Risk factors for morbidity and death in non-cystic fibrosis bronchiectasis: a retrospective cross-sectional analysis of CT diagnosed bronchiectatic patients

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Abstract

Introduction: There is a relative lack of information about the death rate and morbidity of non-cystic fibrosis bronchiectasis and most studies are limited due to referral bias. We wanted to assess death rate and morbidity in those patients at our hospital.

Methods: Adult patients seen at our department between June 2006 and November 2009 were recruited if the key string “bronchiect-” was mentioned in electronic clinical records and if chest CT imaging was available. Clinical records of all patients with confirmed radiologic diagnosis of bronchiectasis were reviewed and clinical characteristics were analyzed.

Results: 539 patients with a radiographic diagnosis of non-cystic fibrosis bronchiectasis were identified in a retrospective cross-sectional analysis giving a prevalence of 2.6% in our hospital population. A wide range of etiologies was found with idiopathic bronchiectasis in 26%. In the 41 months interval, 57 patients (10.6%) died. We found a median exacerbation rate of 1.94 per year. Bacterial colonization status was associated with more deaths, exacerbation rate, symptoms and reduced pulmonary function. Pulmonary hypertension was found in 48% of our patients.

Conclusions: We evaluated a large non-cystic fibrosis bronchiectasis population, and provided new epidemiological data on associations between clinical characteristics and deaths and morbidity in these patients.

Keywords: Bronchiectasis, Non-cystic fibrosis, Mortality, Morbidity, Risk factor

Introduction

First described by Rene Theophile Laënnec in 1819, bronchiectasis (BX) are now defined as permanently dilated airways due to chronic bronchial inflammation caused by inappropriate clearance of various microorganisms and recurrent or chronic infection [1,2]. Diagnosing BX has become significantly easier with the advent of high resolution computed tomography (HRCT), which has proved to be highly sensitive for demonstrating bronchiectatic change in the airways [3]. Overall, postinfectious and idiopathic BX are the most frequent cause of non-CF bronchiectasis (NCFB), although the list of potential etiologies is extensive [4-6].

In the past, several studies evaluated clinical and microbiological characteristics of this NCFB population [5-13]. Although these studies identified a number of risk factors associated with lung function decline, the populations studied are limited due to referral bias. Most descriptive studies recruited patients with NCFB who were referred to their institution with a suspected or established clinical diagnosis of NCFB. As a result, the populations studied consist of a large number of patients with rare diseases and exclude certain subgroups such as smokers and patients with COPD [9-11]. Due to the heterogeneity of these study populations, the true burden of NCFB may be underestimated. There is a relative lack of information...
available about the mortality and morbidity of this condition. Such information is important as it allows us to prioritize treatment options and gain insights for proper design of clinical trials in NCFB. Our aim was to identify all patients with a radiologic diagnosis of BX in an unselected manner in order to assess mortality and morbidity in those patients with NCFB and to identify risk factors for mortality and morbidity.

**Methods**

**Study population and patient assessment**

We performed a search in the electronic patient file database of the University Hospital of Leuven, Belgium. This database lists patient records of all the patients seen at the University Hospital Leuven, which serves both as a local hospital and training center for the region of Leuven/Vlaams-Brabant as well as a national secondary and tertiary referral center. The search was done using these criteria: adult patients with the key string “bronchiect-” mentioned in the clinical records, with a contact at the department of Respiratory Medicine of our hospital between June the 1st 2006 (the furthest date we could go back in the electronic database) & November the 1st 2009 and who had CT imaging of the chest available. Approval was obtained from the local ethical committee of UZ Leuven, Belgium.

The chest CT scan images of all these patients were re-assessed to confirm/exclude the presence of BX. CT scans were performed by one of the UZ Leuven respiratory radiologists or at other centers. Images obtained using 1 mm collimation at full inspiration were reviewed and BX was deemed to be present if there was one or more of the following criteria: a bronchoarterial ratio greater than 1, lack of tapering of the bronchi and visualization of bronchi within 1 cm of costal or paravertebral pleura or abutting the mediastinal pleura [14].

