

Clinical Review

Clinical Review identifies issues in the medical literature of interest to clinicians in Africa. Essential references are given at the end of each section

Dermatology Review

Cutaneous leishmaniasis in Africa: problems of increasing drug resistance and HIV co-infection

Epidemiology and aetiology

Cutaneous leishmaniasis (CL) is a tropical skin disease of major public health importance. It is endemic in more than 80 countries with an estimated prevalence of 12 million cases worldwide, which continues to rise with 1–1.5 million new infections per annum.¹ In Africa, CL is restricted to certain countries: mainly those on the coast of North Africa bordering the Mediterranean, particular foci are in the East African countries of the Sudan, Ethiopia, and Kenya, and in the West African countries of Senegal, Mali, and Niger, with smaller foci reported in other West African countries. A small focus has also been reported in South West Africa in Namibia.²

Humans acquire CL through the bite of an infected sandfly which transmits the *Leishmania* protozoa. There are numerous *Leishmania* species but in Africa *L. tropica*, *L. major*, and *L. aethiops* are the main ones that cause CL. Of the three, *L. aethiops* is the least common and restricted to East Africa, mainly Ethiopia and Kenya. *L. donovani* complex (*L. donovani* and *L. infantum*) is responsible for causing visceral leishmaniasis, a serious and potentially fatal infection which is highly endemic in the Sudan, but occasionally it produces skin lesions as well. New foci of CL are continuing to emerge because of changing habitats of sandflies due to deforestation, urbanisation, or civil conflict.¹

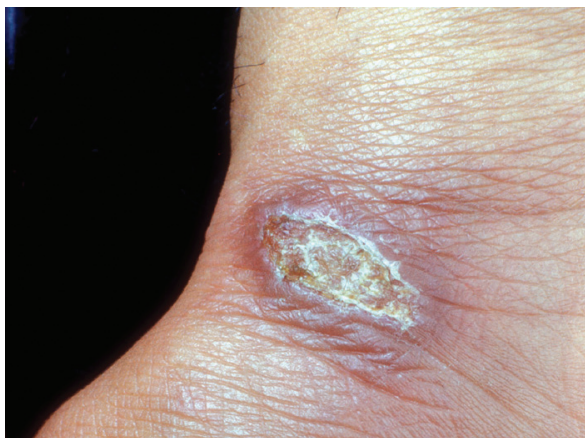


Figure 1 Ulcerative lesion of *L. major*

Clinical presentation

CL has a wide variety of clinical presentations. The incubation period from the bite of a sandfly to clinical disease can vary between a few weeks to several months. Usually exposed parts of the body such as the face or the limbs are affected. Initially there is a patch of non-specific erythema. This then develops into a papular lesion which can progress to a nodular lesion before ulcerating. An ulcerative lesion usually has an inflamed and thickened border (see Figure 1); however, *L. tropica* does not ulcerate and instead produces a thick warty looking lesion (see Figure 2). *L. aethiops* is a more serious infection because in addition to the common localised ulcerative lesion, it can also cause two rare types of CL: mucocutaneous leishmaniasis (MCL) and diffuse CL. Both are potentially severe diseases: MCL is associated with lesions affecting the mucosae of the nose and mouth which can cause destruction of cartilage and lead to breathing and swallowing complications; diffuse CL can produce numerous and chronic non-ulcerative nodular lesions which are widespread and mimic lepromatous leprosy. *L. tropica* and *L. major* have rarely been associated with MCL and diffuse CL, and when it occurs it may be as a consequence of immunosuppression such as with HIV co-infection. CL lesions are often secondarily infected with bacteria such as *Staphylococcus aureus* as well.³

Diagnosis

CL is diagnosed microscopically by the identification of *Leishmania* parasites or amastigotes within macrophages of sample tissue. Tissue samples can be obtained by simple aspiration, scrapings, slit incisions, or skin biopsy. The sampling site within lesions influences the sensitivity of parasitological diagnosis; for maximum sensitivity, samples should be taken from the active edge of skin lesions rather than from the centre or the base of an ulcer or lesion. The samples can be used for any or all of the following investigations: direct microscopy, histopathology, culture, and polymerase chain reaction (PCR). However, microscopy and culture can have low sensitivity, i.e. they can give false-negative results. Histopathology may also fail to demonstrate amastigotes, particularly if the skin lesion is chronic. The development of PCR technology allows



