

Guidance on the management of familial hypercholesterolaemia in Hong Kong: an expert panel consensus viewpoint

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ABSTRACT

In 2016, meetings of groups of physicians and paediatricians with a special interest in lipid disorders and familial hypercholesterolaemia were held to discuss several domains of management of familial hypercholesterolaemia in adults and children in Hong Kong. After reviewing the evidence and guidelines for the diagnosis, screening, and management of familial hypercholesterolaemia, consensus was reached on the following aspects: clinical features, diagnostic criteria, screening in adults, screening in children, management in relation to target plasma low-density lipoprotein cholesterol levels, detection of atherosclerosis, lifestyle and behaviour modification, and pharmacotherapy.

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Introduction

Familial hypercholesterolaemia (FH), an autosomal codominant inherited disorder of lipoprotein metabolism, is characterised by markedly elevated plasma low-density lipoprotein cholesterol (LDL-C) levels and increased risk of premature atherosclerotic cardiovascular disease (CVD), particularly coronary heart disease (CHD).¹⁻³ Familial hypercholesterolaemia is generally caused by mutations in the genes related to the LDL receptor (LDLR) pathway (eg, loss-of-function mutations in the *LDLR* or apolipoprotein B (apoB) gene (*APOB*) or gain-of-function mutations in the proprotein convertase subtilisin-kexin type 9 [*PCSK9*] gene) resulting in marked elevation of plasma LDL-C levels from birth.

Heterozygous (He) FH is one of the most common human genetic disorders. It affects 1 in 200

to 300 individuals in unselected general populations. The prevalence of homozygous (Ho) FH has been estimated at 1 in 1 000 000, based on a frequency of 1 in 500 for HeFH, but it is likely to be more common.^{1,4} Familial hypercholesterolaemia is associated with considerable morbidity and mortality because of CHD. If left untreated, men and women with HeFH typically develop CHD before the ages of 55 and 60 years, respectively; 50% of men and 15% of women die before these ages, whereas those with HoFH may develop CHD very early in life.¹

Early identification and optimal treatment of patients with FH are crucial for the prevention of atherosclerosis progression and coronary complications. Although FH is a very common genetic disorder, it remains largely undetected and undertreated.¹ Recent guidelines and consensus statements in Europe and in some Asia-

Pacific countries highlight the need for the early identification of FH to improve the awareness and management of this condition.^{1,4-7}

As in most other countries,⁸ there are significant gaps in the awareness and management of FH among physicians and the general public in Hong Kong. There is no clear management guideline or consensus statement for FH in Hong Kong. On 22 February 2016, 12 experts on lipid disorders in Hong Kong convened for the local Advisory Board Meeting on the Management of Familial Hypercholesterolaemia in Hong Kong; and on 14 December 2016, 10 experts convened for a second meeting specifically regarding the management of paediatric patients with FH in Hong Kong. The principal objectives were to discuss the evidence for diagnosis, screening, and management of FH, in order to develop a consensus statement relevant to Hong Kong. The panel reviewed both international guidelines and those for individual Asia-Pacific countries, then developed a consensus treatment matrix/guide regarding the diagnosis, screening, and management of FH. The expert panel discussed each issue until they had attained a unanimous consensus.

Clinical features of familial hypercholesterolaemia in Hong Kong

Plasma LDL-C levels in the Hong Kong general population are comparable to those of some Western countries.^{9,10} According to the experts' clinical experience, patients with FH in Hong Kong, especially older adults, tend to exhibit CVD later in life (approximately 70 years of age), compared with patients in Western countries. Many older patients with FH in Hong Kong are free of cardiovascular events in their 70s or 80s; this may be related to their previously healthy lifestyle (eg, substantial physical activity with a healthy diet). However, young patients with FH tend to develop CVD at an earlier age than older patients within the same families. More recently, cardiovascular events have been observed in patients who are in their mid-20s. The increased risk in these young patients is likely due to lifestyle changes in the younger generations. Stroke remains uncommon in patients with FH in Hong Kong, presumably because elevated LDL-C levels are not a strong risk factor for cerebrovascular diseases.¹¹

