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Review Article

An update of the Malaysian Clinical Guidance on the management of glucocorticoid-induced osteoporosis, 2015

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Abstract

Objectives: This Clinical Guidance is aimed to help practitioners assess, diagnose and manage their patients with glucocorticoid-induced osteoporosis (GIO), using the best available evidence.
Methods: A literature search using PubMed (MEDLINE) and The Cochrane Library identified all relevant articles on GIO and its assessment, diagnosis and treatment, from 2011, to update from the 2012 edition. The studies were assessed and the level of evidence assigned. For each statement, studies with the highest level of evidence were used to frame the recommendation.
Results: Consider treatment early in all patients on glucocorticoids (GC) as fracture risk increases within 3–6 months of starting GC. The decision to start treatment for GIO depends on the presence of prior fracture, category of risk (as calculated using Fracture Risk Assessment Tool), daily dose and duration of GC treatment, age, and menopausal status. General measures include adequate calcium and vitamin D intake and reducing the dose of GC to the minimum required to achieve disease control. In patients on GC with osteoporotic fractures or confirmed osteoporosis on dual-energy X-ray absorptiometry, bisphosphonates are the first-line treatment. Treatment should be continued as long as patients remain on GC. Algorithms for the management of GIO in both pre- and post-menopausal women and men have been updated.
Conclusions: In post-menopausal women and men above 50 years, bisphosphonates remain the mainstay of treatment in GIO. In pre-menopausal women and men below 50 years, bisphosphonates are recommended for those with a prevalent fracture or at very high risk only.

Keywords: Glucocorticoids; Corticosteroids; Osteoporosis; Guidelines; Malaysia

1. Introduction

Osteoporosis and fractures are major complications of glucocorticoid (GC) therapy. From epidemiological studies, a significant number of the population are at risk; about 2% of the elderly population use oral GCs in the United Kingdom [1] and in the United States, between 1999 and 2008, 1.2% of the population (in the National Health and Nutrition Examination Survey (NHANES) database) were on GC, with 28.8% taking GC for more than 5 years [2]. Many of the inflammatory conditions that may require GC usage are already associated with an increased risk of fracture [3]. The addition of GC

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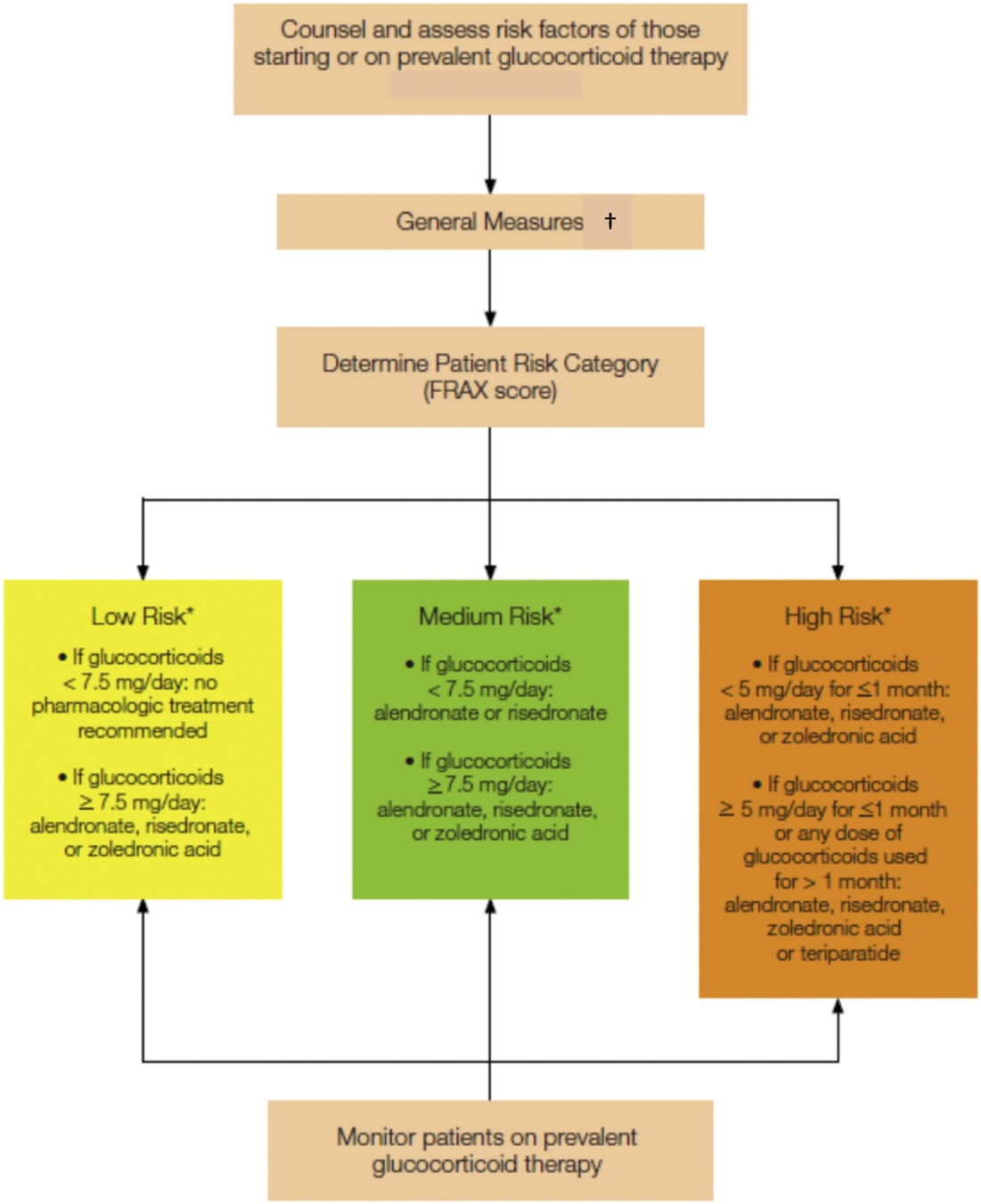


