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REVIEW

Prevention of asthma

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ABSTRACT: Environmental factors which have changed in the last decade or so appear to be largely responsible for the increase in the prevalence of asthma in affluent countries. It should, therefore, be possible to design interventions to reverse these recent trends and reduce the incidence of asthma. Primary preventive strategies have the potential not only to reduce acquisition of sensitization to common allergens and the risk that symptoms will develop subsequently, but also to reduce morbidity in those who already have persistent disease. There is accumulating epidemiological evidence that a dietary exess of sodium and omega-6 fatty acids, a dietary deficiency of antioxidant vitamins and omega-3 fatty acids, reduced rates of breastfeeding and exposure to allergens and environmental tobacco smoke are all involved in the aetiology of asthma. The modification of these factors has the potential to reduce the incidence and thus the prevalence of this disease. Environmental intervention should be particularly effective in children who have inherited or acquired characteristics which put them at high risk of developing asthma. With the evidence now available, it seems reasonable to assume that interventions which are based on our current knowledge of risk factors could achieve a 50% reduction in the prevalence of asthma in the next generation of children.
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Environmental factors which have changed in the last two decades appear to be largely responsible for an increased prevalence of asthma in affluent countries [1–6]. This implies that it is possible to design interventions to reverse these trends and reduce the incidence of asthma. Primary preventive strategies have the potential to reduce rates of acquisition of sensitization to common allergens and the risk that symptoms will subsequently develop and also to reduce morbidity in those who already have persistent disease. This review examines the evidence that there are avoidable factors which, if modified, have the potential to reduce the incidence and, thus, the prevalence of asthma.

Reducing the prevalence of asthma

Applied epidemiological studies can provide a systematic approach to reducing the prevalence of asthma. As many as 25% of children in affluent countries now report that they have wheezed in the last year [7–10], although only half this number have an asthmatic illness which has clinical importance. Data from studies which have measured the burden and distribution of asthma and which have quantified the aetiological factors can be used to estimate the fraction of illness that is attributable to modifiable risk factors [11], but different types of studies will be needed in the future to estimate the effectiveness and the economic implications of preventive interventions.

An interventionist approach to preventing asthma is urgently needed because recent advances in managing asthma have led to only small reductions in the overall burden of morbidity in the community. Although improvements in treating and managing asthma have led to decreases in asthma mortality rates in recent years in Australia and New Zealand [12], increases in hospitalizations for childhood asthma were reported up to 1990 [13], and improvements in management skills, in awareness and in the promotion of preventive medications have not been accompanied by an expected decrease in the prevalence of asthma. Recent studies in Australia show that 25% of 8–11 year old children have used a beta-agonist inhaler in the previous year, and at least 10% use a preventive medi-cation for asthma [14].

Because it is unlikely that new advances in management practices in the near future will substantially reduce morbidity or cure asthma, it is important that an interventionist approach to control or to modify environmental and dietary factors is considered. This type of approach will depend on the reallocation of health funds to information services, to resources for interventions and to educational strategies. Such interventions will be cost-effective in the long-term because asthma management incurs substantial costs once the disease has become a chronic condition [15–17].

Environmental risk factors

Inhaled allergens.

The vast majority of asthmatics (approximately 80–90%) are sensitized to at least one common allergen [18, 19].

Different allergens are dominant in different climatic regions but indoor allergens are especially important because many people spend most of their time indoors. Some allergens may be more closely associated with asthma for the following reasons: the particles are smaller and, therefore, more respirable; the allergens are more potent in their enzymic activity; exposure reaches very high levels or is perennial.

Allergen exposure clearly influences the development of an atopic phenotype. It has been suggested that allergen exposure during very early life when the immune system is developing, may produce memory T-cells which manufacture specific immunoglobulin E (IgE) antibodies when re-exposed to allergens in later life [20]. We found that children who become sensitized in early childhood are at a much higher risk of having asthma than those who become sensitized later [21], and that children with high levels of sensitization are most likely to have symptoms which are clinically important and which impact on lifestyle [22]. In a prospective cohort study of infants, SPORIK *et al*. [23] found that the development of wheeze was related to the level of house-dust mite allergens in the child's bed, and that children who were exposed to high levels were five times more likely to have asthma at the age of 11 yrs [23]. These studies imply that reduction of allergen exposure in early life has the potential to delay sensitization and to reduce the risk that severe asthma will develop.