Clinical characteristics have been reported for 252 Hong Kong Chinese patients from 87 pedigrees who were clinically diagnosed with FH during 1990-2000 (mean [standard deviation] age 37 [17] years, including 43 patients aged <18 years).¹⁰ The mean plasma LDL-C level was 7.2 (1.5) mmol/L.¹⁰ Tendon xanthomata was present in 40.6% of males and 54.8% of females. The prevalence of known CHD was relatively low: 9.9% in males and 8.5% in females.¹⁰

香港家族性高膽固醇血症管理指引：專家組共識

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兩組包括治療血脂異常及家族性高膽固醇血症的專家和兒科專科醫生在2016年舉行兩次會議，討論香港患有家族性高膽固醇血症的成年人及兒童的多方面管理。在回顧家族性高膽固醇血症的診斷、篩查和管理的臨床數據及指引後，他們就家族性高膽固醇血症的管理在下列方面達成共識，包括臨床特徵、診斷標準、成人篩查、兒童篩查、管理血液低密度脂蛋白膽固醇的目標，動脈粥樣硬化的檢測、生活方式和行為改變，以及藥物治療。

Diagnostic criteria of familial hypercholesterolaemia

Although FH is generally considered to be a monogenic condition, it is typically diagnosed on the basis of clinical features and family history, rather than a genetic test. There are several sets of clinical criteria for diagnosing FH (Table 1^{7,12-15}), including the Simon Broome Register diagnostic criteria,¹² the Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria,¹³ and the Dutch Lipid Clinic Network Diagnostic Criteria¹⁴ (DLCNC; online supplementary Appendix); however, none of these are universally accepted as the best approach. More recently, Japanese experts have developed specific criteria for the diagnosis of FH in Japan.⁷

The DLCNC¹⁴ use a point system to assess the following characteristics: family history of FH, history of premature CVD, physical examination of tendinous xanthomata and premature arcus cornealis, LDL-C levels, and DNA analysis. There is a point score for each item; a total point score of >8 is regarded as definite FH, 6 to 8 as probable FH, 3 to 5 as possible FH, and <3 as unlikely FH. Similar to the DLCNC, the Simon Broome criteria¹² use family history of FH, physical signs (excluding arcus cornealis), LDL-C levels, and genetic tests to predict the probability of the diagnosis of FH. The MEDPED criteria¹³ rely on plasma total cholesterol and LDL-C levels in the probands and their family members, without consideration of other phenotypes. The MEDPED criteria have a higher sensitivity, but lower specificity than the Dutch and Simon Broome diagnostic criteria. The Japanese FH criteria,¹⁶ which are similar to the Simon Broome criteria, use a population-specific LDL-C level >4.7 mmol/L for adults and >3.6 mmol/L for children as a criterion for the diagnosis of FH.

The Dutch criteria were developed from patients who had been genotyped; thus, these comprise the only set of criteria validated by genetic tests. The panel agreed to apply the Dutch criteria for

TABLE I. Comparison of diagnostic criteria for familial hypercholesterolaemia^{7,12-15}

Criteria set	DLCNC ¹⁴	Simon Broome Register diagnostic criteria ¹²	MEDPED criteria ¹³	Japanese FH criteria ⁷
Family history of premature CVD or elevated cholesterol	✓	✓	✓	✓
History of premature CVD	✓	✗	✗	✗
Physical signs and symptoms (eg, tendon xanthoma)	✓	✓	✗	✓
LDL-C cut-off level (mmol/L)	<ul style="list-style-type: none"> • ≥8.5 mmol/L: 8 points • 6.5-8.4 mmol/L: 5 points • 5.0-6.4 mmol/L: 3 points • 4.0-4.9 mmol/L: 1 point 	<ul style="list-style-type: none"> • Adult: >4.9 • Children >4.0 	<ul style="list-style-type: none"> • Specific levels based on individual's age and a family history of FH 	<ul style="list-style-type: none"> • For HeFH: Adult: >4.7 • Children: >3.6 • For HoFH: Total cholesterol: >15.5 mmol/L
DNA analysis	✓ (optional)	✓ (optional)	✗	✗
Possible diagnosis	<ul style="list-style-type: none"> • Definite FH • Probable FH • Possible FH • Unlikely FH 	<ul style="list-style-type: none"> • Definite FH • Possible FH 	<ul style="list-style-type: none"> • With FH 	<ul style="list-style-type: none"> • With FH
Pros	<ul style="list-style-type: none"> • Each criterion is weighted • Higher specificity than MEDPED 	<ul style="list-style-type: none"> • Higher specificity than MEDPED criteria 	<ul style="list-style-type: none"> • Higher sensitivity than DLCNC 	<ul style="list-style-type: none"> • High specificity and sensitivity in Japanese population
Cons	<ul style="list-style-type: none"> • Not applicable to children • Lower sensitivity than MEDPED criteria 	<ul style="list-style-type: none"> • Lower sensitivity than MEDPED criteria 	<ul style="list-style-type: none"> • Without regard to physical symptoms and a history of premature CVD • Lower specificity than DLCNC and Simon Broome diagnostic criteria 	