Figure 2 Warty lesion of *L. tropica*

rapid detection of *Leishmania*-specific DNA and is 100% specific and has high sensitivity. Unfortunately, this technology is not readily available, and in Africa its use has been limited to research studies. Only PCR and culture will determine the *Leishmania* species. Isoenzyme analysis of *Leishmania* culture requires technical expertise and is time-consuming, and facilities for this are also usually not available. Instead, clinicians rely on the clinical features to decide which is the most likely *Leishmania* species, e.g. *L major* produces ulcerative lesions which typically heal by 3–6 months, and *L tropica* produces warty lesions that take much longer to heal, the majority requiring up to 1 year. Clinicians also have some idea of which *Leishmania* species are endemic to their region as this has often been identified in previous published studies. In endemic areas patients with localised, uncomplicated CL may be treated with local therapies on the basis of a clinical diagnosis only, and this acceptable. Where systemic treatment might be required, microbiological confirmation of infection at the very least, by either direct microscopy or histopathology, should be sought because treatment may need to be given for prolonged periods of time and are often associated with toxic side-effects.

Treatment

Uncomplicated CL is usually self-limiting. Lesions resolve over months leaving a scar. Different *Leishmania* species have different self-resolution times, *L aethiopicum* and *L tropica* being characteristically much longer than *L major*. Treatment choice is determined mainly by disease severity: the size, number, location, and likely chronicity of lesions; the potential of the *Leishmania* species to disseminate; established mucocutaneous or diffuse disease; and the presence of co-morbidities and immunosuppressant states such as HIV co-infection. The goal of treatment is to accelerate healing, reduce complications, and prevent the risk of dissemination. However, the clinician may decide that treatment is unnecessary: for example *L major* usually has a short healing time and therefore if the lesion is beginning to heal, treatment is usually not given other than for any secondary bacterial infection if present. Similarly, a limited number of small lesions of CL whether they are caused by *L major* or *L tropica* can be left alone without treatment. Treatment is sometimes given to minimise scarring particularly in a visible area, such as the face. It is worth noting that children especially appear to heal well without significant scarring. However, active treatment is required if a patient is suspected of having *L aethiopicum* infection or is immunocompromised, as in both situations there is a risk of the infection spreading.

There are a wide variety of treatments for CL: topical, physical (thermotherapy and cryotherapy), intralesional, and systemic. Although a number of studies of the efficacies of these different treatments have been published, the majority of them are of poor quality as they do not always include placebo-controls, which are important in any disease that has a tendency for spontaneous resolution. They often fail to define clinical endpoints or follow-up periods and therefore it is difficult to make comparisons between them.⁴

Parenteral antimonials (sodium stibogluconate or meglumine antimoniate) have been the gold standard therapy. Intravenous or intramuscular injections are given for 20–28 days at 20 mg/kg/day. The drawbacks are that parenteral therapy is inconvenient and uncomfortable, and systemic antimonials are associated with significant adverse effects (cardiotoxic, hepatotoxic and nephrotoxic). In addition, there are also reports of increasing resistance to antimonials: in a recent study from Tigray, northern Ethiopia, 28% of patients with *L aethiopicum* CL have been found to be resistant to a standard 28-day course of meglumine antimoniate. A poor response to treatment was also identified in patients who had relapsed and were subsequently given prolonged antimonial therapy with 52% failing to achieve cure.⁵

Although systemic antimonials have been recommended as first-line therapy for CL by the World Health Organization because of their high efficacy,³ systemic treatment is not usually needed for the vast majority of cases of a single or few lesions of CL caused by *L major* or *L tropica*. Topical and physical therapies have the advantages that they are easy to administer, inexpensive, and not associated with systemic adverse effects. However, topical paromomycin is not readily available and its efficacy is very variable. Weekly intralesional injections of antimonials until cure can be very effective. However, the injections are painful, especially for children, and they require some degree of expertise by the clinician giving them. Cryotherapy (weekly treatment of two freeze/thaw cycles for 10–25 seconds until cure) has demonstrated up to a 70–80% efficacy rate when used to treat *L major* or *L tropica* and is probably the most widely available treatment. Thermotherapy (1–3 applications of radiofrequency waves at 50°C for 30 seconds), which applies local heat to CL lesions, has demonstrated 70% efficacy for the treatment of *L tropica*. However, these physical therapies are also associated with some discomfort and in darker skins they can produce disfiguring hypopigmentation although this usually improves after time. These local therapies can also be combined with each other, e.g. topical paromomycin may be combined with intralesional antimonials to produce higher efficacy rates.⁶