House-dust mites. House-dust mites are the most important documented risk factor for airway hyperresponsiveness (AHR) and asthmatic symptoms [24–26], and the severity of sensitization which develops is directly related to exposure levels [27, 28]. Exposure levels also influence the severity of asthma as measured by medication requirements [29], peak flow variability [30], and risk of admission to hospital [31–33]. This relationship occurs even in regions where allergen levels are quite low [34, 35], which suggests that there is no safe threshold.

House-dust mites are especially important in the aetiology of asthma because they are ubiquitous and occur perennially, and because they release proteases which are particularly potent allergens. House-dust mite levels are directly related to ambient levels of outdoor humidity [27], to air exchange rate and indoor humidity [36, 37], to damp and the amount of furnishings [38], to the regularity with which furnishings are laundered [39], and to a low ventilation rate, which increases indoor humidity [40–42].

Recent studies have demonstrated a dose-response relationship between exposure to house-dust mite allergens and several markers of asthma severity, including AHR, symptom severity and lung function. In a study of six random population samples of children, we conservatively estimated that there is a doubling in risk of children having current asthma for every doubling of *Dermatophagoides pteronyssinus* antigen I (*Der p* I) level [27], but the data could be less conservatively interpreted to indicate a quadrupling of risk at exposure levels above 10 $\mu g \cdot g\ dust^{-1}$. Similarly, a study of asthmatics in the UK found that there was a onefold increase in AHR for every twofold increase in *Der p I* level [26]. Together with the evidence that relatively small changes in allergen exposure levels influence the degree of AHR and the severity of symptoms [43], these data suggest that even modest reductions in house-dust mite allergen levels will lead to a significant reduction in the severity of asthma.

Other indoor allergens. Indoor allergens from pets, cockroaches and moulds can also play an important role. In the USA, New Zealand and the UK, pets, particularly cats, are a well recognized source of domestic allergens which are associated with asthma [25, 32, 33, 44] and, in regions with low house-dust mite allergen levels, cat and dog allergens become a major cause of sensitization associated with asthma [45]. Levels of sensitization to cat allergens in children have been related to the cumulative duration of exposure [46].

Outdoor allergens. Outdoor allergens, such as Alternaria mould spores and ryegrass pollens, have a primary importance in the aetiology of asthma in dry agricultural regions and have been documented as causing acute exacerbations of severe illness [47–51]. Alternaria is the only allergen which has been reported to cause respiratory arrest [51]. Levels of Alternaria and ryegrass allergens are often determined by local agricultural and crop management practices, and peaks in exposure levels can occur under specific meteorological and seasonal conditions.

Environmental tobacco smoke

The effects of environmental tobacco smoke (ETS), which is the most common indoor air pollutant, on the respiratory health of children has been scientifically reviewed [52]. Mothers who smoke during pregnancy or parents who smoke in the same indoor environment as their child approximately double the risk of the child having a serious respiratory infection, such as pneumonia, bronchiolitis or bronchitis, in infancy which requires hospitalization [53–60] or treatment by a doctor [61–70]. Such infections are, in themselves, a risk factor for the later development of asthma [71–75], but it is not known whether they lead to the development of asthma or are the first expression of an asthmatic phenotype. There is evidence that exposure to ETS increases the risk of wheeze in infants and children, with an odds ratio of approximately 1.5–3.0 [59, 63, 70, 76–82].

The effects of smoking during pregnancy, which is associated with preterm delivery and low birthweight [83, 84], and of postnatal exposure to ETS, which may compound the effects of prenatal exposure, have not been separated. Children with a low birthweight are at risk of having narrow airways and/or early respiratory symptoms [56, 84–88], and of developing allergic sensitization or wheeze in early childhood [70, 76, 78, 89, 90]. Studies conducted in China, where few women smoke, suggest that the effects of exposure to ETS in infancy are different from those of maternal smoking during pregnancy [54, 55]. Animal studies, which are the only type of study able to separate out the pre- and postnatal effects, suggest that both types of exposure independently facilitate mechanisms which promote the development of AHR [91, 92].