Abbreviations: CVD = cardiovascular disease; DLCNC = Dutch Lipid Clinic Network Criteria; FH = familial hypercholesterolaemia; HeFH = heterozygous familial hypercholesterolaemia; HoFH = homozygous familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; MEDPED = Make Early Diagnosis to Prevent Early Deaths

the diagnosis of FH adults in Hong Kong; however, because of lower reported LDL-C levels in local patients with FH, the panel recommended a lower threshold for LDL-C levels indicative of definite FH, probable FH, possible FH, and unlikely FH.¹⁰ Secondary causes of increased LDL-C levels, such as hypothyroidism and nephrotic syndrome, should be excluded before considering a diagnosis of FH.

Screening for familial hypercholesterolaemia in adults in Hong Kong

Universal screening for FH in adults is not practicable in Hong Kong or in most other countries. General screening for FH as primary prevention in Hong Kong can be challenging, as it is difficult to convince asymptomatic patients to participate in the screening programme. A regular body check, including measurement of the plasma lipid profile, is becoming more popular in Hong Kong. The panel recommended that greater attention should be given to the cholesterol profile as a routine body check item, together with documentation of family history of FH and premature CHD; this approach may increase the likelihood of identifying potential index FH cases. The risk of cardiovascular events

in patients with FH largely depends on the plasma LDL-C level; however, other risk factors, such as smoking, hypertension, diabetes, and elevated levels of lipoprotein(a) [Lp(a)], are also important. Targeted LDL-C screening in high-risk patients, especially younger patients with premature CHD, is encouraged.

The panel recommended that adults with a plasma LDL-C level >5 mmol/L should be regarded as potential probands. For patients at high risk of FH, such as patients with a family history of FH or premature CHD, the LDL-C level threshold could be 4.5 mmol/L. Tendon xanthomata, arcus cornealis, and tuberous xanthoma or xanthelasma are typically observed in patients with FH who exhibit very high LDL-C levels. Xanthelasma and arcus cornealis are not specific clinical signs for FH. Tendon xanthomas are more specific for FH and occur in patients with markedly elevated LDL-C levels (typically >7.0 mmol/L); these are rarely present before adulthood in patients with HeFH. They can also occur in patients with sitosterolaemia and cerebrotendinous xanthomatosis.

Cascade screening for relatives of patients with FH is recommended in both the private and public sectors. Although this may be challenging in the private sector due to financial constraints, cascade

screening is the most cost-effective approach for the identification of new patients with FH; moreover, it is recommended by international and national bodies, such as the European Atherosclerosis Society and the American Heart Association.^{1,5} The relatives of patients with FH can be screened with a combination of plasma lipid profiles and genetic testing. If the causative mutation is unknown or genetic testing is unavailable, screening can be performed by using plasma lipid profiles alone. Currently, a potential patient with FH must wait several months for counselling and genetic testing in the public sector (ie, the Hong Kong Department of Health Clinical Genetic Service) and the cost of genetic testing may not be covered by the public health care system.