Given the limitations of all of these treatments there is a need for a readily available, inexpensive, well-tolerated and effective oral treatment for CL. For this reason, oral azoles have been trialled as they are known to have some anti-leishmanial properties. They appear to be effective for only *L major* infection, and there is good data to support the use of oral fluconazole 200 mg daily for 6 weeks, which has few adverse effects. Ketoconazole is not recommended because of low efficacy and risks of hepatotoxicity. Parenteral pentamidine and amphotericin, and oral miltefosine are other treatment options for CL. However, their use is limited by poor availability and high cost. In addition, pentamidine and amphotericin are associated with toxicity and miltefosine is teratogenic and therefore not suitable for women of child-bearing age.⁶ However, pentamidine has demonstrated high efficacy for antimonial-resistant CL in Ethiopia with a cure rate of 88% making it a useful

second-line agent,⁵ and miltefosine is one of the few drugs that are effective for diffuse CL.

Cutaneous leishmaniasis and HIV

Leishmaniasis is an emerging opportunistic infection in HIV-infected patients. It has been a significant problem with visceral leishmaniasis co-infection, and these patients respond poorly to treatment and often relapse. Anti-retroviral (ARV) therapy and secondary prophylaxis (i.e. continuing with long-term, low-dose anti-leishmanial drugs) may reduce relapse. A similar clinical picture is emerging with HIV co-infection with CL: these patients usually present with atypical and severe skin lesions which progress more rapidly and are at increased risk of disseminating to the mucosae and possibly viscerae. They respond poorly to conventional local therapy and require systemic therapy (often at high doses for long treatment periods) together with ARVs. Padovese and colleagues⁵ describe a small cohort of patients with CL and HIV co-infection (n=5) in northern Ethiopia who despite starting on ARVs relapsed, even after prolonged antimonial treatment. They were not subsequently treated with pentamidine because it was unavailable at the time. With increasing HIV prevalence in regions endemic for CL in Africa, physicians are likely to encounter difficulties in managing such challenging cases.

CL is a complex and diverse infection with a wide spectrum of treatment options. It can cause considerable disfigurement and usually afflicts those of the lowest socioeconomic strata of populations. Poor drug availability and costs associated with treatment pose considerable challenges and efforts need to continue in disease prevention and new affordable drug development. *Mahreen Ameen, Department of Dermatology, Royal Free Hampstead NHS Trust, London, UK*

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Public Health Review

A new vision for maternal health – can we prevent maternal mortality?

International development assistance for health (DAH) has seen dramatic increases over the past decade.¹ The major focus of the new energy and resources has been on programmes to control major diseases including HIV/AIDS, tuberculosis, and malaria. Now, three recent events mark an important shift in DAH.

First, earlier this year, the US Government's new Global Health Initiative (GHI) was announced with an aim 'to contribute to major improvements in health outcomes – with a particular focus on women, newborns and children – through transformational advances in access to, and the quality of, healthcare services in resource-poor settings.'¹ One major goal of GHI is to, 'save approximately 360 000 women's lives by reducing maternal mortality by 30% across assisted countries.'²

A few months later the second event occurred when Melinda Gates explained at the Women Deliver Conference in Washington that, 'tens of millions of women never get to experience that moment of beauty (when they give birth to a healthy baby). For these women, childbirth is filled not with joy, but with dread, pain, and sorrow. They know they might die during delivery. If they survive, they are terrified their baby might die.'³ She then announced a new \$1.5 billion direction for the Gates Foundation embracing maternal and child health (MCH). She confirmed that, 'Most maternal and newborn deaths can be prevented with existing, low-cost solutions.'⁴