* For low and medium-risk patients, recommendations are for an anticipated or prevalent duration of > 3 months of glucocorticoid treatment

† See section 3.2.1

***FRAX Score**
Low Risk (<10% 10-year risk of fracture)
Medium Risk (10-20% 10-year risk of fracture)
High Risk (>20% 10-year risk of fracture)

Fig. 1. Approach to postmenopausal women and men age >50 years initiating or receiving glucocorticoid therapy [17].

therapy increases risk of sustaining fractures over and above that of the underlying disorder [4] (Level III).

Bone loss occurs most rapidly in the first 6–12 months of oral GC therapy [5], with an increase in fracture risk that appears within 3–6 months of starting GC [5,6] (Level Ia). Thus, it is important to consider bone protective strategies at the onset of GC therapy. Furthermore, at similar levels of bone mineral density (BMD), postmenopausal women taking GCs, as compared with nonusers of GCs, had considerably higher risks of fracture [7] (Level Ib).

Prednisolone $\geq$ 5 mg daily or its equivalent, for more than 3 months is associated with osteoporosis and an increased risk of fractures [8], but doses of prednisolone $\leq$ 2.5 mg daily have also been associated with an increased relative risk of vertebral fracture [6] (Level III).

Standard doses of inhaled or topical GC use have not been shown to adversely affect BMD. However, the cumulative inhaled GC dose in asthmatics have been inversely associated with BMD [9] and inhaled high potency GC usage (greater than 1500 μg daily) have been associated with both vertebral [10] and hip fractures [11] (Level IIa).

2. Methods

The previous Clinical Practice Guidelines published in 2012 was used as the baseline. To update the document, a systematic review and literature search by the members of the Working Group, using PubMed (MEDLINE), identified all relevant articles on GIO and its assessment, diagnosis and treatment, from 1st January 2011 to 31st December 2015. The date 2011 rather than 2012 was chosen so that all studies published just before and after the last guidelines would be reviewed and none inadvertently overlooked. The search on PubMed using the keywords "glucocorticoid" and "osteoporosis" during the above time frame, limited by "Human" and "English", produced 527 articles. Of these, 158 were on osteoporosis in general unrelated to GIO, 131 were studies that did not have any relationship to GIO for example, studies using GC in various diseases, 38 were on childhood GIO/GC usage, and 69 were studies related to the molecular mechanism of action of GC; this left 131 studies that were further assessed for this paper. A search of the Cochrane Library website (www.cochrane.org) from 1st January 2011 to 10th October 2016, just before this manuscript was completed showed 1 new review "Bisphosphonates for treating osteoporosis caused by the use of steroids" published in 5 October 2016.