Genetic testing may not always be necessary or cost-effective. Patients with high LDL-C levels typically must be treated, regardless of the genetic test results; notably, these test results may not substantially alter treatment strategies. Although there may not be great advantages to genetic testing, there are potential benefits in genotyping.¹⁷ For similar LDL-C levels, the risk of cardiovascular events is greater in patients with FH than in those without, due to their lifelong exposure to high LDL-C levels since birth. Treatment may not be necessary in patients with FH who have mildly elevated LDL-C levels. In contrast, long-term follow-up is necessary in patients with FH who have similar LDL-C levels. With the increasing affordability of genetic testing, the resulting genetic information will help improve the precision of diagnosis and management of FH.

Screening for familial hypercholesterolaemia in children in Hong Kong

Universal screening of plasma cholesterol levels in children has been proposed in some Western countries, including Australia¹⁸ and the US.^{19,20} Early diagnosis can lead to effective treatment with lifestyle modification and pharmacotherapy, as appropriate. By reducing the lifetime exposure to LDL-C from an early age, these patients experience substantial benefits in terms of CVD prevention. Thus, universal cholesterol screening in children is more cost-effective than identical screening in younger or older adults. Although it is expensive, universal cholesterol screening in childhood may offer the best and most effective strategy for diagnosing FH.¹⁸ The paediatric panel agreed that universal screening should target all citizens below 20 years of age, ideally before puberty; moreover, it should identify potential cases of FH based on age- and gender-specific plasma LDL-C levels.

Cascade screening is highly recommended in children with elevated LDL-C levels and in children with relatives who exhibit FH phenotypes. Children

with a relevant family history and an LDL-C level >3.6 mmol/L are likely to have FH. In a local survey of Chinese adolescents in Hong Kong (median [interquartile range] age, 16 [14-17] years), the mean (standard deviation) LDL-C level was 2.15 (0.60) mmol/L in boys and 2.24 (0.61) mmol/L in girls; thus, the 95th percentile would be approximately 3.4 mmol/L.²¹ In children with a plasma LDL-C level >4.9 mmol/L and/or physical signs (eg, xanthomata), FH is likely; these children should be screened at any age, as soon as they are identified. Because FH and sitosterolaemia share several clinical characteristics, sitosterolaemia should also be considered in these patients, especially if both parents appear to exhibit normal lipid levels. Sitosterolaemia can be identified by measuring the plasma levels of plant sterols; the genetic defect can be detected by sequencing the genes for the ABCG5 and ABCG8 transporters.²² After consideration of international recommendations and the increasingly early age of acquisition of other risk factors, including obesity and diabetes, in our local population, the paediatric panel suggested a screening age of 5 to 10 years to identify FH; moreover, the panel suggested that a lower threshold for LDL-C levels should be used in children, relative to that used in adults. The paediatric panel also agreed that genetic testing, if available, should be provided for all children who are suspected to have FH, after counselling. Genetic testing would be particularly useful in children whose LDL-C levels are not sufficiently high to make a definite diagnosis of FH when a mutation has been detected in an affected parent or sibling. Genetic counselling should be provided to the family before undergoing genetic testing to ensure a clear understanding of the implications of such tests.

Despite these recommendations, the panel emphasised that additional surveys are required regarding the distribution of plasma cholesterol levels among local children, in order to improve the screening strategy for FH in children.

Management of familial hypercholesterolaemia

Target plasma low-density lipoprotein cholesterol levels

The prognosis of FH largely depends on the plasma LDL-C levels; these should be maintained as low as possible. The panel suggested that, for primary prevention of CHD, the target LDL-C level for Hong Kong Chinese patients with FH should be <2.5 mmol/L. The panel agreed that patients with established atherosclerotic CVD or other cardiovascular risk factors, such as diabetes, elevated Lp(a) level ≥ 50 mg/dL, pretreatment LDL-C level ≥ 6.72 mmol/L, family history of premature CHD, or advanced age, should be considered as very high

risk. For very-high-risk patients, the target LDL-C level should be <1.8 mmol/L; for paediatric patients (>10 years of age) with FH, the panel recommended that the target LDL-C level should be <3.4 mmol/L.