In the patients with BX confirmed on chest CT scan, clinical records were retroactively reviewed and the following characteristics were noted: age, sex, weight, age at diagnosis, smoking history, BX diagnostic investigations that were performed and/or final diagnosis listed, current respiratory symptoms at diagnosis and outside an exacerbation (presence/absence of chronic cough, sternal pain, wheezing, hemoptysis or shortness of breath; total number of respiratory symptoms (1 to 5)), the number of exacerbations the first year after CT based diagnosis of BX (defined as the need for antibiotic treatment due to increased respiratory symptoms), presence of gastro-esophageal reflux disease (GERD)(defined as presence of esophagitis on gastroscopy and/or an abnormal 24 hour pH monitoring), presence of sinusitis (defined as an abnormal sinus CT scan and/or suggestive symptoms such as postnasal drip, chronic (purulent) discharge from the nose or symptoms of pain or tenderness over one of the sinuses) and the presence of pulmonary hypertension (PH)(defined as a systolic pulmonary arterial pressure of ≥36 mmHg on echocardiography assuming normal right atrial pressure of 5 mmHg) [15]. All sputum culture results obtained during the study period were reviewed and bacteria found since the diagnosis of BX were registered even during an exacerbation. All patients underwent spirometry according to ATS criteria [16-18] and the best results at diagnosis and outside an exacerbation were noted. Follow-up was by the different outpatient pulmonary clinics and depended on severity and stage of the underlying etiology and disease with a minimum of once per year. Standard follow-up at the NCFB outpatient clinic is once every three to four months.

**Statistics**

Associations between characteristics were analyzed using a broad set of statistical tests. Logistic, Poisson and linear regression models were used for binary, count and continuous outcomes respectively. Chi square tests with calculation of odds ratios (OR) were used for frequency distributions and non-parametric tests such as Mann-Whitney U test were chosen when the assumption of normal distribution was violated. Data were analyzed with GraphPad Prism4.01 and SAS9.1.3. The p-values reached significance if lower than 0.05 and two-tailed testing was performed.

**Results**

**Patient characteristics**

The patient selection algorithm is shown in Figure 1 and Additional file 1: Supplement text S1. Further analysis and chart review was done in this population of 539 NCFB patients. Patient characteristics are listed in Table 1.

Patient medical files were reviewed to identify the underlying etiology. We did not find a clear underlying cause for the BX in 170 patients. In 22 of these patients there were two possible diagnoses and for the subgroup analysis, patient data were included in both diagnostic subgroups. 148 patients lacking a final diagnosis, although full diagnostic work-up had been performed, were labeled as having idiopathic NCFB. The underlying etiology of the BX is shown in Figure 2 and Table 2. Analysis showed that BX due to thoracic cancer (OR = 3; p = 0.004), COPD (OR = 4; p < 0.0001) and interstitial lung disease (OR = 2; p = 0.02) were mostly male. Patients with idiopathic BX were predominantly female (OR = 2; p < 0.0001).

During the study period, a total of 20,998 patients were seen at least once in the department of adult Respiratory Medicine of which 539 had a radiological diagnosis of NCFB, giving an estimated prevalence of 2.6% amongst the overall patient population seen for respiratory problems at our hospital.
Symptoms

There was more sinusitis in NCFB patients with Primary Ciliary Dyskinesia (PCD) and idiopathic BX and less in patients with COPD, thoracic cancer and interstitial lung disease. Patients with sinusitis had more different species of bacteria present in sputum (p < 0.0001) with significance for PA (P = 0.0026; OR = 1.88), encapsulated Pseudomonas aeruginosa (PA) (p = 0.0013; OR = 2.35) and Staphylococcus aureus (SA) (p = 0.0063; OR = 1.85). Patients with sinusitis had more symptoms than others (p = 0.0004) with a significant association between sinusitis and cough (p = 0.01; OR = 1.93), wheezing (p = 0.033; OR = 1.57) and sternal pain (p = 0.0247; OR = 1.65), independent of the underlying etiology. Other results on symptoms can be seen in Additional file 1: Supplement text S2.

Gastro-esophageal reflux

Signs of GERD were present in 28% of our patients with NCFB. There was no significant difference in the presence of GERD between patients with different NCFB etiologies. The presence of shortness of breath was significantly associated with GERD (p = 0.001; OR = 2.4) and remained significant after correcting for underlying etiology. Cough, when controlled for etiology was also significantly associated with GERD (p = 0.0162; OR = 1.98). Overall, the number of symptoms in patients with GERD was higher than in patients without documented GERD (p = 0.0051). These patients with GERD also had more different bacteria present in their sputum cultures than patients without GERD (p = 0.016). The presence of SA (p = 0.0007; OR = 2.16) but not PA (p = 0.068; OR = 1.48) was associated with the presence of GERD.