The studies were assessed by 2 of the Working Group members and those that were used in the Clinical Guidance were graded with the levels of evidence as used by the National Guideline Clearinghouse, Agency for Healthcare Research and Quality, U.S. Department of Health & Human Services, USA [12] (Appendix 1). For each statement, studies with the highest levels of evidence were used to frame the statements. The grade of recommendation was taken from the Scottish Intercollegiate Guidelines Network grading system [13] (Appendix 1).

3. Results and discussion

3.1. Assessing risk and diagnosis

The use of BMD measurement for the diagnosis of GIO is not crucial, but may be useful in the monitoring of therapy. BMD should be measured at the lumbar spine and hip by dual-energy X-ray absorptiometry (DXA), although the lumbar spine measurement may be artefactually elevated in the elderly due to degenerative changes [14]. As there are data showing that postmenopausal women taking GC have a higher fracture risk compared to those not taking GC at a similar BMD [7], a treatment threshold at a T-score of <-1.5 has been suggested [14,15]. Diagnostic thresholds in GIO have not been established for peripheral densitometry using either DXA or ultrasound, which therefore should not be used for assessment or monitoring [14].

The more recent GIO guidelines have used Fracture Risk Assessment Tool (FRAX) [16] to categorise patients into low, medium and high risk groups with respect to the 10-year risk of fracture, rather than relying on BMD measurement alone.

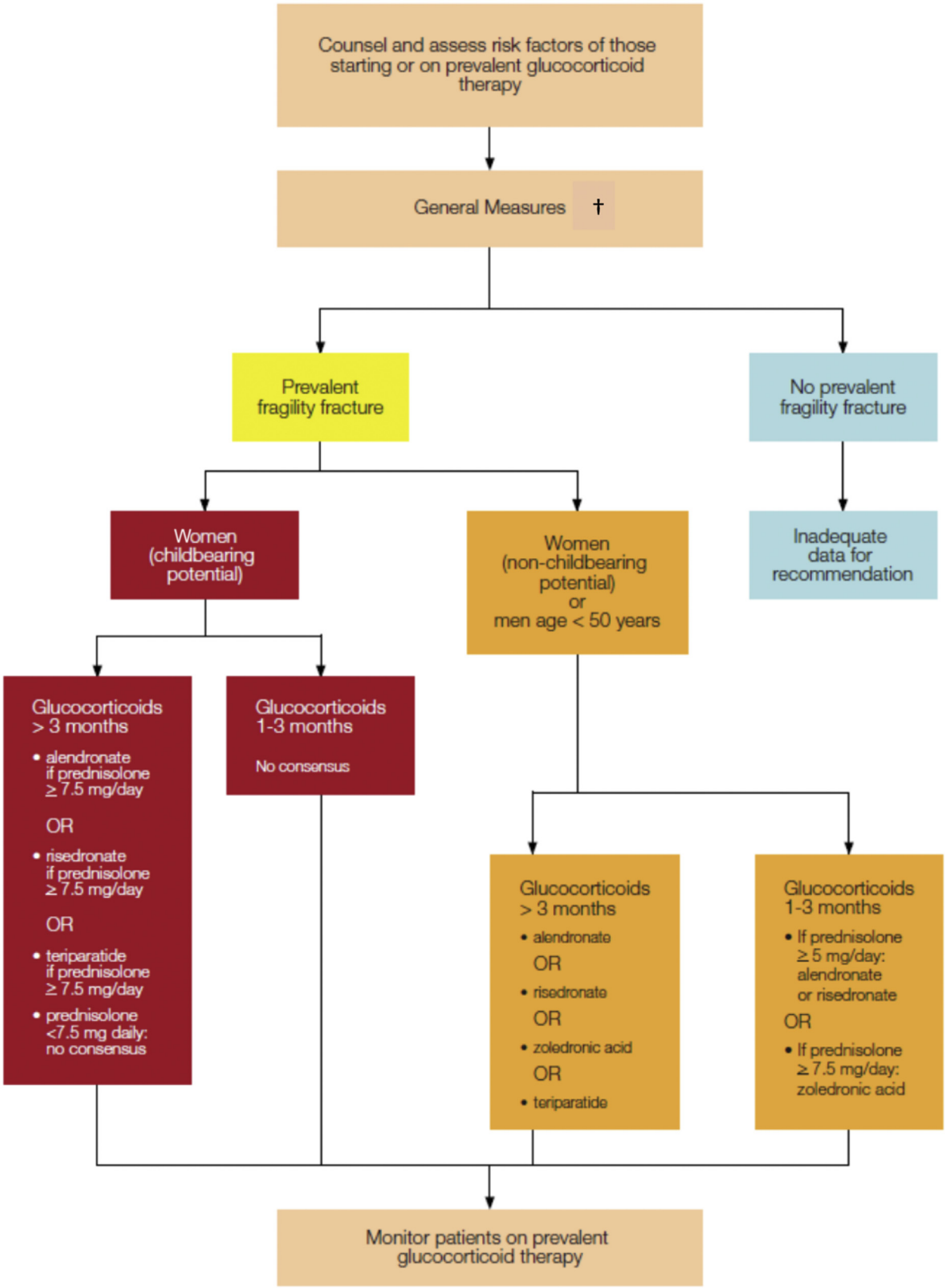
In postmenopausal women and men over 50 years old with low risk of fracture, treatment is recommended when prednisolone (or its equivalent) $\geq$ 7.5 mg daily is taken for more than 3 months. In medium risk patients, treatment is recommended at any dose of GC when taken for more than 3 months. In high risk patients, treatment is suggested for any dose of GC taken for any length of time [17] (see Fig. 1). In addition to the calculated FRAX risk estimates, Table 1 lists the clinical factors that may shift an individual to a greater risk category for GIO [17].