Dietary factors

It has been hypothesised that dietary changes have contributed to a higher prevalence of asthma in affluent countries [93, 94]. Several dietary factors, including a higher consumption of processed foods, omega-6 oils and salt, and a lower consumption of omega-3 fatty acids and fresh foods plus lower rates of breast-feeding, are all implicated because of their potential influence on inflammatory reactions. However, there have been relatively few epidemiological studies, which have examined the effects of diet, and most have been in adults whose airways may be less responsive to dietary factors. A deficient diet may increase susceptibility to adverse environmental exposures, such as allergens, ETS and infections, and, conversely, a "healthy" diet may protect against the effects of such exposures. It is also possible that dietary effects are larger than have been estimated from population studies in which the analyses have not been limited to a susceptible subgroup, such as children whose airways are still developing, atopics who are most at risk for the development of asthma, or subjects with prior respiratory symptoms.

Fatty acids. Circumstantial and epidemiological evidence suggests that consumption patterns of omega-3 and omega-6 fatty acids influence the development of airway inflammation. Omega-3 fatty acids, which are stored in cell membranes, have an important role in controlling inflammation [95], but are easily replaced by omega-6 fatty acids, which facilitate the development of inflammation. Omega-3 fatty acids are found in high quantities in fish oil and in monounsaturated oils, such as canola oil, whereas omega-6 fatty acids are found in polyunsaturated fats, such as safflower and sunflower oils, which have been consumed in increasing amounts in recent years following campaigns to reduce heart disease. The twofold increase in the prevalence of childhood asthma in Australia has coincided with an eightfold increase in the ratio of consumption of butter (which contains omega-3 fatty acids) to polyunsaturated margarine [93, 96].

In population studies of children, we found that children who eat fish more than once a week, and who, therefore, consumed larger amounts of omega-3 fatty acids, were 30–70% less likely to have asthma than children who ate fish less often [22, 75]. We confirmed this association in a more recent study using a food frequency questionnaire, in which we found that children who ate oily fish regularly were protected against asthma with an odds ratio of 0.3 (95% confidence interval (95% CI) 0.1–0.7) [97]. There was no difference in nonoily fish consumption between asthmatics and nonasthmatics, which suggests that parents of asthmatic children do not selectively prevent them from eating fish.

It is thought that asthma and other inflammatory diseases have a low prevalence in Greenland Eskimos because of their high fish intake [98]. In Mediterranean countries, where olive oil, which is low both in omega-3 and omega-6 fatty acids, is commonly used, the prevalence of AHR in children is also low [99]. Dietary fish oil has also been shown to protect against coronary heart disease in middle-aged and elderly people [100], and against the development of airway narrowing [101, 102], chronic airflow limitation in smokers [103], and other diseases with an inflammatory component [104–106].

Electrolytes. Because sodium is implicated in many aspects of the regulation of smooth muscle tone, a diet with a high salt content is thought to predispose towards the development of airway disease. BURNEY [107] first suggested a circumstantial link between increased salt intake and mortality from asthma, and BURNEY *et al*. [108] went on to show a close relationship between salt excretion and AHR in males. A gender difference in the importance of salt intake is plausible because animal and skeletal studies show gender differences in sodium metabolism which may influence muscle tone [109].

Further evidence comes from studies which have found a significant association between salt intake and AHR in subjects aged 9–16 yrs [110], and in adult males [111]. A study of males in the USA found a relationship between potassium and AHR, but found no influence of sodium intake [112]; and a study in the UK found a small relationship between dietary sodium and airways responsiveness in only one of three study samples [113]. Only two studies have enrolled both males and females. In Britain, no association was found between 24 h sodium urinary excretion and AHR in males and females [114] and, in the USA, both the level of potassium and the ratio of sodium to potassium were found to predict wheeze and bronchitis in adults [115]. Discrepancies between studies may result from problems with misclassification because dietary intakes are variable and inherently difficult to quantify, or from the inadequacy of the measurement of salt excretion as a marker of total dietary salt intake over a prolonged period.

Magnesium may also influence airway disease because it is involved in maintaining the electrical potential across cell membranes and may, therefore, have a bronchodilator effect on the airways. A population study in the UK found that, after adjusting for major confounders, such as atopy, age, sex and smoking history, magnesium intake had a significant association with measurements of AHR, forced expiratory volume in one second (FEV_1) and self-reported wheeze [116].