Detection of atherosclerosis

The detection of atherosclerosis should begin by taking a complete medical history and performing a thorough physical examination. If the patient is suspected to have atherosclerotic CVD, it may be appropriate to refer them to a cardiologist or other appropriate specialist for further investigation. Computed tomographic coronary angiography is a useful and non-invasive tool to detect coronary atherosclerosis and determine CVD risk. Stress echocardiography can be used to assess myocardial functional capacity and the possibility of silent ischaemia. Carotid ultrasound imaging is non-invasive and can identify early-stage atherosclerosis; it can be used to assess carotid artery disease, predict the risk of stroke, and determine the requirement for intensive treatment in patients with FH. The ankle-brachial index is a useful diagnostic test for early peripheral arterial disease and has been shown to predict CVD and all-cause death in Chinese populations.^{23,24} Pulse wave velocity is a non-invasive measure of arterial stiffness which also correlates with cardiovascular events, such as the development of CHD.

Lifestyle and behaviour modification

All patients with a clinical diagnosis of FH should be counselled on lifestyle modification, particularly healthy eating, regular exercise and physical activity, weight control, and cessation of smoking.

Pharmacotherapy

First-line treatment for hypercholesterolaemia for reducing the risk of CHD involves the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or statins, which significantly reduce the risk of CVD and progression of atherosclerosis in FH. In a long-term cohort study involving more than 2000 patients with FH without prevalent CHD in the Netherlands, patients treated with statins showed a 76% risk reduction (hazard ratio=0.24; 95% confidence interval=0.18-0.30; $P<0.001$) for CHD compared with untreated patients.²⁵ In patients with HoFH, statin-treated patients showed a 66% reduction in all-cause mortality and 51% reduction in major cardiovascular events compared with statin-naïve patients; however, the mean reduction in LDL-C level was only 26.4% with lipid-lowering therapy.²⁶

A recent Mendelian randomisation analysis revealed that prolonged exposure to lower LDL-C levels, beginning early in life, reduced the risk of CHD

by three-fold, when compared with the risk reduction achieved by lowering LDL-C level with a statin started later in life.²⁷ The European Atherosclerosis Society Consensus Panel recommended early detection (from age 5 years, or earlier if HoFH is suspected) in children; the panel suggested lifestyle modification and statin therapy for the treatment of children with FH, as early as age 8 to 10 years.⁶

Typically, adult patients with FH should be treated with high-intensity statin therapy. Female patients should be advised that statins are contraindicated during pregnancy and should be avoided during lactation.⁵ If the target LDL-C level cannot be achieved with statin monotherapy, a combination therapy with concurrent ezetimibe and/or a bile-acid sequestrant or niacin can be considered. Generally, Lp(a) levels are increased in patients with FH,²⁸ and are considered an independent predictor of CHD in FH after adjustment for other modifiable risk factors.^{1,29,30} It is desirable to measure the Lp(a) level if the assay is available. Niacin can reduce plasma Lp(a) levels by 30% to 40%; notably, the LDL-C level lowering-effect of niacin is largely dependent on baseline LDL-C levels.^{31,32} Therefore, if available, niacin may be used in patients with FH who do not reach their target LDL-C levels with statin therapy. Lipoprotein apheresis will also reduce Lp(a) level, but is not readily available in the public hospitals in Hong Kong; however, plasmapheresis is currently used.

In Hong Kong, statins are the main therapy for paediatric patients with FH. All available statins are approved for use in patients with HeFH aged ≥ 10 years (Table 2³³). However, in exceptional circumstances, such as when there is a family history of premature CHD, statins are used before age 10 years, as recommended by the guidelines from the United Kingdom National Institute for Health and Care Excellence.³⁴ A 2017 Cochrane review analysed nine randomised controlled trials comparing the efficacy and safety of statins versus placebo in 1177 children with FH aged 6 to 18 years; the authors concluded that statins seem to be safe in the short term, but long-term safety remains unknown.³⁵

Patients are initially treated with the lowest doses, which can be increased as necessary. Some patients are prescribed bile acid sequestrants (eg, colestyramine) as early as age 1 year, and ezetimibe at age ≥ 10 years (Table 2³³). Plasmapheresis is reserved for patients with severe disease uncontrolled by conventional therapy. It should be emphasised that lifestyle interventions should be the first-line treatment for paediatric patients with FH; they should not be disregarded, even if pharmacotherapy is used.