For premenopausal women of non-childbearing potential and men under 50 years old with a prevalent osteoporotic fracture, treatment is recommended if prednisolone $\geq$ 5 mg daily is given for >1 month. For premenopausal women of childbearing potential, treatment is recommended when prednisolone $\geq$ 7.5 mg daily is given for >3 months [17] (see Fig. 2).

There has been a recommendation that the FRAX risk estimates should be adjusted according to the daily dose of GC. For low-dose exposure (< 2.5 mg daily of prednisolone or equivalent), the probability of a major fracture is decreased by about 20% depending on age. For medium doses (2.5–7.5 mg daily), the unadjusted FRAX value can be used. For high doses

Table 1
Clinical factors that may shift an individual to a greater risk category for glucocorticoid-induced osteoporosis [17].

Low body mass index
Parental history of hip fracture
Current smoking
$\geq$ 3 alcoholic drinks per day
Higher daily glucocorticoid dose
Higher cumulative glucocorticoid usage
Intravenous pulse glucocorticoid usage
Declining central bone mineral density measurement that exceeds the least significant change



† See section 3.2.1

Fig. 2. Approach to premenopausal women and men age <50 years initiating or receiving glucocorticoid therapy [17].

Table 2
Grades of recommendation for preventive and therapeutic interventions in glucocorticoid-induced osteoporosis (GIO).

Drug	Primary Prevention	Secondary Prevention	Vertebral Fracture Reduction	References
Alendronate 10 mg od	A	A	A	[25,33]
Alendronate 70 mg/wk	A	A	ND	[34]
Alfacalcidol	A	A	ND	[35,36]
Calcitriol	A	ND	ND	[37]
Calcium and vitamin D	ND	A	ND	[38]
Denosumab[a]	ND	A	ND	[39,40]
Hormone Therapy (in females)	ND	A	ND	[41]
Ibandronate[a]	A	A	ND	[42]
Pamidronate[a]	A	A	ND	[43,44]
Raloxifene[a]	ND	A	ND	[45]
Risedronate	A	A	A	[26,46]
Teriparatide	ND	A	A	[24]
Testosterone (in males)	ND	A	ND	[47]
Zoledronate	A	A	ND	[23]

Primary Prevention: Given within 3–4 months of initiation of glucocorticoid therapy.
Secondary Prevention: Treatment following an osteoporotic fracture or use of glucocorticoid for longer than 3–4 months.
ND: No benefit demonstrated/no data.
[a] These agents have studies showing efficacy in GIO but they do not have an indication from regulatory authorities for the treatment of GIO.

(> 7.5 mg daily), probabilities can be revised upward by about 15% [18].