The G8 Summit in Canada hosted the third event and became a venue for creating a wider international partnership for MCH. In its final communiqué, the G8 declared that, 'Although recent data suggests maternal mortality has been declining, hundreds of thousands of women still lose their lives every year, or suffer injury, from causes related to pregnancy and childbirth. Much of this could be prevented with better access to strengthened health systems, and sexual and reproductive healthcare and services, including voluntary family planning.'⁵

Gates,⁴ pointed out that low-cost solutions to maternal mortality are available and pointed to recent studies from researchers at the Institute for Health Metrics and Evaluation (<http://www.healthmetricsandevaluation.org/>) that provide compelling new evidence of global progress: 'the number of women dying from pregnancy-related causes has dropped by more than 35% in the past 30 years – from more than 500 000 annually in 1980 to about 343 000 in 2008.'⁶ Hogan and colleagues offered four key trends as explanations for the overall downward trend:

1. Reductions in total fertility rate – maternal mortality rate and total fertility rate are strongly correlated.
2. Increases in income per capita that offer increased access to better nutrition and health services.
3. Improvements in female education.
4. A slow but steady rise in the number of skilled birth attendants.

What are the other low-cost solutions to reducing maternal mortality and what exactly is the evidence that they work?

Amy Tsui and colleagues⁷ have just published a review on family planning which has been 'shown to significantly lower maternal mortality.' A simple explanation is that when a woman is not pregnant or plans to have a pregnancy at a safer time or interval, she is less at risk of dying from pregnancy and related complications. Tsui explains that, 'Although it is difficult to attribute change in the maternal mortality ratio to a

particular cause, evidence exists to show that meeting the need for family planning can reduce maternal mortality. An analysis of DHS data indicated a strong negative correlation between maternal mortality ratios and contraceptive prevalence rates.⁷ Other specific findings on the preventive aspects of family planning are given below:

- Without contraception, the number of maternal deaths would be 19% higher (Uganda).
- Fulfilling unmet contraceptive need can prevent an additional 150 000 maternal deaths annually.
- Fertility decline was responsible for a 30% reduction in maternal deaths (Bangladesh).
- Current use of contraception has resulted in 490 000 fewer maternal deaths compared with no contraceptive use (Uganda).
- Egypt's maternal mortality ratio was reduced 50% between 1992 and 2000, a development concurrent with increased uptake of family planning and other maternal health improvements.

Such studies provide an evidence base that Tsui and colleagues hope will influence policy makers to adopt more supportive and enabling policies toward family planning.

Dorothy Shaw⁸ observes that at least 13% of maternal mortality is caused by unsafe abortion, mostly in poor and marginalised women. She described an initiative launched by the International Federation of Gynecology and Obstetrics (FIGO) in 2007 to prevent unsafe abortion and its consequences. She also outlines four key interventions that ultimately prevent maternal mortality from unsafe abortion:

- Primary prevention: the promotion of contraception and sexuality education to reduce the incidence of unwanted pregnancies.
- Secondary prevention: the promotion of safe abortion practices to reduce the need to resort to unsafe abortion.
- Tertiary prevention: post-abortion care and the management of abortion complications.
- Prevention of the repetition of abortion in the same women, through the provision of contraception counselling and services immediately after the abortion.

A working group of 54 member societies of FIGO was formed and currently 43 are active in promoting the above interventions. Other articles in the July 2010 issue of *International Journal of Gynecology & Obstetrics*, where Shaw's article appears, describe planning by the working group members which include policy change, increasing the use of modern contraceptive methods, introducing or improving sex education, improving adolescent-friendly reproductive health services, making adequate abortion services available, within the full extent of the national laws, improving post-abortion care, including post-abortion contraception and facilitating child adoption services.⁹ We await reports of actual programme implementation and effects.

Anaemia in pregnancy is associated with increased maternal mortality.¹⁰ Two key risk factors were low socio-economic status and poor knowledge about anaemia in pregnancy. As noted from the article on trends in maternal mortality, poor economic status influences access

to a nutritious diet and is not immediately amenable to low-cost solutions, but the knowledge gap could be addressed through health education at antenatal clinics with an emphasis on low-cost food alternatives. Enhancing antenatal care attendance and provision of iron supplements are also important low-cost interventions.

