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ZIKA VIRUS AND THE SKIN

KEY WORDS

Zika virus, ZIKV, Aedes aegypti, congenital malformations, pregnancy risk, Guillain-Barré syndrome.

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Zika virus (ZIKV) outbreaks across south America and the Caribbean have triggered the World Health Organisation to declare an International Health Emergency. Amongst the 50 countries with current active transmission is Brazil, the host for the summer Olympics 2016. Several prominent athletes have withdrawn from competing on health risk grounds. ZIKV was first identified in Zika forest in Uganda in 1947. Since then there has been low grade transmission in many parts of Africa and SE Asia. The current pandemic has seen ZIKV spread to new areas of the globe and has infected huge swathes of the population who are infection-naive and living in densely populated areas. ZIKV is mainly transmitted by the aggressive daytime biting *Aedes aegypti* (Fig 1)and to a lesser extent the *Ae. Albopictus* mosquitoes. Vertical transmission and infection through sexual intercourse has also been identified. There is also a theoretical risk of transmission through saliva and urine in patients with a high viral load.

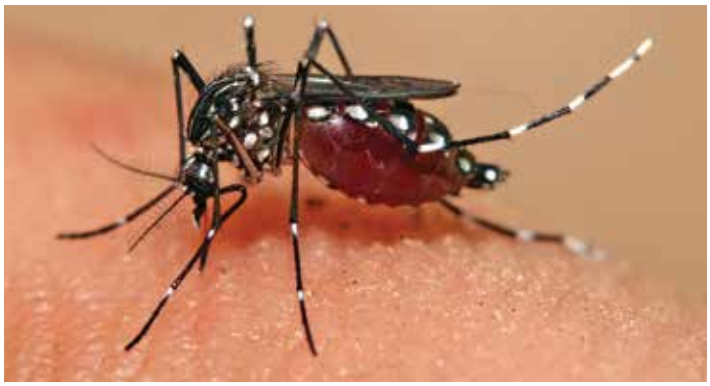

Fig 1. *Aedes aegypti.*

ZIKV is a flavivirus in the same family as dengue and chikungunya, and mainly causes an asymptomatic or a mild self-limiting viral illness. However, recent evidence from this outbreak suggests that ZIKV can also cause Guillain-Barré Syndrome (a temporary viral-induced paralysis) and congenital malformations including microcephaly (Fig 2), eye/ear abnormalities, intractable seizures and intrauterine death. The incubation period is thought to be 3-10 days with rash being a prominent feature around day 4 of the illness. The rash is usually widespread, starting on the head/neck and spreading caudally to the trunk and limbs. Palms and soles can also be affected. A fine erythematous maculopapular rash (Fig 3 overleaf) is the usual presentation with the typical appearances of a classic morbilliform viral exanthem. Patients usually have a low grade fever, retro-orbital headache, conjunctivitis and arthralgia which lasts about 1 week. Management is supportive and reduction in onwards transmission to others.

Fig 2. Microcephaly.

The WHO recommends pregnant women should avoid travelling to areas with current ZIKV transmission if at all possible. Pregnant women should also avoid having unprotected sex with a male partner during pregnancy, condoms should be used. Any woman whose male partner has been infected with ZIKV, who wishes to conceive, should wait six months post infection.

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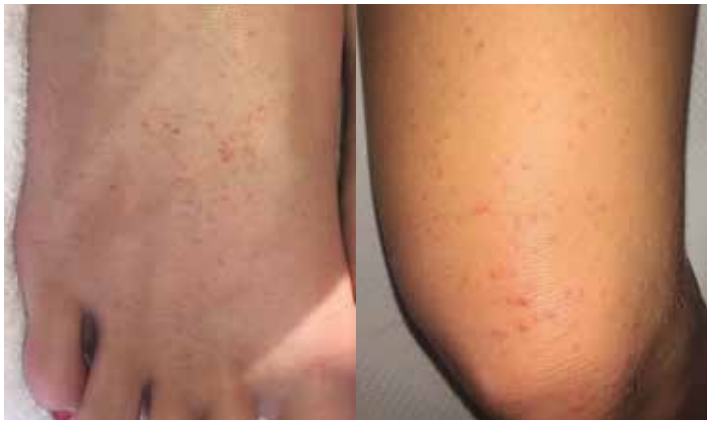

Fig 3a. Erythematous Maculopapular rash (Photo: Rachael Morris-Jones).

