Treatment of *Chlamydia pneumoniae* Infection in Adult Asthma: A Before–After Trial

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Background. Some diseases previously believed to be noninfectious, eg, peptic ulcer disease, are now known to be caused by chronic infection. Recently, chronic *Chlamydia pneumoniae* infection has been suggested as a cause for adult-onset asthma. The purpose of this study was to determine whether antichlamydial treatment would affect the natural history of this disease.

Methods. An open-label, before–after treatment trial was performed in a community-based, primary care office. Forty-six patients (mean age 47.7 years; range 17 to 78) with moderate to moderately severe, stable, chronic asthma were treated a median of 4 weeks (range 3 to 9) with oral doxycycline (100 mg twice daily), azithromycin (1000 mg once weekly), or erythromycin (1000 mg daily). Post-treatment pulmonary function and asthma symptoms were compared with baseline values. Follow-up was an average of 6 months (range 1.5 to 36) post-treatment.

Results. Four patients with *C pneumoniae* respiratory tract infection developed chronic asthma, which disappeared after treatment in each case. Of the remaining 42 seroreactive patients who were treated a mean of 6 years after the development of chronic asthma, one half had either complete remission or major clinical improvement (3 and 18 patients, respectively). This improvement was significantly more likely to occur in patients with early disease ($P=.01$) and before the development of fixed obstruction ($P<.01$).

Conclusions. Antimicrobial therapy appeared to "cure" or significantly improve asthma in approximately one half of treated adults, and the response pattern was consistent with chlamydial pathogenesis. *C pneumoniae* infection in asthma may be clinically important and should be investigated further.

Key words. Chlamydia pneumoniae, asthma, bronchitis, antibiotic therapy. (*J Fam Pract 1995; 41:345-351*)

Asthma is a common, chronic inflammatory condition of the airways whose causes are not completely understood.[1] There appears to be a heritable component in asthma, but the principal determinants of asthma prevalence are unknown environmental factors.[2] Recognition that the pathogenesis of asthma involves chronic inflammation has led to recommendations for antiinflammatory treatment.[3] Little is known, however, about environmental factors that may initiate or promote the inflammation responsible for asthma symptoms.

Recent discoveries implicating bacteria in conditions such as peptic ulcer disease (*Helicobacter pylori*) and chronic arthritis resembling rheumatoid arthritis (*Borrelia burgdorferi*) have led to increasing acceptance of the concept that a microbial cause will be found for many chronic inflammatory diseases of previously unknown origin.[4] Regarding asthma specifically, Smith[5] recently hypothesized that an infectious component explained the epidemiologic associations of atopy and various forms of asthma. It is generally recognized that viral infections often exacerbate established asthma,[6] and there is speculation that viral respiratory infections may be associated with the subsequent development of asthma,[7] but a role for respiratory infection as an initiator or promoter has not been definitively established.[8] Recently, attention has been directed to proposed models of initiation and promotion of asthma following viral respiratory tract infec-

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tions, including respiratory syncytial virus (infant bronchiolitis)[8] and persistent adenoviral infection (childhood asthma).[9]

Nonviral respiratory pathogens including *Mycoplasma pneumoniae*,[10,11] *Chlamydia trachomatis*,[12,13] and *Chlamydia pneumoniae*[14-16] have also been associated with possible initiation and promotion of asthma in both children and adults. Weiss et al[12] found that one third of children developed asthma 7 to 8 years after hospitalization for chlamydial pneumonia of infancy. Recently, Bavastrelli et al[13] cultured *C trachomatis* from a group of asthmatic children and presented evidence suggesting that they were chronically infected since birth. Emre et al[16] cultured *C pneumoniae* from inner-city children during asthma exacerbations and reported that asthma improved when *C pneumoniae* was eradicated after treatment; one of these culture-positive children presented with asthma for the first time. Using a sensitive polymerase chain reaction test, Cunningham et al[17] found evidence for chronic *C pneumoniae* infection in 46.9% of children with asthma followed prospectively.

Associations between *C pneumoniae* antibody titers and adult asthma have also been noted,[14,15,18] and it has been suggested that these *C pneumoniae* antibody titers, although not diagnostic of chlamydial infection by present criteria, may represent acute reinfection or ongoing chronic infection.[14] Since it is important to know whether appropriate treatment of *C pneumoniae* infection in asthma will hasten resolution of the associated airway irritability,[19] I treated suspected *C pneumoniae* infection and documented changes in symptoms and pulmonary function for an average of 6 months after treatment.