Anti-oxidant vitamins. Antioxidant vitamins are the first-line of defence against oxygen free radicals, that are capable of damaging cellular components and which contribute to inflammation. It is hypothesized that a diet which is low in antioxidants, such as vitamins A and C, may reduce natural defences and increase susceptibility to oxidant attack and airway inflammation [94]. There is evidence from two population studies of adults living in the UK that a diet with a low intake of fresh fruit and vegetables is a risk factor for decreased lung function [117, 118], but studies in the USA and in the Netherlands have found no relationship between low vitamin A intake and the degree of airway obstruction as assessed by various measures of lung function, even though detailed diaries were used to estimate dietary exposures [119, 120]. In a study of females over a 10 year period, no association was found between antioxidant intake and the presence of asthma [121]. Although there was a suggestion that vitamin E had a modest protective effect, the trial was complicated by the fact that females who were at high risk of having asthma had supplemented their diet with vitamins C and E.

Breast-feeding. Breast-feeding is a source of immunoglobulin A (IgA), which has an anti-infective action and may prevent epithelial damage from respiratory infections. Thus, breast-feeding may have a beneficial effect because it postpones the age at which respiratory infection first occurs or because infants are protected from the foreign proteins present in cow's milk, which can increase allergic symptoms [122]. Infants who are breastfed have lower serum IgE levels [123], and have less allergic illness in early childhood [124–129] and through to adolescence [130]. Breast-fed infants have also been found to have less sensitization to house dust-mites at the age of 1 yr [131], and fewer respiratory symptoms [132].

Respiratory infections

The role of viral and bacterial respiratory infections in the development of asthma is complicated. It has been hypothesized that bacterial infections in the first few weeks of life protect against the development of an allergic phenotype. Thus, it is thought that decreased exposure to infections in the first few weeks of life as a result of smaller family sizes and better hygiene has played a part in the higher prevalence of asthma in affluent populations. In Europe, small family size is associated with increased rates of atopy and allergic symptoms, with the first born children being at highest risk [133, 134]. Respiratory infections in early life may downregulate the production of IgE by influencing the development of a predominantly type 1 or type 2 T-helper (Th-1 or Th-2) response. Viral infections may activate a Th-1 profile and, by preventing the proliferation of Th-2 cell populations, protect against later allergic responses and the development of sensitization [135, 136].

However, there is also evidence that serious respiratory infections in early life are associated with the later development of asthma [59, 71, 73, 75, 137]. This suggests that early bacterial infections may protect against the development of atopy, whereas viral infections may provoke the first expression of asthma or may increase the risk of later asthma by causing airway inflammation or by facilitating allergens to cross the airway epithelium.

Characteristics of "at-risk" groups

The characteristics of children who are most at risk for the development of asthma and who need to be targeted for interventions are documented. Children who have a parent with asthma or an allergic illness are easily identified as being at risk of developing a similar illness [138–140], but cord IgE levels are not sensitive predictors of later asthma [123]. Children who have serious respiratory infection in early life [75], or who acquire sensitization to common allergens at an early age [21], are also at significant risk of having asthma in later childhood. Boys are at greater risk in that they have higher levels of atopy, AHR, symptoms and hospitalizations for asthma during childhood [141–144], and are more sensitive to changes in asthma severity with dietary salt intake [109].

Longitudinal studies show that children who develop a high level of sensitization to house-dust mite allergens are at the greatest risk of having a diagnosis of asthma, and of having reduced lung function and morbidity which has a significant impact on lifestyle [19, 22, 145]. Other "at-risk" groups include children who are exposed to ETS *in utero* or in early life, and children who have a low birthweight, who are not breast-fed, or who have a low omega-3 fatty acid or antioxidant vitamin intake. A 25 year longitudinal study found that frequent episodes of asthmatic symptoms and poor lung function in childhood predicted ongoing asthma in adulthood [146]. In subjects who are potentially susceptible to asthma, modifications in diet and in exposure to allergens and to ETS in early life are likely to be highly effective strategies for preventing and reducing morbidity caused by asthma.