3.2. Treatment options

3.2.1. General measures

a) Prescribing the lowest effective dose of GC for the shortest period of time for good disease control [17].
b) The use of alternative route of administration [14] (e.g. inhaled GC in asthma)
c) Consider the use of GC-sparing agents
d) Modification of lifestyle - adequate calcium intake, adequate mobilisation, regular weight-bearing exercise, stopping smoking, avoiding excessive alcohol intake (<2 drinks per day) and prevention of falls [17]

(Grade C, Level IV)

3.2.2. Specific measures

In hypogonadal states, replacement therapy with sex steroids should be considered (Grade A, Level Ib).

All patients on GC should be supplemented with calcium and vitamin D (1000–1500 mg/day and 800 IU/day respectively) [19,20] (Grade A, Level Ia).

Drugs that have been shown to be effective in GIO are shown in Table 2. The management algorithm for the management of postmenopausal women and men over the age of 50 years on GC is shown in Fig. 1 and for premenopausal women and men under the age of 50 is shown in Fig. 2.

In patients on GC with osteoporotic fractures or confirmed osteoporosis on DXA, bisphosphonates are the first-line treatment (Grade A, Level Ib).

In a study comparing alendronate, vitamin D and calcitriol, alendronate increased lumbar spine BMD by 5.9% over 2 years, compared to 0.5% and 0.7% loss on vitamin D and calcitriol respectively. There was no difference at the femoral neck [21]. In a prevention study comparing alendronate and alfacalcidol over 18 months, patients on alendronate maintained or improved their lumbar spine and femoral neck BMD compared to BMD loss in the alfacalcidol group [22]. IV zoledronate produced a better gain in lumbar spine and femoral neck BMD compared to oral risedronate over 1 year [23]. Over 3 years, teriparatide led to a better gain in lumbar spine and femoral neck BMD and reduced the incidence of new vertebral fractures compared to alendronate [24]. Alendronate and risedronate also reduced vertebral fractures in patients on GC therapy [25,26]. Overall, the recent Cochrane review supports the use of bisphosphonates to reduce the risk of vertebral fractures and the prevention and treatment of GC-induced bone loss [27].

In women of child-bearing age who may wish to conceive after stopping active osteoporosis medication, drugs which have a fast off-set of effect on bone turnover markers, such as denosumab [28], ibandronate [29], risedronate [30] or teriparatide [31], may be considered. (Grade C, Level IV).

Treatment should be continued for as long as the patient is on GC. Expert consensus recommends that therapy may be withdrawn in a subject on GC if BMD is close to normal and the patient is no longer at increased risk of fracture or when GC are stopped [32] (Grade C, Level IV). Once GC therapy is stopped, fracture risks decreased towards baseline values over the following 1 year [6] (Level III).

In conclusion, we hope that this guidance document will provide practical and relevant help to health care practitioners when making clinical decisions on managing their patients with GIO. This article is not meant to be a comprehensive review of all aspects of GIO, neither is it prescriptive. The key messages are to think of bone protection measures in all patients on GC, and, in patients at high risk of osteoporosis, bisphosphonates are the mainstay of treatment.

Key points

- Patients should be prescribed the lowest dose of GC for the shortest period of time that will give good disease control.
- Patients with a prevalent osteoporotic fracture should receive active osteoporosis medication.
- Patients who are on GC doses equivalent to prednisolone >5 mg daily should be assessed with BMD measurement and/or FRAX to assess future fracture risk and treatment options.
- Active osteoporosis therapy should be continued for the duration of GC therapy.

Conflict of interest

All the authors of this guidance have declared no conflicts of interest. The development of this guidance was fully funded by the Malaysian Osteoporosis Society.

Appendix 1.

Levels of Evidence and Grades of Recommendation

Levels of Evidence [12]

Levels	Type of evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials (RCTs)
Ib	Evidence obtained from at least one RCT
IIa	Evidence obtained from at least one well designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies e.g. comparative studies, correlation studies, case-control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities, or both

Grades of Recommendation

Grades	Recommendation
A (evidence levels Ia and Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (evidence levels IIa, IIb and III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation
C (evidence level IV)	Required evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicated absence of directly applicable clinical studies of good quality

Modified from the Scottish Intercollegiate Guidelines Network (SIGN) [13]

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