Bacterial colonization

Sixty patients did not have any record of sputum culture or bronchoalveolar lavage (BAL) culture during the study period. The sputum culture results of the other patients are summarized in Figure 3. The main bacteria found are PA in 30%, Haemophilus influenzae in 31%, SA in 23%, Aspergillus fumigatus in 20%, Streptococcus pneumonia in 20% and Moraxella catharralis in 15% of the patients. Other bacteria found are listed in Additional file 1: Supplement text S3.

Underlying etiology was associated with the number of total different bacteria cultured in sputum. Idiopathic BX
(p = 0.003), sarcoidosis (p = 0.03), rheumatic (p = 0.05) and interstitial lung disease with BX (p < 0.0001) had less often bacteria present in sputum while bacteria were found more often in sputum cultures of patients with ABPA (p = 0.001), PCD (p = 0.001) and COPD (p < 0.0001). Subanalysis showed that PA, Moraxella catarrhalis, Streptococcus pneumonia and Escherichia coli were seen significantly more often in COPD patients and the former three significantly less in patients with interstitial lung disease (p = 0.001). As expected, Aspergillus was present more often in patients with ABPA (p = 0.0003).

Lung function
The mean spirometry values at diagnosis are shown in Table 1. Spirometry results were related to the underlying etiology (FEV₁ p < 0.0001; FVC p = 0.008) with a significantly lower FEV₁ in COPD patients as compared to the NCFB patients with other etiologies (p < 0.0001). There was a significant negative association between FEV₁ and number of respiratory symptoms, with a decrease of 104 ml (p = 0.0063) or 3.7% (p = 0.0012) per symptom. Airway resistance and residual volume were correlated with total number of bacteria in sputum, while FEV₁ and FVC were negatively correlated with total number of cultured bacteria (all: p < 0.0001). A worse lung function was associated with presence of PA (p < 0.0005), Haemophilus influenzae (p = 0.05), Streptococcus pneumonia (p = 0.05), SA (p = 0.05), Moraxella catharralis (p = 0.001) and Stenotrophomonas maltophilia (p = 0.01).

Pulmonary hypertension
Echocardiography data were available in 289 of the 539 patients (53.6%). In total 140 of the 289 (48.4%) patients were diagnosed with PH, with information about their systolic pulmonary arterial pressure in 130 patients (without the right atrial pressure of 5 mmHg; median 37.5 mmHg; IQR 33-48). We found that 10% of the patients with PH died during the study interval of 41 months. There was no significant correlation between the presence of PH and the colonization status or the number of exacerbations. There was a difference in presence of PH between the different etiologies (p = 0.012): there were more NCFB patients with PH in the COPD group and less patients with PH in the postinfectious group. The severity of PH (systolic pulmonary artery pressure in mmHg) was not significantly different between different etiologies (p = 0.067). Patients with PH had worse FEV₁ than patients without PH (p = 0.01), with a trend for FVC (p = 0.08). There was a significant inverse correlation between the systolic pulmonary artery pressure (mmHg) and FEV₁, FVC, TLC, RV