Strategies for prevention

There are both occupational and experimental models which demonstrate that avoidance of a relevant environmental factor can reduce asthma morbidity, and that preventive strategies for asthma can be successful. Because environmental interventions may have little effect once asthma has become a chronic condition, interventions which commence in early life, or during early exposure, have the greatest potential. Interventions have mainly been tested as a method for reducing morbidity in patients who have already developed asthma, but they are likely to have a far greater potential as a method for preventing susceptible children from developing asthma in the first instance.

Environmental and occupational models

In Barcelona, many people developed sensitization to soya beans following intermittent exposure to small amounts of soya bean dust, which was generated from the unloading of ships in the harbour [147, 148]. Under certain atmospheric conditions, which occurred only infrequently, the city was exposed to high levels of soya bean dust, with a consequent significant increase in the number of patients attending hospital with acute exacerbations of symptoms. However, the installation of efficient silo filters has prevented ongoing intermittent high exposures and has eliminated further epidemics of asthma hospitalizations [149].

An encouraging model of avoidance is also provided by occupational exposure to Western red cedar. Some workers become sensitized to Western red cedar and develop respiratory symptoms [150], but their asthma abates if they then avoid exposure. However, continued exposure leads to the development of a chronic condition, which cannot be improved with avoidance [151, 152]. These models suggest that respiratory illness can be prevented or moderated at an early stage of the disease by protection from clinically relevant exposures but may not be easily prevented once a chronic condition is established.

Allergen avoidance

House-dust mite allergens. Avoidance of house-dust mite allergens has the most potential to reduce asthma in humid

regions. House-dust mites thrive in places with sufficient humidity [37], and their proliferation can be prevented by depriving them of moisture. Indoor humidity levels can be reduced by dehumidifiers [153], by increased ventilation in bathrooms and kitchens and by removal of other sources of humidity, such as fish tanks. In practice, the control of indoor humidity requires many techniques, including changes in the use of heating, ventilation and air-conditioning systems. In the long-term, better housing design will be required to maintain low humidity environments in order to prevent the accumulation of allergens in furniture and bedding [154].

Many studies have concentrated on removing allergens from floors. Laundering mats and rugs or exposing them to sun for extended periods can kill mites but does not remove allergens [154]. Reductions in allergen levels in soft floor coverings can be achieved in the short-term with acaracides [155], but their effect on long-term reduction remains contradictory [156–159]. Moreover, the clinical importance of measures which address only floor levels remains debatable because the most clinically relevant source of house-dust mites is from the bed, presumably because the airways are in close proximity to the allergen source for extended periods of time [27].

Allergen levels in beds can be reduced relatively easily by covering mattresses with occlusive covers [42, 160], by regular washing and by regular replacement of pillows, which can be cheaper and more comfortable than covering with occlusive materials. In regions where allergen levels are high, a very active strategy may be required [157]. Cleaning of toys, curtains and soft furnishings is also important because they can harbour huge amounts of allergens [154]. It is encouraging that there are wide variations in *Der p* I levels in climates that favour the growth of house-dust mites [161], and that low levels have been recorded in public places in regions where domestic levels are high [162, 163] because this endorses the feasibility of attaining low allergen levels in humid climates.

Removal of house-dust mite sensitized children to a low allergen environment decreases their AHR and improves symptoms [164–166]. However, the low allergen environment needs to be maintained long-term because AHR returns to former levels when the children return to higher exposures [167], although treatment with budesonide can prevent this [168]. Allergen avoidance together with effective treatment may achieve the greatest benefits for children who have already developed AHR.

A controlled intervention trial with blinded assessments of an "at-risk" birth cohort has successfully demonstrated that a significant reduction in the incidence of asthma can be attained [128, 169–171]. In this trial, several dietary and house-dust mite avoidance interventions were undertaken simultaneously so that the separate effects are not known, but it is encouraging that children who underwent active intervention had significantly less sensitization to allergens at the age of 1 yr, and significantly less asthma at the age of 2 yrs.

Cat allergens. The cat allergen (*Fel d* I) from the sebaceous glands and saliva, which dries on the pelt, can be carried on very small particles which remain airborne for long periods, or continuously [172]. After eviction of a cat, it can take more than 6 months for airborne *Fel d* I levels to return to levels comparable with cat-free homes [173]. Limiting the cat to living outdoors will reduce exposure but, for people who refuse this, measures such as weekly washing of the cat, hard floors, the presence of minimal furnishings and increased ventilation rates can help to maintain low airborne allergen levels [38], although it is unlikely that these are practical. Significant exposures to cat allergens can also occur in schools and public buildings [39, 174, 175].