Methods

Study Setting

Between 1989 and 1994, study subjects were recruited from a family practice office affiliated with a multisite, multispecialty group practice. The practice is located in a midsized midwestern city whose population is mostly white and middle class.

Patient Selection Criteria

Patients were eligible if they (1) had moderate to moderately severe, stable, chronic asthma symptoms for at least 3 months prior to treatment, (2) met American Thoracic Society criteria for reversible airway obstruction,[20] (3) were not dependent on daily oral steroids, and (4) were not in the acute phase of an asthma exacerbation, ie, had stable baseline symptoms against which post-treatment changes could be reliably assessed. Moderate asthmatics were defined as those with two or more symptomatic episodes per week who reported nocturnal symptoms and typical triggers, such as exercise or environmental exposures. Moderately severe asthmatics were those with a history of previous oral steroid bursts, previous hospital admissions for treatment, or both. These definitions resemble those of the National Asthma Education Panel (NAEP) guidelines.[3] Patients meeting NAEP criteria for mild asthma (less than two symptomatic episodes per week, no baseline abnormalities in pulmonary function, or both) were excluded because lack of a well-defined baseline precluded interpretation in this before–after trial.

Microbiologic Methods

Pretreatment serologic testing for polyvalent (mixture of IgM, IgG, IgA) antibody to *C pneumoniae* was performed using the microimmunofluorescence (MIF) test developed by Wang and Grayston[21] and described previously.[14] Seroreactivity was defined as a polyvalent MIF titer of 1:16 or greater.

Treatment

Eligible patients were prescribed antichlamydial antimicrobial therapy providing they (1) were seroreactive to *C pneumoniae*, (2) were willing to accept empiric therapy, and (3) had no contraindication to prolonged antimicrobial administration.

Empiric therapy consisted of doxycycline, 100 mg twice daily, azithromycin 1000 mg once weekly, or erythromycin 1000 mg daily for 3 to 9 weeks. These antibiotics were chosen based on in vitro susceptibiltiy data.[22] Duration of therapy was based on previous clinical observations that permanent remissions in asthma required 3 weeks or more of treatment.[23, 24]

Patients were informed of the empiric nature of the therapy. They were told that it represented an unapproved indication for approved antibiotics likely to be effective against a chlamydial infection if one were present. To mitigate expectation bias, patients were not informed of the time course for improvement reported by other patients. All patients provided verbal consent prior to treatment.

Outcome Measures

Outcome measures were (1) change in pulmonary function, and (2) change in asthma symptoms, using pretreatment pulmonary function and symptoms as baseline.

Pulmonary Function

Change in pulmonary function is reported as the relative percent change in FEV_1 (forced expiratory volume in 1 second) after empiric treatment, calculated as:

$$100 \times (\text{post-treatment } FEV_1 - \text{pretreatment } FEV_1)/\text{pretreatment } FEV_1$$

Degrees of chronic obstructive pulmonary disease (COPD) were classified as "none," "mild," "moderate to moderately severe," and "severe to very severe," according to published American Thoracic Society (ATS) criteria.[20]

Patient Global Improvement Score

Clinical improvement was measured by an ad hoc patient global improvement (PGI) score based on an ordinal scale ranging from 0 to ±4. Scores reflected overall improvement or worsening in post-treatment asthma symptoms and medication use as compared with pretreatment baseline: 0 (unchanged); 1 (minimal improvement); 2 (modest improvement); 3 (major improvement); and 4 (complete improvement). Analogous negative ordinal values were recorded for patients reporting post-treatment worsening. In making the overall assessment, patients were instructed to consider four symptom areas: (1) nocturnal wheeze, dyspnea, and inhaler use, (2) daytime wheeze and dyspnea, (3) daytime inhaler use, and (4) exercise-induced symptoms (when present). For many patients a separate ordinal value was also recorded for each of the four subscales; however, only the overall PGI score was universally recorded because of significant ($P<.01$) correlations ranging from .75 to .90 between the four subscales and the overall score. PGI scores were obtained at post-treatment follow-up visits; the last reported value was used as the symptom outcome variable. Most subjects reporting major improvement (PGI score=3) also had clinically significant decreases in asthma medication use. All patients reporting complete improvement (PGI score=4) discontinued all asthma medication. *Treatment responders* were defined as patients reporting a final PGI score of 3 or more.

