is due to aspiration and/or GERD (33). A recent study has described a higher prevalence of GERD in patients with primary SS (34). Long-term exposure of the esophagus to acid reflux may increase the risk of microaspirations, contributing to chronic bronchial inflammation leading to bronchiectasis. In addition,

Helicobacter pylori infection should also be investigated (35). Therefore, GERD and H. pylori infection should be investigated and correctly treated in patients with primary SS, especially in those with bronchiectasis.

Our patients with bronchiectasis had a 20-fold increased prevalence of respiratory infections compared with patients without bronchiectasis. Bronchiectasis is characterised by airflow obstruction, which may be associated with inflammation of the small airways, thus facilitating airway colonisation by potentially pathogenic micro-organisms. The most-commonly observed bacteria are *Haemophilus influenzae*, *Pseudomonas spp*. and *Streptococcus pneumoniae* (14), which were also the most-frequently detected pathogens in our patients with primary SS and bronchiectasis.

The immunological profile of our patients with bronchiectasis was characterised by a lower frequency of hypergammaglobulinemia and anti-Ro/SS-A antibodies (which might be related to the older mean age and the lower frequency of fulfillment of the 2002 criteria), and a higher frequency of anti-SMA antibodies, which are detected in nearly 60% of patients with primary SS (36) but until now without clinical significance. Airway smooth muscle is critically important in modulating bronchomotor tone, and responds to inflammatory mediators by contracting, thereby increasing luminal resistance. New evidence, however, suggests that effector cells in the submucosa, including airway smooth muscle, may play an immunomodulatory role by expressing cellular adhesion molecules and secreting chemokines and cytokines (37). Possible autoimmune damage to airway smooth muscle, expressed as a higher frequency of anti-SMA antibodies, might play an etiopathogenic role in the development of bronchiectasis in a specific subset of patients with primary SS.

Our findings might have practical implications in the management of primary SS patients with pulmonary involvement. Firstly, bronchiectasis should be considered the most-frequent cause of pulmonary disease in primary SS patients with respiratory symptoms, especially in patients aged >60 years and those with positive anti-SMA antibodies. Secondly, GERD may be associated with bronchiectasis in nearly half the cases. Thirdly, the high rate of pulmonary complications in these patients requires multidisciplinary management including pneumologists and family physicians. Acute exacerbations should be treated promptly with short courses of systemic antibiotics while, in the case of frequent exacerbations, scheduled administration of either rotated or aerosolised antibiotics (26, 33) should be considered. In these patients, influenza and *S. pneumoniae* vaccination is recommended due to the concurrence of various predisposing factors including age, chronic disease and the high risk of pulmonary infections. In contrast to ILD, which should be considered as one of the most frequent causes of death due to extraglandular involvement in primay SS (38), bronchiectasis are more insidious and less expressive, with less direct impact on mortality but increasing morbidity, mainly in the form of repeated respiratory infections.

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