To prevent infection and therefore ongoing transmission insect repellent containing 50% Deet should be applied to exposed skin, wear dark clothing with long sleeves/legs covered and use bed-nets at night. Local governments are trying to destroy *Aedes* habitats and use insecticides.

ZIKV Symptoms

- Maculopapular rash
- Conjunctivitis
- Headache (retro-orbital)
- Fever
- Arthralgia

ZIKV Transmission

- Mosquito bites
- Sexual intercourse (men to women, men to men)
- Vertical transmission (to fetus in the womb)
- Possibly saliva, urine, blood transfusion

ZIKV Complications

- Guillain Barre Syndrome (temporary paralysis)
- Congenital microcephaly
- Congenital defects of eyes/ears
- Congenital seizures
- Intrauterine death

CONTACT ALLERGY AND PATCH TESTING IN RESOURCE POOR AREAS

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KEY WORDS

contact dermatitis, allergy, irritant contact dermatitis, patch testing, resource poor countries

I would regard the major principles of management of contact allergy are firstly recognition of its possibility, secondly identifying the culprit, thirdly elimination of the causative agent(s) and finally active treatment. These apply no matter how well one is resourced but the ability to identify the source of the problem will be constrained where resources are meagre.

Recognition

The case history is all important in alerting the carer of the patient to the possibility of contact allergy. In some instances suspicion may be high such as when skin eruption appears or is exacerbated consistently whenever a particular article, medicament or cosmetic is in contact with that site.

It is essential to ascertain the first site of involvement as secondary spread may have occurred by the time the patient is seen. Is there a previous history of reacting to materials e.g. metal, adhesive tapes? It is important to ask about a time relationship of the condition to occupational and spare-time activities as well as seasonal variation. There are certain sites and conditions where the cause of the contact dermatitis can be difficult to identify, most notably the hands as well as medicament allergy affecting the eyes, external ears, perianal area and varicose eczema. It is vital to ask about everything that has been applied to the skin including medicaments obtained from sources other than the doctor such as over-the counter remedies from pharmacist and material obtained from traditional medicine practitioners.

The patient's skin should be examined in full. Even though the presenting problem may be elsewhere, an allergy for example to something carried in a trouser pocket can easily be overlooked without a full examination. The anatomical distribution may help and I have outlined commoner site/allergen combinations in Table 1.

Table 1

Site	Commoner Allergens
Foot	• Leather (chromate) • Rubber Chemicals • Glues • Dyes
Lower Leg (Varicose)	• Components of Medicaments • Components of dressings and hosiery (Adhesives, Rubber chemicals, dyes.)
Trunk	• Nickel and rubber components of clothing.
Flexures (axillae/groins)	• Perfumes • Clothing Dyes and Resins/Formaldehyde.
Neck	• Perfumes • Nail Varnish/Artificial Nails
Face/Eyes	• Components of Cosmetics (including Nail) • Hair Dye • Components of Moisturisers • Perfumes • Components of Medicaments
Exposed Sites	• Plants/Weeds • Epoxy Resins • Vapours/Dusts including sawdust
Ears	• Nickel • Components of Medicaments
Hands	• Anything!!
Finger tips	• Garlic • Plants

By definition the problem must start in the area(s) of the skin which is in direct contact with the allergen. The presenting features will be those of dermatitis with itching and redness in the affected sites. There may be

weeping in more acute cases but more generally there is dryness, scaling and cracking of the skin with increased pigmentation especially when the skin is dark.

Contact allergy is an immunologically cell-mediated reaction and is distinct from contact dermatitis caused by irritants which although morphologically similar, results from direct damage to the skin. Examples of irritants are listed in Table 2. Some materials e.g. cement can be both irritants and allergens.

Table 2

Common Irritants				
Soaps	Detergents	Shampoos	Raw Food	Solvents
Oils	Cement	Acids/Alkalis	Hands	Finger tips

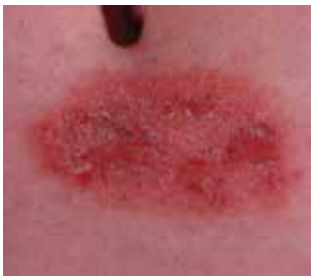

Fig 1. Contact Allergy to Nickel from metal stud in jeans (Photo: author).