Medication Confounding

This trial made no restrictions on the introduction of new conventional anti-asthma medications or on the administration of increased doses of previously prescribed medications, as clinically required for control of symptoms during the post-treatment observation period. Such changes in conventional therapy affect interpretation of results, and are referred to as *medication confounding*. Presence or absence of such confounding was recorded, and outcomes were analyzed separately for those without and with confounding (Groups 1 and 2, respectively).

Statistical Testing

Differences in the means of continuous variables were assessed by ANOVA or *t* test. Fisher's exact test was used to analyze 2×2 contingency tables. A nonparametric one-sample sign test was used to estimate the significance of post-treatment improvement in median PGI scores. The Mann-Whitney *U* test was used to analyze group differences in geometric mean titer and PGI scores. Ordinal regression was used to analyze associations of COPD (1=none, 2=mild, 3=moderate to moderately severe, and 4=severe to very severe) and PGI score.

Results

Fifty of the 51 eligible patients accepted treatment. This report includes results for 46 (90.2%) of the 51 eligible patients, and does not include results for three who were followed less than 6 weeks post-treatment, one who failed to return for evaluation, and one who was not offered treatment. The median polyvalent *C pneumoniae* titer for the 46 study group patients was 1:128 (1:16, two patients; 1:32, six patients; 1:64, twelve patients; 1:128, thirteen patients; 1:256, nine patients and 1:512, four patients).

The median duration of antichlamydial antimicrobial therapy was 4 weeks. Three weeks and six weeks of treatment were most common (17 patients each). Twenty-nine patients were treated with azithromycin, 16 received doxycycline, and one patient was prescribed erythromycin. Mean post-treatment follow-up was 6.4 months (median 4.75 months, range 1.5 to 36). Gastointestinal upset resulted in premature discontinuation of therapy in two patients (one receiving azithromycin and one receiving doxycycline). Some patients reported loose stools for 1 day following administration of azithromycin, but this mild side effect did not alter treatment. No other adverse effects were noted.

Pulmonary Function Results

For the entire treated group, baseline FEV_1 averaged 2.32 liters (range 0.78 to 4.3), representing a mean percentage of predicted value of 67.8% (range 31% to 96%). Post-treatment pulmonary function results were available for 42 (91.3%) treated patients. Post-treatment mean FEV_1 increased 12.5% (95% confidence interval [CI], 4.6% to 20.3%; $P=.003$ compared with baseline values).

For Group 1 patients (without medication confounding, n=30), pulmonary function improvement correlated significantly with PGI score (R=.42, $P=.03$), and mean improvement in FEV_1 was significantly greater for responders than for nonresponders (270 mL vs 2 mL,

Table 1. Baseline Characteristics for Total Group and by Clinical Response Category

	Total Group, % (N=46)	Clinical Response Category*		
		Responders, % (N=25)	Nonresponders, % (N=21)	*P* value
Age in years, mean (range)	47.7 (17–78)	47.6 (17–78)	47.8 (26–66)	NS
Male, %	48	50	58	NS
Current smoking status, %†	41	38	45	NS
Positive allergy skin tests, %‡	48	44	58	NS
Asthma clinical characteristics				
Age at first reported symptoms, mean yrs (SD)	42.2 (16.7)	44.5 (18.7)	39.5 (13.9)	NS
Duration of asthma symptoms at treatment, mean yrs (SD)	5.5 (6.9)	3.1 (3.8)	8.3 (8.7)	.01
Initial symptoms associated with respiratory infection, %	80	92	67	NS
Clinical diagnosis, %				
Asthma	78	84	71	
Asthma with chronic airway obstruction	22	16	29	NS
Medication at time of treatment, %				
Inhaled albuterol	98	96	100	NS
Inhaled steroid	41	24	62	.02
Inhaled ipratropium	11	8	14	NS
Theophylline	41	32	52	NS
Pretreatment pulmonary function				
Prebronchodilator FEV_1,				
Mean liters (SD)	2.3 (.85)	2.3 (.81)	2.3 (.91)	NS
Mean % predicted (SD)	67.8 (16.5)	71.3 (16.7)	63.6 (15.6)	NS
Best FEV_1/FVC, mean (SD)	71.1 (11.9)	75.2 (10.5)	66.1 (11.8)	.008
Chlamydia pneumoniae geometric titer§	105.2	128.0	83.3	NS