Since India accounts for a large portion of the world's maternal mortality, Goldie and colleagues¹¹ investigated cost-effectiveness of alternative strategies to prevent the problem at different stages along a continuum, ranging from actions prior to pregnancy to interpartum and delivery periods. The researchers found that, 'Increasing family planning was the most effective individual intervention to reduce pregnancy-related mortality. If over the next 5 years the unmet need for spacing and limiting births was met, more than 150 000 maternal deaths would be prevented; more than US\$1 billion saved; and at least one of every two abortion-related deaths averted.' Further reductions in maternal mortality were found to require reliable access to intrapartum and



Low-cost interventions could mean the difference between life and death for these women



emergency obstetrical care (EmOC). Overall the 'principal findings are that early intensive efforts to improve family planning and provide safe abortion, accompanied by a systematic stepwise effort to scale up intrapartum and EmOC, could reduce maternal mortality by 75%.'

Specifically, the Indian researchers recommend that, 'In settings with limited infrastructure, investing in "intermediate" facilities (e.g., birthing centres) is very cost-effective, provided there is reliable referral capacity and transport to an appropriate EmOC facility if necessary.'¹¹ They also found that a community-based strategy where oral misoprostol would be available in homes and birthing centres would also be cost-effective, but this needs to be backed up with reliable intrapartum care and EmOC centres.

While Hogan *et al*⁶ showed improvements in maternal mortality world-wide, they did map out most of sub-Saharan Africa as a high-risk area for pregnant women. While more research is needed on the effect of specific interventions to prevent maternal mortality, there are some general lessons to be learned from the studies outlined here and applied in the context of USAID's Global Health Initiative, the G8 countries' commitment to MCH, and the Gates Foundation promises. First and foremost, maternal lives are not saved by one intervention. Women need a continuum of services from long before they become pregnant to the time of delivery, from family planning and good nutrition to delivery by skilled birth attendants and availability of EmOC. These interventions are not costly, and more than justify their implementation by the lives saved as well as the families and communities preserved.

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Pharmacy

Rational use of medicines

In addition to drawing up the Essential Drugs list, the World Health Organization (WHO) is involved with other aspects of the use of medicines.

WHO has just published a fact sheet¹ on the rational use of medicines. The headline of the document is that more than 50% of all medicines are prescribed, dispensed, or sold inappropriately, and half of all patients fail to take medicines correctly. This is not the fault of the patients, but of those who supply the medicines. If patients are given accurate information about their medicines they will learn about the importance of compliance with medication. For example, tuberculosis medication requires 6 months' treatment, but patients often feel better after a few weeks and if they stop treatment, the bacteria become resistant to further treatment.

There are international and national guidelines for the best treatment of many conditions. In the UK, the organisation NICE (National Institute of Health and Clinical Excellence) recommends the most cost-effective treatments and draws up guidelines for treatment options. The NICE guidelines are not restricted to choice of medication, but include public health. One of the forthcoming guidelines is 'Preventing unintentional road injuries among under-15s: education and protective equipment'; this is currently in draft form and is expected to be published in December 2011.

The WHO fact sheet says the proportion of patients treated according to clinical guidelines for common diseases in primary care is less than 40%. Of particular note is that fewer than 60% of children with acute diarrhoea receive necessary oral rehydration therapy, yet more than 40% receive unnecessary antibiotics; and only 50% of people with malaria receive the recommended first-line antimalarial. This, as well as depriving patients of the most suitable treatment, encourages the spread of disease resistance with a future impact on public health.

Last year the WHO published a report² that contains survey results from 1990 to 2006 to see if prescribing patterns are changing to comply with established protocols. The results are not encouraging, and much more work needs to be done. For example, in the treatment of diarrhoea, one of the most common acute illnesses, the use of oral rehydration therapy has doubled from 33% to 68%. However the use of antibiotics is unchanged at 50%. The overall compliance with guidelines has remained the same at 37% to 40%.

The report makes suggestions of the best ways to improve prescribing.

- Have a national list of essential drugs. This is not enough unless the drugs are available and prescribers use the list.
- Have clinical guidelines and prescribe according to the guidelines.
- Reduce the number of drugs taken by each patient (avoid 'polypharmacy').
- Avoid over-use of antibiotics and injections.
- Do not prescribe medicines just because they are promoted by the local pharmaceutical industry, and

certainly never take inducements to prescribe them. Patients can also improve their treatment:

- be educated in the use of medicines; don't always expect antibiotics and injections ('a pill for every ill');
- only purchase medicines from an official supplier; medicines sold from markets are more likely to be counterfeit or sub-standard;
- take medicines according to instructions (improve compliance).