The distribution of the eruption will often give a clue to contact allergy. It may occur directly under materials worn on the skin, especially metal (usually containing Nickel) (Figure 1) and items made from wood especially from the tropics. Rubber and tanned leather in gloves, footwear (Figure 2), belts etc. will induce dermatitis in the sites where they are worn. It is the chemicals added to rubber (thiurams, mercaptans, carbamates and IPPD) and the tanning agents (usually chromates) for leather which are responsible. Glues especially containing formaldehyde resins or Colophonium can also cause problems in footwear and watchstraps. Clothing resin and dye allergy tends to produce a distribution of rash around rather than within the flexures. Perfumes are a common cause of contact allergy either in their own right or from within cosmetics and other materials applied to the skin. One may become allergic to one or more other components of cosmetics e.g. preservatives, lanolin or other excipients. Allergy to components of medicaments is also common not only from excipients but also the active components e.g. Neomycin or even the active corticosteroid . Furthermore, a pre-existing dermatitis can be exacerbated by medicaments used to treat the condition. This problem is particularly likely to occur from over-the-counter and traditional remedies.

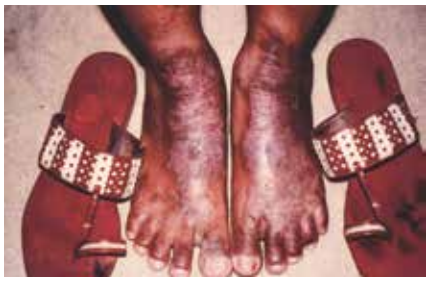

Fig 2. Contact allergy to red dye in footwear (Photo: Dr Paul Buxton).

Fig 4. Allergy to compositae (airborne pattern) in an Ethiopian farmer (Photo: Dr Chris Lovell).

Hair dyes contain p-phenylenediamine (PPD) and may induce severe reactions around the scalp if allergy to it has developed (Figures 3abc). In some cultures PPD is used to dye the beard with similar results in this site. Furthermore this chemical is being increasingly used in temporary tattoos causing severe blistering and persistent pigmentary changes as a result.

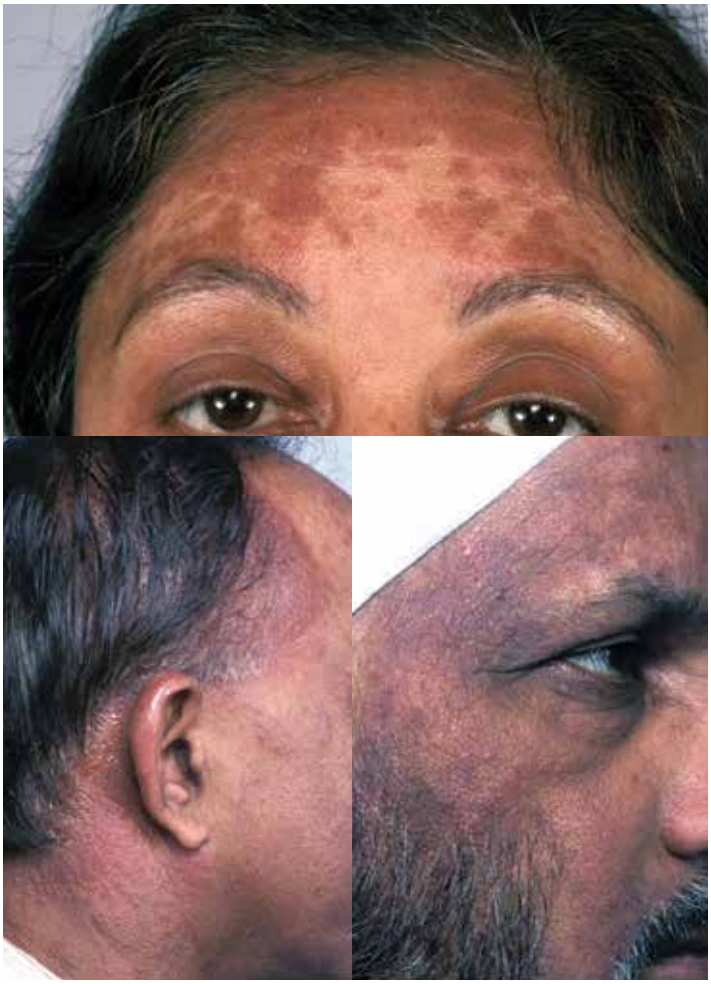

Fig 3 a,b,c. Examples of contact Allergy to paraphenylenediamine (PPD) in hair dye (Photos: Dr John McFadden).