Table 2 Further definition of the underlying NCFB etiologies

| Postinfectious (84) | COPD (64) | Interstitial lung disease (57) | Rheumatic lung disease RA (29), Sjogren (5), Scleroderma (4), AS (1), MCTD (1) (40) | Immunodeficiency (29) | Thoracic cancer (38) | Other causes (44) |
|--------------------|-----------|-------------------------------|---------------------------------|----------------------|---------------------|------------------|
| TB (37), MAC (5), Pertussis (3), Invasive Aspergilliosis (2), Measles (1), Diptheria (1), Blastocystis hominis (1), unkown (34) | GOLD II (18), GOLD III (28), GOLD IV (26) | EAA (15), IPF/NSIP (27), BOOP (9), drug induced ILD (3), UIP (3) | CVID (1), HIV (1), hyper IgE syndrome (1), other immunoglobulin deficits (14 dysgammaglobulinemia, 1 agammaglobulinemia, 2 hypogama-globulinemia), Navajo poikiloderma (1), different types of post transplants (5) (3 kidney, 1 liver and 1 heart), non-thoracic Non-Hodgkin lymphoma (2), chronic lymphatic leukemia (1) | adenocarcinoma (9), large cell anaplastic carcinoma (1), squamous cell carcinoma (16), small-cell lung carcinoma (3), thoracic Non-Hodgkin lymphoma (3), carcinoïd (1), mesothelioma (2), solitary pulmonary nodule without tissue diagnosis (3) | sarcoidosis (13), anatomic malformations (6), UC (6), Crohn (3), SJM (3), aspiration/infiliation (3), α1-ATD (2), CS vasculitis (2), Wegener (2), MK (1), PE (1), WC (1), Microscopic polyangitis (1) |

The number in brackets states the number of patients. AS = Ankylosing Spondylitis, α1-ATD = α1-antitrypsin deficiency, BOOP = Bronchiolitis Obliterans Organizing Pneumonia, COPD = Chronic Obstructive Lung Disease, CS = Churg-Strauss, CVID = Common Variable Immunodeficiency, EAA = Extrinsic Allergic Alveolitis, ILD = Interstitial Lung Disease, IPF = Idiopathic Pulmonary Fibrosis, MAC = Mycobacterium avium complex, MCTD = Mixed Connective Tissue Disease, MK = Mounier-Kuhn Syndrome, NSIP = Nonspecific Interstitial Pneumonia, PE = Pseudoxanthoma Elasticum, RA = Rheumatoid Arthritis, SJM = Sayer-James-McLeod Syndrome, TB = Tuberculosis, UC = Ulcerative Colitis, UIP = Usual Interstitial Pneumonia, WC = Williams-Campbell syndrome
and TLCO (Additional file 1: Table S4). The significance remained after correcting for underlying etiology, with the exception of RV.

**Exacerbation rate**

Yearly exacerbation rate is listed in Table 1. Factors associated with more exacerbations were sinusitis (p < 0.0001), GERD (p = 0.048), low FEV$_1$ (p = 0.0003; r = -0.15) number of different bacteria cultured in sputum (p < 0.0001; r = 0.34), presence of (encapsulated) PA (both p < 0.0001) and SA (p = 0.0003) in sputum culture. Etiologies associated with an increased exacerbation rate were PCD (p < 0.0001), immunodeficiency (p < 0.0001), anatomical malformations (p < 0.0001) and COPD (p = 0.049). Fewer exacerbations were noted in patients with thoracic cancer (p = 0.015), interstitial lung disease (p < 0.0001) and sarcoidosis (p = 0.0003).

**Death rate**

During the 41-month period, 57 patients died (10.6%) (Additional file 1: Figure S5). Subgroup analysis showed lower 41 month deaths in patients with idiopathic or postinfectious BX (3.4% and 7.1% respectively) with significance for idiopathic NCFB (OR = 0.23; p = 0.0008) as opposed to other etiologies. Patients with thoracic cancer and COPD had the highest deaths (30% and 26% respectively; OR = 4.32 and 3.93; both p < 0.0001). More deaths were also seen in active smokers (OR = 1.98; p = 0.05) and in former smokers (OR = 1.87; p = 0.045). Death was associated with number of different bacteria in sputum cultures, with more deaths when more different species were present (p = 0.002). Only *Escherichia coli* (p = 0.0003) and *Aspergillus species* (p = 0.034) showed significant association with death but trends were seen for PA (p = 0.077), *Haemophilus influenzae* (p = 0.11), SA (p = 0.11) and *Moraxella catharralis* (p = 0.056). The number of symptoms was not associated with death and neither was the number of exacerbations. Low FEV$_1$ and FVC (p = 0.0008 & p = 0.002, respectively) and presence of PH (p = 0.01) were associated with more deaths.

**Discussion**

Radiological diagnosis NCFB was confirmed in a total of 539 patient which results in a NCFB prevalence of 2.6% in the patient population of the department of respiratory medicine at the University Hospital of Leuven, Belgium. The use of the electronic medical records database of our hospital to capture potential patients and thorough review of CT scan and clinical data allowed us to identify NCFB patients in an unselected manner. We are confident that we have obtained a nearly full estimate of patients with NCFB at our hospital, which explains the larger number of patients than similar studies reported in the literature. The setting of our study does not allow us to give an exact population estimate of NCFB, which has been estimated to be much lower.