Emerging therapies

Monoclonal antibodies to PCSK9 have emerged as

TABLE 2. Oral lipid-lowering drugs approved for use in children or adolescents in Hong Kong³³

Drug	Indicated age for children or adolescents	Dosage
Atorvastatin	HeFH, 10-17 years	Initial: 10 mg once daily Max: 20 mg once daily Adjustment should be made at intervals \geq 4 weeks
Ezetimibe	\geq 10 Years	10 mg once daily
Fluvastatin	HeFH, \geq 9 years	Initial: 20 mg. May be adjusted at 6-week intervals Max: 40 mg twice daily/80 mg once daily
Rosuvastatin	HeFH, 10-17 years HoFH	Initial: 5-20 mg once daily Max: 20 mg once daily Initial: 20 mg once daily
Simvastatin	HeFH, 10-17 years	Initial: 10 mg once daily
Pravastatin	HeFH • 8-13 Years • 14-18 Years	Max: 40 mg once daily • 10-20 mg once daily • 10-40 mg once daily
Colestyramine	Hyperlipidaemia, 6-12 years	240 mg/kg daily in 2-3 divided doses or calculated as percentage of the adult (70 kg) dose Max: 8 g once daily

Abbreviations: HeFH = heterozygous familial hypercholesterolaemia; HoFH = homozygous familial hypercholesterolaemia

the most promising treatment option for patients with FH. This class of agents, given by subcutaneous injection once or twice monthly, reduced LDL-C levels by 50% to 70% in patients with HeFH who were treated with statins with or without ezetimibe,^{36,37} as well as in patients with primary hypercholesterolaemia with or without statin therapy.^{38,39} Two PCSK9 inhibitors, alirocumab (previously known as REGN727 and SAR236553, Sanofi and Regeneron Pharmaceuticals, Inc) and evolocumab (AMG-145, Amgen) were approved by the US Food and Drug Administration (FDA) and European Medicines Agency in 2015 for their proven efficacy in reducing LDL-C levels in patients at risk for CVD; these drugs are available in Hong Kong. By using this group of drugs, very low LDL-C levels (eg, <1.0 mmol/L) can be achieved in patients with HeFH.

Mipomersen is an apoB antisense oligonucleotide which inhibits the biosynthesis of apoB, thus reducing hepatic very low-density lipoprotein cholesterol (VLDL-C) production and secretion.⁴⁰ In clinical trials, subcutaneous injection of mipomersen reduced plasma LDL-C levels by 25% and 28% in patients with HoFH⁴¹ and HeFH,⁴² respectively. The major side-effects of mipomersen include frequent injection site reactions, short-lived fatigue and myalgia, hepatic steatosis, and elevations in plasma aminotransferases. These hepatic changes typically resolve upon drug discontinuation. Mipomersen is not available in Hong Kong.

Lomitapide is an orally available microsomal triglyceride transfer protein inhibitor which decreases the hepatic production and secretion of VLDL-C. Lomitapide has been approved for the treatment of

HoFH in the US and Europe as an add-on therapy. In a multi-centre study of patients with HoFH, lomitapide reduced LDL-C levels by 50%, 44%, and 38% at 26, 56, and 78 weeks, respectively.⁴³ However, lomitapide may increase plasma aminotransferases and intrahepatic fat content. Lomitapide is not available in Hong Kong. Both mipomersen and lomitapide work via pathways independent of the LDLR and are effective in patients with HoFH who exhibit null mutations. These two drugs have been approved by the FDA for use in patients with HoFH.

Conclusion

Patients with FH remain underdiagnosed and undertreated in Hong Kong. Increased awareness, early identification, and optimal treatment are essential to reduce the risk of premature CHD, thereby restoring decades of healthy, normal life in patients with FH. Developing a model of care for FH in Hong Kong will help to bridge the gap in prevention of CVD and improve outcomes in patients with FH. Action is needed to collect more population-based data to further guide recommendations and the development of models of care for the management of FH. While these data are gathered, this consensus statement aims to serve as a guide to inform clinical practice and future research.

Supplementary information

Online supplementary information (Appendix) is available for this article at www.hkmj.org.

Author contributions

All authors have made substantial contributions to the expert

panel consensus viewpoint and provided critical revision for important intellectual content. B Tomlinson is responsible for drafting of the article.

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Declaration

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