**Clinical response categories are based on a patient global improvement (PGI) score reflecting patient-reported post-treatment clinical improvement as follows: 0=no change from baseline, 1=minimal improvement, 2=moderate improvement, 3=major improvement, and 4=complete improvement.* Responders *are defined as those who reported final post-treatment PGI scores of 3 (significant decrease in asthma symptoms and use of bronchodilators, 18 patients) or 4 (complete disappearance of asthma symptoms and no further use of asthma medications, 7 patients).* Nonresponders *reported final post-treatment PGI scores less than 3 (PGI score=2, 5 patients; PGI score=1, 4 patients; PGI score=0 or less, 12 patients).*

†Recorded for only 44 patients.

‡One or more positive skin tests against a battery of common aeroallergens. Performed in 21 patients.

§Pretreatment polyvalent antibody.

SD denotes standard deviation; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

respectively; $P<.05$). Group 2 patients (with medication confounding, n=16) had a correlation of similar magnitude (R=.43) that did not achieve statistical significance ($P>.05$).

Patient Global Improvement Results

For the treated group as a whole, the median post-treatment PGI score was +3 (range −2.5 to 4, $P<.001$ compared with baseline values). The PGI score was not normally distributed, tending to cluster between +3 to +4 (major to complete clinical response, n=25) and around 0 (little or no clinical response, n=21). There was no significant difference ($P>.05$) in the median PGI scores for patient groups receiving doxycycline or azithromycin.

Table 1 presents baseline patient characteristics for the treatment group as a whole and compares treatment responders (PGI scores ≥3) with nonresponders (PGI scores <3). Compared with nonresponders, responders reported a shorter duration of symptomatic asthma (3.1 vs 8.3 years, $P<.01$) and had a higher FEV_1 to forced vital capacity (FVC) ratio (75.2 vs 66.1, $P<.01$). Responders tended to be older than nonresponders when asthma first became symptomatic, reported more frequently that initial asthma symptoms began after respiratory infections, and had higher *C pneumoniae* polyvalent titer (GMT), but these differences were not statistically significant. There were no significant differences between responders and nonresponders in current age, sex, smoking, atopy as measured by skin testing, use of anti-asthma medications other than inhaled steroids, or FEV_1 levels before treatment with bronchodilators. Nonresponders had higher frequency use of previously prescribed inhaled steroids (62% vs 24%, $P<.02$).

Group 1 (without medication confounding) had a median post-treatment PGI score of +3 (range −2.5 to

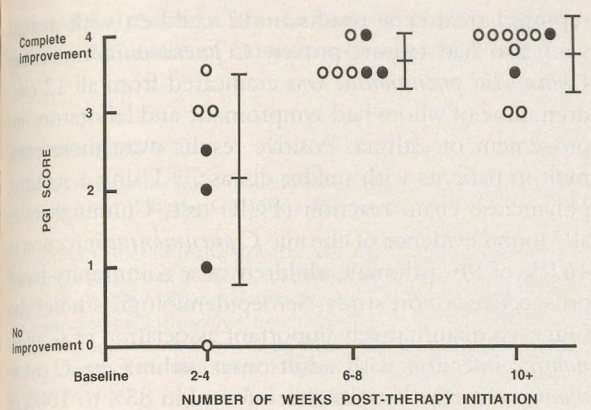

Figure 1. Time course for symptomatic improvement in asthma patients who responded to antichlamydial antimicrobial therapy and who did not add or increase conventional anti-asthma medications after antichlamydial antimicrobial therapy (without medication confounding). Y-axis: Asthma improvement (0=no change from baseline, 1=minimal improvement, 2=moderate improvement, 3=major improvement, and 4=complete improvement). *Treatment responders* shown in this figure reported final post-treatment patient global improvement (PGI) scores of 3 (significant decrease in asthma symptoms and use of bronchodilators) or 4 (complete disappearance of asthma symptoms and no further use of asthma medications). *X*-axis: Number of weeks post-therapy initiation. Closed circles designate culture-positive patients or patients with antibody meeting criteria for acute infection. Open circles designate culture-negative seroreactive patients without acute antibody. Vertical bars denote ±1 standard deviation from the mean.