A major problem in tropical areas has arisen from Compositae (Asteraceae) weeds whose components may cause severe allergic contact dermatitis over the exposed sites (Figure 4) being particularly extensive and severe in those who wear few clothes. Other plants may cause reactions but these tend to be more localised. Garlic allergy classically affects the tips of the thumb, index and middle fingers of the non-dominant hand (Figure 5).

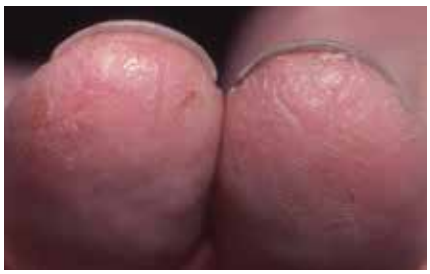

Fig 5. Fissured fingertips from garlic allergy (Photo: author).

Commoner occupational allergic hazards in addition to the above include chromate in cement affecting mainly construction workers (Figure 6), epoxy resins and hardeners (two part), rubber exposure eg from gloves and handling tyres, and preservatives e.g. in paints.

It is vital that whenever you see a rash with features of eczema or dermatitis that you consider the possibility of contact allergy. The problem is that contact allergy may mimic or exacerbate constitutional disorders and is therefore commonly unsuspected. If the diagnosis is missed you may be subjecting your patient to continuing and lasting disability.

Continued overleaf…

Fig 6. Occupational exposure to cement in Ethiopian construction workers (Photo: Dr Chris Lovell).

Investigation

Patch testing is the best way to confirm or identify contact allergy but this requires time and resources. In ideal circumstances it is normal and good practice to screen suspected subjects with a series of common allergens but this may be difficult where finances are limited and furthermore test units are needed to keep the allergens applied to the back for 48 hours. Allergens for testing normally come pre-loaded in syringes and put into special test chambers. The major suppliers in Europe are Chemotechnique® and Hermal®.

If funds are restricted, you may nevertheless be able to get together enough test materials to make a limited standard series of maybe 10 – 20 materials. I think I would try and include Nickel, Cobalt and chromate, formaldehyde, Thiuram mix, Mercapto mix, Fragrance mix, Myroxylon pereirae, Colophonium, Compositae or Sesquiterpene lactone mix and p-Phenylenediamine (PPD), Methylisothiazolinone/ Methylchlorisothiazolinone plus any allergen you have identified as frequent in your own population. The allergens should be kept in a refrigerator if at all possible. If you have friendly visiting dermatologists from the developed world, they may be able to donate some materials or units to help in this respect.

You can also patch test with the patient's own materials but there needs to be caution. Generally materials meant to be directly applied to the skin such as cosmetics and medicaments can be tested undiluted as can clothing including pieces of shoes. Application of an undiluted irritant will cause a false positive reaction which could be very severe. Do not test undiluted soaps, shampoos, work materials, known irritants such as those in Table 2.

Table 3.
Recording of Patch Test Reactions (Modified ICDRG criteria)

Morphology	Scoring
Negative	-
Doubtful reaction, faint erythema	±
Weak positive - palpable erythema, infiltration, possibly papules	+
Strong positive – erythema, infiltration, papules, vesicles	++
Extreme positive – intense erythema and infiltration, coalescing vesicles, blisters	+++
Not tested	NT
Interpretation of reactions is then required. Most strong reactions will be allergic but false positive irritant reactions may occur and may be difficult to identify.	