Outdoor allergens. Because outdoor allergens are not easily avoided, a lateral approach to prevent both sensitization and symptoms will be required, and may involve both optimal medical management and filtration of incoming air. For young children who experience episodic symptoms, treatment with preventive medications solely during periods of critical exposure has the potential to prevent AHR or symptoms from increasing in severity, although there are no reported studies of this approach. For people who spend a considerable amount of time at home, such as infants and the elderly, air-conditioning systems or indoor air cleaners with a high efficiency particulate (HEPA)-filter have the potential to reduce exposure to allergens which blow indoors but this also has not been tested, although filters which reduce airborne particulate matter were shown to be effective in reducing symptoms of rhinitis and asthma in a clinical trial in the USA [176].

Environmental tobacco smoke

Avoidance of early exposure to ETS will prevent the subsequent outcome of an increased risk of a serious respiratory infection in infancy. The ban on smoking in public places has generally reduced exposure to ETS in the community but ETS in the home, which is the predominant place of exposure for many young children, has not been fully addressed. Moreover, smoking rates in young adult females have not changed substantially over the last decade and have not mirrored declining rates of smoking by males, which suggests that educational campaigns need to focus on young mothers or those planning to have children.

Dietary interventions

Fatty acids. Several clinical trials have investigated the effects of supplementation with fish oils on asthma and most show that the omega-3 fatty acids are incorporated into cell membranes and reduce the production of leukotrienes and cytokines, which are involved in inflammatory processes [177–181]. However, no clinical improvement in the severity of asthma has been demonstrated, perhaps because the trial periods were only 8–10 weeks and longer periods may be required before an expected anti-inflammatory effect in the airways is sufficient to reduce symptom severity. Although one study found that episodic asthma did not improve after 6 months of supplementation [180], another study of 9 months of supplementation found significant increases in FEV_1 [181].

Salt and antioxidant intake. The clinical benefits of altering salt intake are uncertain. In a small open study,

doubling of salt intake for 1 month resulted in a modest increase in AHR [182], but an open, randomized 2 week trial was unable to demonstrate an effect of altered salt intake on the severity of asthma as assessed by peak expiratory flow rate or beta-agonist use, even though good compliance was confirmed by measurements of sodium excretion [183]. However, the patients were mild asthmatics and self-monitored peak expiratory flow rates are not a sensitive indicator of AHR or symptom severity. Larger studies with a stronger design and longer periods of salt intake have been more encouraging. A study of asthmatic males, who were established on a low sodium diet before being randomized to receive a slow sodium or placebo intake, found a relationship between salt intake and the clinical indicators of AHR, bronchodilator use, peak flow readings and AHR [184]. Also, a randomized, double-blind, cross-over trial in the UK found more severe AHR in males supplemented with sodium, but not in females [185].

Economic implications

Prevention of asthma has several economic implications. Ideally, environmental interventions will reduce use of medical services and asthma medications and will provide a cost-effective method for improving quality of life both for asthmatics and potential asthmatics. However, the costs of different interventions will vary considerably and some groups of asthmatics may require both intervention and optimal use of asthma medications to improve their condition. Interventions which address diet and exposure to ETS will be less expensive than avoidance of indoor allergens, which requires significant changes to the indoor environment and/or a major commitment to maintain.

It is difficult to judge the economic effectiveness of preventive strategies because there are few data relating to the costs and economic efficiency of current asthma management and there has been no assessment of the costs of prevention. We estimated that the total cost of asthma in New South Wales was $209 million in 1989, of which $142 million was spent on direct health care costs [15]. In a more recent study, the mean annual cost to the family of an asthmatic child outside of government Medicare costs was $212, which rose to $884 if the child had asthma which was severe enough to require admission to a hospital [17]. It seems reasonable to assume that interventions which are based on our current knowledge of risk factors could achieve a 50% reduction in the prevalence of asthma, and that this would be accompanied by a similar reduction in the costs of treatment and care.

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