Much of this is to do with education and the report says that public education and re-validation of prescribers are necessary. It recognises that health workers are over-worked, but if patients only attended for treatable conditions, not those that get better by themselves (self-limiting), the workload would be significantly less.

Over-worked health professionals are more likely to make mistakes in diagnosis and are more likely to prescribe if pressured by patients.

In the UK a lot of pressure is taken from general practitioners and hospital Accident and Emergency departments (Emergency Rooms) by the use of 'walk-in centres' where patients are assessed and treated by nurses and referred to doctors only if essential. These walk-in centres were not popular when they first started, but are becoming increasingly used as more patients are referred to them by doctors.

Stopping medication

Prescribing and taking medicines appropriately is part of the healthcare system. Another important factor is knowing when to stop medication. The Welsh Medicines Resource Centre (WeMeReC) published a bulletin regarding stopping medicines.³ It says that there is advice on when to start therapy but less to support stopping therapy. It reminds us that at the point of prescribing the prescriber must think about the length of treatment required (or even if treatment is required at all). Sometimes prescribing one drug is just to counteract the side-effects of the first, so the logical step is to change the first drug.

Medicines can be stopped for a variety of reasons: serious adverse reactions; change in guidelines showing that a medication is less effective or more risky than first thought; the patient gets better or worse; and treatment is no longer effective.

There are some medicines that must never be stopped suddenly either because the patient will get withdrawal symptoms, or the patient's original condition may flare up (get significantly worse).

The medicines that must not be stopped suddenly are:

- opiates, e.g. morphine, codeine;
- hypnotics and tranquilisers, e.g. diazepam;
- antipsychotics and antidepressants, e.g. amitriptyline, chlorpromazine;
- anticonvulsants (anti-epileptics), e.g. phenobarbitone (phenobarbital);
- beta-blockers (beta adrenergic antagonists) e.g. propranolol;
- alcohol (in alcoholics).

Some medicines must be stopped before surgery, especially those that can cause excessive bleeding, e.g. aspirin and anticoagulants, e.g. warfarin. In general

these can be stopped a week before planned surgery.

For medicines that need to be reduced slowly, e.g. diazepam and antidepressants, careful planning is needed. Antidepressants take from 2 to 6 weeks to have full effect and unless a patient has significant adverse effects they should not be stopped until the patient has been well for 6 to 12 months. Before that time the patient will relapse when treatment is stopped.

Anticonvulsants present a particular problem as when patients are free from seizures they may be tempted to stop taking the medicines as they may think they are cured; equally a patient may not be able to afford the medication and have to stop it.

The British National Formulary (BNF) says:

- 'Abrupt withdrawal, particularly of the barbiturates and benzodiazepines, should be avoided because this may precipitate severe rebound seizures. Reduction in dosage should be gradual and, in the case of barbiturates, withdrawal of the drug may take months.
- The decision to withdraw antiepileptic drugs from a seizure-free patient, and its timing, is often difficult and depends on individual circumstances. Even in patients who have been seizure-free for several years, there is a significant risk of seizure recurrence on drug withdrawal.
- In patients receiving several antiepileptic drugs, only one drug should be withdrawn at a time.'

Because of the serious risk of rebound seizures it may be better to keep a patient on medication if they remain fit free.

Medicines for children

It can be difficult to calculate doses of drugs for children. There have been very few trials of the correct ways of calculating doses. In small children the liver and kidneys have not reached their full ability to eliminate drugs and their metabolites. Small children have a higher proportion of water in their bodies than do adults.

Doses of different medicines may be calculated from weight, or age, or even calculated according to the patient's body surface area. These factors can make it difficult to find the correct doses.

In the UK, since 1995 a companion volume to the BNF (British National Formulary), the *BNFc British National Formulary for Children* has been published. This is updated annually.

WHO has just published *WHO Model Formulary for Children*. At the moment it is only available on-line at http://www.int/selection_medicines/list/WMFc_2010.pdf. It is a big file (2.8Mb) and not suitable for downloading without a good internet connection. I expect a paper copy to be published in a few months.

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