Patch test are normally left on the back for 48 hours and then removed with a further reading taking place 2-5 days later. A morphological assessment of the reactions is made according to the criteria in Table 3 and if there is an allergic reaction then relevance should be sought. (Figures 7a and 7b)

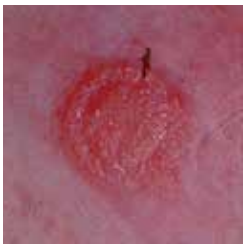

Fig 7a. Strong ++ patch test reaction.

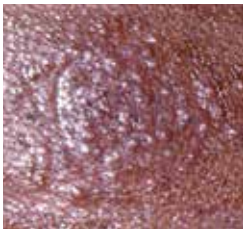

Fig 7b. Strong ++ reactions may be harder to detect on dark skin.

However, what if you do not have access to these materials or cannot afford them? What can you do? I will make some suggestions. Firstly always ask yourself "Could this condition be caused by contact allergy?" If the answer is yes then list all the possibilities. If the patient can avoid some or all of these then give them a trial without for at least 6 weeks. If they improve or recover then reintroduce the agents 1 at a time and see if the dermatitis returns or flares.

If the suspected agent is a medicament or cosmetic, then you can ask the patient to undertake a Repeated Open Application Test – ROAT. This is normally undertaken on the upper arm or the flexural aspect of the forearm. The suspected material is applied twice daily to the same site (the area should be at least 5cm² for 4 weeks or until a reaction develops over the application site which indicates a likelihood of allergy.

Elimination of the Allergen(s)

When an allergy is found with patch testing then it is crucial to find relevance by identifying a source containing that allergen which could be responsible for the patient's condition. For example looking at the ingredient label (when present) of an applied medicament or cosmetic may confirm the allergen to be present. Sometimes it is not easy to establish relevance. If you have a textbook which lists potential sources then this may be helpful. Even better, if you have access to the World Wide Web, there are many sites which can give listings for sources of allergens and this may help to pinpoint the cause. If complete removal of the cause is feasible then this would be expected to alleviate the condition or even result in a cure. Unfortunately sometimes it is impossible to eliminate the allergen completely but for example improved protection with gloves or other protective clothing may help.

Treatment

Treatment will be required while the dermatitis is active. Normally this will involve a topical corticosteroid but systemic steroids may be necessary in very severe cases. Potassium permanganate soaks (1 in 8000 dilution in warm water) 4 times a day for weeping and blistering hand and foot eruptions, is helpful in the acute stages. General advice should include the avoidance of contact with irritants, including soap, and the liberal use of moisturisers. Treatment may be ineffective if the patient continues to be exposed to the causative allergen.

Conclusion

If you are able to follow the principles I have outlined whenever you see a patient with eczema/dermatitis then I hope this will assist in diagnosing allergic contact dermatitis, particularly when it may have been unsuspected. The consequences of missing avoidable contact allergens can be substantial for those affected, so I would encourage carers and clinicians always to think about the possibility.

THERAPY UPDATE: Miltefosine for the Treatment of Leishmaniasis

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KEY WORDS

Leishmaniasis, parasitic infection, miltefosine, India, antiprotozoal therapy

Introduction

In 2014, the U.S. Food and Drug Administration (FDA) approved the use of miltefosine for the treatment of leishmanasis[1]. This drug has been a great advance in this area of tropical medicine as it is the first and only oral medication that can be used to treat both cutaneous and systemic forms of the disease.

Leishmaniasis

Leishmaniasis is a tropical infection caused by the protozoal *Leishmania* parasite[2]. There are over 20 different species of *Leishmania* that cause this infection, and they are transmitted to humans via a bite from an infected female phlebotomine Sandfly[3]. The WHO (World Health Organisation) reports 900,000-1.3 million new cases annually[3], most commonly seen in the poorest areas of South East Asia, the Mediterranean, North Africa-Eurasia, East Africa and South America[3].

There are three main forms of leishmaniasis causing a range of clinical manifestations. Cutaneous leishmaniasis (CL)(Fig 1) is the most common form, presenting as papules which subsequently develop into nodules and ulceration of the skin[2]. This form usually heals spontaneously, over a period of 6 months, but can cause severe scarring and morbidity[2].