4, $P<.001$ compared with baseline values). The median score for Group 2 (with medication confounding) was +2 (range −2 to 3.5, $P<.001$ compared with baseline values). The median PGI score for Group 1 was significantly ($P=.01$) greater than that of Group 2. Group 1 contained significantly ($P=.03$) more responders (67%) than did Group 2 (31%); ie, responders usually did not need additional medication, rather they decreased it or discontinued it altogether.

Time Course for Improvement in Responders

When it occurred, the positive treatment response developed in a stereotypical fashion that was not related to the length of follow-up. Improvement in responders usually began by 2 to 4 weeks after starting antichlamydial antimicrobial treatment, and the maximum therapeutic response was noted by 6 to 8 weeks after treatment initiation (Figure 1). The usual first indication of a positive response was an improvement in nocturnal symptoms. Some responders have had apparent asthma remissions lasting several years post-treatment without seasonal exacerbations.

Results by COPD Category

Ordinal regression on COPD category showed that increasing degrees of fixed obstruction were positively associated with age ($P=.005$) and asthma duration ($P=.03$), and negatively associated with PGI score ($P=.003$). Figure 2 illustrates the quantitative association between a decreased liklihood of a positive treatment response with increasing amounts of fixed obstruction.

C pneumoniae *and Asthma Initiation*

Before developing chronic asthma, a criterion for inclusion in this study, four patients were followed prospectively during episodes of acute asthmatic bronchitis, and all four were found to have evidence of *C pneumoniae* infection, verified by persistent culture isolation in two and diagnostic antibody titers in the other two. Following treatment, all four patients experienced normalization of pulmonary function and complete symptom remission.

Discussion

Of the 46 seroreactive patients in the treatment group studied in this trial, eight had antibody titer levels meeting criteria for acute infection.[25] Whereas serodiagnostic criteria for acute infection are generally accepted,[25] antibody titer levels in chronic *C pneumoniae* infection are often indistinguishable from titer levels representing previous exposure in the general population.[26] This trial, therefore, enrolled all seroreactive asthma patients meeting other

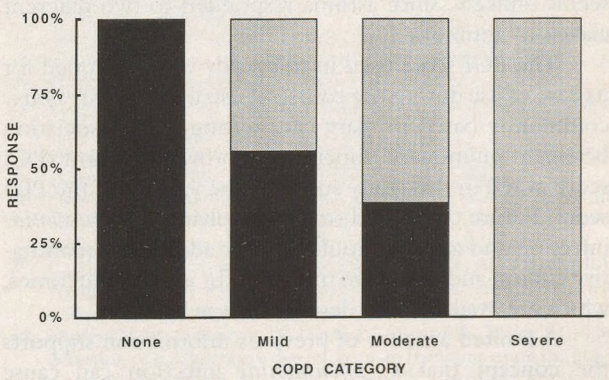

Figure 2. Response to antichlamydial antimicrobial therapy related to the degree of chronic obstructive pulmonary disease (COPD) accompanying the asthma (total study group, 46 patients). *Solid bars:* Percentage of patients responding to therapy (patient global improvement [PGI] score ≥3). *Shaded bars:* Percentage of patients not responding (PGI scores <3). *X*-axis: Amount of COPD accompanying the asthma. *P* value for trend =.004.

eligibility requirements and found that 54% appeared to benefit from antichlamydial treatment. This group of treatment responders included seven patients with moderate to moderately severe asthma who had complete post-treatment remissions, as defined by disappearance of all asthma symptoms and normalization of pulmonary function. One of these patients has been followed since 1988 and remains free of asthma. Because this was an uncontrolled, open-label trial subject to a number of potential biases, it cannot be concluded that these rather dramatic results prove that treatment of seroreactive asthmatics is efficacious. The results do, however, support the argument that definitive randomized, controlled, double-blinded trials should be carried out as rapidly as possible, since, if these preliminary findings can be confirmed, the benefit to patients could be great.