**Figure 3** Percentage of bacteria present in sputum or bronchoalveolar lavage culture of NCFB patients. Only bacteria with a prevalence of more than 5% are shown.

**Goeminne et al. Respiratory Research 2012, 13:21**
http://respiratory-research.com/content/13/1/21
than our data, ranging from 52 per 100 000 in the over-
all US population to 1 per 625 Auckland Pacific Island
children [19-21]. Even incidence estimates fall within
this range, running from 3.7 to 17.2 per 100 000 per
year [22-24].

Our database included almost all possible underlying
etiologies in BX [4]. Our population included similar
numbers of idiopathic BX as reported in other cohort
studies but for other etiologies, the number of patients
derived somewhat [5-13]. This discrepancy may be due
to the fact that patients with NCFB were recruited on
the basis of radiological evidence of BX and not only on
the basis that they were referred to our hospital because
of NCFB. As a result, patients with NCFB due to
COPD, ILD or thoracic cancer were also recruited. Gen-
der distribution in our study population showed a small
male predominance, which is due to the inclusion of
patients with NCFB due to COPD, thoracic cancer and
ILD. Previous studies suggested that chronic airway
infection due to NCFB was a more common and more
virulent disease in women [5-11,13,25]. In our study
population, patients with idiopathic BX were predomi-
nantly female.

Our 41 month death rate of 10.6% is in line with the
findings of Loebinger et al. who found survival rates of
91% at 4 years [26]. We found a lower death rate in idio-
pathic BX, indicating that a lack of underlying etiology of
NCFB bears a favorable prognosis. One possible explana-
tion for this marked difference could be the absence of
comorbidities in patients with idiopathic NCFB as com-
pared to etiologies such as COPD and rheumatic disease.
Another possible explanation might be that patients with
idiopathic BX have a less severe pathophysiological
vicious cycle of impaired mucociliary clearance, infection
and inflammation and as a result develop lung damage
more gradually than other known etiologies. In a study
by Reiff et al. patients with idiopathic BX were shown to
have less extensive disease on CT images than other
etiologies, which is in agreement with our findings [27].
Kong et al. found that patients with idiopathic BX had a
low neutrophil oxidative burst, which may result in less
severe airway inflammation [28]. Children with idiopathic
BX had less viscous sputum than children with CF or
chronic bronchitis, which may lead to improved cough
transportability of sputum [29]. Additional research is
needed to unravel the pathogenesis of idiopathic BX. Our
finding of a high presence of sinusitis in this subgroup
suggests an upper airways dysfunction.

In our study population, we observed an exacerbation
rate of nearly 2 exacerbations per year, indicative of a sig-
nificant burden of disease in patients with NCFB. This
exacerbation rate was slightly higher than previously
reported by O’Donnell et al. (1.5 exacerbations per year in
patients with idiopathic BX) [30]. The higher exacerbation
rate is probably due to the inclusion of other etiological
groups such as COPD, where recent research has shown a
difference in oxidative stress in the lungs of COPD
patients versus BX patients. Tzortzaki et al. showed a
higher specific sputum marker of oxidant-induced DNA
damage in COPD patients versus BX patients [31].
Another reason for differences in reported exacerbation
rate might be the criteria we used to define exacerbation,
given the lack of a clear definition of a NCFB exacerbation.
In the current study, an exacerbation was defined not
merely on the basis of symptoms, clinical or radiologic
changes but on the need for a therapeutic intervention
with antibiotics (oral or IV). Interstitial lung disease, sar-
coidosis and thoracic cancer showed a lower exacerbation
rate. These patients also had a lower number of symptoms
and lower number of different bacteria in sputa, explaining
their lower exacerbation rate. They could be regarded as
having ‘dry’ bronchiectasis, a term previously used to
describe patients with BX but without expectoration of a
lot of sputa [32].

Our data showed a significant negative correlation
between FEV1 and exacerbation rate and the FEV1 was
on an average 104 ml or 3.7% lower per symptom
reported by our patients. This is in line with Wilson et
al. who found that lung function correlated with St.-
George’s Respiratory Questionnaire (SGRQ) [33].