Mucocutaneous leishmaniasis (MCL) is characterised by infiltration into the mucosa including the nose, lips and oropharynx[2]. Patients can develop mucosal bleeding, perforation of the nasal cartilage and palate and respiratory complications. Visceral leishmaniasis (VL), Kala-azar, is the most severe form, causing disease in the skin and reticuloendothelial system presenting with skin manifestations as well as hepatomegaly, splenomegaly and diarrhoea[2]. This form is fatal if left untreated[4].

Miltefosine

Miltefosine is an alkylphosphocholine drug used to treat leishmaniasis. It has been licensed for the treatment of visceral leishmanisasis in India for over 10 years[4], and was used in India's Kala-azar elimination programme[5]. More recently it has been included in the WHO Model List of Essential Medicines[6] and in 2014 it was approved by the U.S. Food and Drug Administration (FDA) for the treatment of CL, MCL and VL[1]. The significance of miltefosine is that it is the first and only oral medication that can treat both the cutaneous and systemic form of the disease. This has positive implications on disease prognosis and has the potential to reduce the need for hospitalisation.

Most clinical trials of miltefosine were carried out in India, where miltefosine has been found to be a safe and effective treatment for CL and VL. Trials in Nepal, India and Bangladesh reported good cure rates for VL[7]. Sundar et al[8] found that the final cure rate of VL was 90.3% at 6 months follow up. Most of the trials done in New World (Latin America), showed that miltefosine is more effective than standard therapy in both adults and children[4,9].

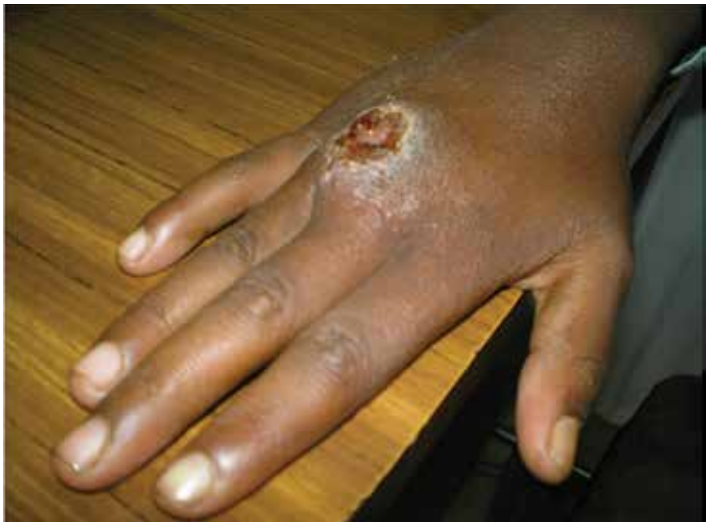

Fig 1. Cutaneous leishmaniasis in an Ethiopian farmer (Photo Chris Lovell).

Clinical Use

Miltefosine is available in 10mg and 50mg capsules[4]. The FDA recommended dose for patients who weigh 30-44kg is 50mg twice a day (breakfast and dinner) for 28 days, and 50mg three times a day (breakfast, lunch and dinner) for patients who weigh >45kg[10]. Post Kala-azar dermal leishmaniasis may require a longer course of treatment; 150mg/day for 2 months or 100mg/day for 3 months[11].

Few serious adverse effects have been reported with miltefosine, but the drug is associated with mild gastrointestinal upset including loss of appetite, diarrhoea, nausea and vomiting[4]. These side effects decrease when the drug is taken with food[4]. Miltefosine is also associated with a rise in creatinine, probably due to fluid loss, and a transient rise in ALP and AST[4]. Patients should have regular blood tests to monitor their liver function and creatinine[12]. Animal studies have shown that there is a risk of male and female infertility[12], but more research is needed.

Miltefosine is contraindicated in pregnancy due to its teratogenic effects[12]. Before commencing treatment, women of reproductive age should have a negative pregnancy test. Effective contraception should be used during treatment and for five months after treatment[10]. Women should also be advised not to breastfeed during this time.

Discussion

Miltefosine for the treatment of leishmaniasis has been a great advance, yet it is not without its challenges. Due to the vast geographical variation in Leishmania species and differences in species susceptibility to the drug, the results obtained from trials in one particular area may not produce similar clinical benefits in another one[13]. In order to address this issue, a wider range of species specific research needs to be done, to evaluate which treatments are most effective in a particular geographical area.