Given the low prevalence of spontaneous remissions for adult asthma,[27,28] the positive responses documented in this study are unlikely to be attributable to chance. Placebo responses or patient and physician bias are possible explanations for some of the results of this uncontrolled open study; however, it seems unlikely that patient or physician reporting bias could account for the persisting objective improvements in pulmonary function. Nonantibiotic effects of the antichlamydial agents chosen, such as a macrolide "steroid-sparing" effect,[29] alterations of theophylline metabolism,[30] or effects on inflammatory cell migratory function,[31] are also unlikely explanations, since the study subjects were not dependent on steroids, less than one third of responders used theophylline, and improvement persisted long after the discontinuation of therapy. A nonantibiotic effect persisting long after discontinuation of the antimicrobial cannot be excluded, but seems unlikely, since asthma responded to two different classes of antibiotic.

The PGI score used in this study was developed for its ease of use during the course of usual practice in a busy community-based primary care setting. The association between pulmonary function improvement and PGI score noted in this study supports the validity of the PGI score. Future controlled studies involving *C pneumoniae* infection and asthma should employ additional quantitative clinical and symptom measures for asthma outcomes, which are available and described elsewhere.[32]

A limited amount of previous information supports the concept that *C pneumoniae* infection can cause asthma and may be quantitatively important to its origin. Case reports describing successful antimicrobial treatment of asthma in adults who also had confirmed *C pneumoniae* infection have been published.[23,26,33] Inadvertent *C pneumoniae* infection of a laboratory worker has resulted in asthma (personal communication, Dr Pekka Saikku, Helsinki, Finland, 1992). Emre et al[16] recently reported treatment results in 12 children with asthma who also had culture-proven *C pneumoniae* infection. *Chlamydia pneumoniae* was eradicated from all 12 children, nine of whom had symptomatic and laboratory improvement of asthma. Positive results were more common in patients with milder disease.[16] Using a sensitive polymerase chain reaction (PCR) test, Cunningham et al[17] found evidence of chronic *C pneumoniae* infection in 46.9% of 96 asthmatic children in a community-based prospective cohort study. Seroepidemiologic studies also suggest a quantitatively important association of *C pneumoniae* infection with adult-onset asthma, as *C pneumoniae* seroreactivity has been found in 85% to 100% of patients reporting asthma onset after age 40.[14,15,34]

Recognition of bacterial causation for chronic illnesses once believed to have a nonbacterial source, such as peptic ulcer disease, the hemolytic-uremic syndrome, and cat-scratch disease, was delayed because of factors such as fastidious growth characteristics, unestablished biological mechanisms, low bacterial concentrations, uncommon sequelae of common infections, and the power of dogma.[4] Inability to uniformly culture chlamydiae from inflammatory target tissue is a characteristic of established chlamydial diseases, including trachoma[35] and tubal infertility.[36] A noncultivatable form of chlamydiae, indicated by persisting chlamydial DNA detected by in situ hybridization in fallopian tube tissue of infertile women[37] or by PCR in conjunctival tissue of trachoma patients,[38] has been demonstrated recently. In the study population reported here, *C pneumoniae* was cultivated from two of four patients with acute wheezing illness that developed into asthma, but from only one of 15 patients with established chronic asthma for whom cultures were obtained. Bronchoscopic sampling of asthmatic lungs for evidence of chlamydiae would appear to be warranted in future studies.

A well-described characteristic of chronic inflammatory diseases caused by *C trachomatis* infection is the development of immunopathologic-mediated irreversible inflammatory damage in target tissues related to disease chronicity.[39] It is tempting, therefore, to speculate about the superior therapeutic responses in recently symptomatic asthma before development of COPD, as was found in this study. It is conceivable that a narrow "window of opportunity" exists wherein antichlamydial therapy may eliminate the pathogen before irreversible inflammatory damage, which is a perpetuating cause of asthma, is produced by chlamydial infection within the asthmatic lung. Confirmation of this hypothesis must await the results of future studies, which are of high priority given the magnitude of asthma's contribution to respiratory morbidity. In the meantime, recommendations for or against anti-

chlamydial treatment for asthma should be deferred pending the results of randomized, controlled trials.

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