In our population of NCFB patients 48% of the patients
with an echocardiographic evaluation had evidence of PH
and the presence of PH was associated with more severe
lung disease (decrease in lung function parameters). These
data are in agreement with similar study data that these
showed that PH was present in one out of three patients
with NCFB and correlated with radiographic stage [34].
Alzeer et al. saw that right ventricular dysfunction and
right ventricular dimensions were greater in cystic BX
and were positively correlated with systolic pulmonary
artery pressure and negatively correlated with partial
pressure of oxygen in arterial blood. In more severe BX
disease, there is an impaired perfusion with more capil-
lar bed destruction and left-to-right shunt, leading to
impaired cardiac function and pulmonary gas exchange
[34]. This might explain the bad prognostic factor of PH
in NCFB. Due to the high prevalence of PH, cardiac
assessment with echocardiography is indicated in patients
with NCFB and more severe lung disease. There was no
association between PH and other clinical characteristics.
Despite these findings, PH in BX did not have a signifi-
cant impact on death in our population.

The main advantage of our study is the large patient
sample and the unbiased recruitment with as main inclu-
sion criterion the radiological documentation of BX. Not
only those patients who were referred to our center for
management of their NCFB were recruited but also
patients with other underlying diseases, in whom the
presence of BX was perhaps considered to be a confounding or complicating factor. The main limitation of this study is its retrospective design. All clinical data were collected by reviewing patient medical records, leaving error for underreporting. Despite these disadvantages, data are in line with previous studies. Previous reports suggest that a triad of mucus plugging in the airways, infection and inflammation may reinforce each other, lead to progressive lung damage and result in mortality and morbidity [23]. It is clear that BX remains a significant health problem, requiring further research [35]. Our study revealed some additional factors influencing death and morbidity and may help to further clarify the different elements that are important in NCFB (Additional file 1: Table S6 [36]). The association between the bacterial colonization status and several clinical outcome parameters suggest the potential importance of anti-infective treatment. Dhar et al. reported their experiences with nebulised colistin in a small cohort of patients with NCFB infected with PA. Regular colistin reduced the exacerbation and hospitalization rate, a finding which needs confirmation in larger controlled trials [37].

Conclusion

In summary, NCFB was confirmed radiologically in nearly 3% of the patients seen at the department of respiratory medicine of our hospital with a wide spectrum of underlying etiologies. Although the general death rate of our NCFB population is comparable to literature data, we found that idiopathic BX showed lower death rate, emphasizing that a full work-up for NCFB may have prognostic implications. Repetitive bacterial follow-up with sputum culture is necessary as presence of PA was high and culture results were correlated with other factors such as symptoms, lung function, exacerbation rate and death rate. Presence of sinusitis and GERD was also associated with an increased exacerbation rate. Our analysis showed PH in 48% of the patients, underlining the need for echo-cardiographic evaluation in patients with BX.

Additional material

Additional file 1: Supplementary data text S1 shows patient selection algorithm; text S2 describes extra data on symptoms; text S3 gives additional information on bacteria found; table S4 shows correlation between lung function and severity of pulmonary hypertension; figure S5 shows deaths in non-cystic fibrosis bronchiectasis; table S6 indicates the associations between the different morbidity factors.

Abbreviations

ABPA: Allergic broncho-pulmonary aspergillosis; ANOVA: Analysis of variance; BX: Bronchiectasis; CF: Cystic fibrosis; CFLD: Cystic fibrosis like disease; COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; GERD: Gastro-oesophageal reflux; HRCT: High resolution computed tomography; IBD: Inflammatory bowel disease; ILD: Interstitial lung disease; IV: Intravenous; NCFB: Non-cystic fibrosis bronchiectasis; OR: Odds ratio; PA: Pseudomonas aeruginosa; P25-75: Percentile 25 and 75; PCD: Primary Ciliary Dyskinesia; PH: Pulmonary hypertension; RA: Rheumatoid arthritis; RV: Residual volume; SA: Staphylococcus aureus; SGRQ: St-George’s respiratory questionnaire; TLC: Total lung capacity; TLCO: Transfer factor of the lung for carbon monoxide.

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