Considerations for future research include treatment in immunocompromised patients and ongoing trials assessing miltefosine combination therapies, which may be a more cost effective option[14].

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COMMENT: Antivenom Crisis in Africa

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KEY WORDS

snakebite, antivenom, sub-Saharan Africa, resource poor communities; traditional healers

Estimates of burden of snakebite in sub-Saharan Africa

Venomous snakes might seem an unlikely menace in a rapidly urbanizing world, yet by cautious estimates at least five million people worldwide are bitten by snakes each year. Furthermore, snakebites kill more than 125,000 people every year and 400,000 experience permanent physical and mental disabilities. Snake bite has a mortality rate equivalent to one fifth of deaths due to malaria worldwide, and half of that due to HIV/AIDS in India. Yet snake bite is largely invisible to WHO, other international and national health agencies, many African governments, and to the big donors, and has been marginalised even within the neglected tropical diseases community.[1]

It is uncertain how many people are bitten or die from snakebites in sub-Saharan Africa and snakebite mortality could be much higher than anecdotal reports suggest, as for many African countries there are no reliable data. According to Médecins Sans Frontières, (MSF; also known as Doctors Without Borders) whose health-care workers treat snakebites through field programs in the Central African Republic and South Sudan, an estimated 30,000 people die each year and at least 8,000 more undergo amputations. One reason for the under reporting of snakebite, is that many victims of snakebite die before they reach a hospital, or waste precious time with traditional healers before seeking more conventional medical help.[2]

Medically important snakes of Africa (*most important)[3]

West: ***Echis ocellatus**, **E. leucogaster**, **E. jogeri**, **Bitis arietans***, spitting cobras (***Naja nigricollis***, N.katiensis), N. haje, N. senegalensis, N. melanoleuca, Dendroaspis polylepis, D. viridis, D. jamesoni

East: ***Echis pyramidum**, **Bitis arietans***, spitting cobras (***N. nigricollis**, **N. pallida**, **N. ashei***, N. nubiae), N. haje, Dendroaspis polylepis, D. angusticeps

Central: ***Bitis arietans***, spitting cobras (***N. mossambica***), N.haje

South: ***Bitis arietans***, spitting cobras (***N. mossambica**, **N. nigricincta***), ***N. nivea**, **N. annulifera**, **D. polylepis**, **D. angusticeps****

Image 1. Puff Adder (*Bitis arientans*)

Image 2. Black Mamba (*Dendroapsis polyepis*)

Bites by venomous snakes can cause acute medical emergencies involving severe paralysis that may prevent breathing; bleeding disorders that can lead to fatal haemorrhage; irreversible kidney failure and severe local tissue destruction that can cause permanent disability and may result in limb amputation. Children suffer more severe effects than adults due to their smaller body mass. This type of injury is often found among women, children and farmers in poor rural communities in low and middle-income countries. It is mainly in countries where health systems are weakest and medical resources sparse.

Image 3. Young child who was bitten on the hand by a puff adder and received antivenom at the Snake Park clinic, Meserani, Tanzania

Antivenom production and overview of African snake antivenom products

The only effective treatment for snakebite is to give antivenom, an antibody serum that reduces the quantity of venom circulating in the blood of a snakebite victim. This is made from the purified plasma of horses previously injected with small quantities of snake venom. Antivenoms need be effective against the local species of snake.

There are three types of products.[3]

1. 'Pan African' polyspecific e.g. Fav-Afrique manufactured in France by Sanofi-Pasteur
2. 'Sub-regional' polyspecific - SAIMR Polyvalent manufactured in South Africa by SAVP and EchiTabPlus manufactured in Costa Rica by ICP
3. Monospecific (several manufacturers)

The most useful types of antivenom are those that are polyspecific i.e. cover several species of snake so that identifying the snake causing the bite is not so important. Many victims are bitten at night and are unable to know which snake has bitten them.[4]

For many African countries it is also important that the product is safe enough for use in underequipped, peripheral health centres, physicochemically stable enough for shipping and storage in the African climate, and readily accessible to victims, who are usually people living in rural areas with few resources and little financial support.[5]

In 2014, the French drug firm Sanofi Pasteur in Lyon ceased production of Fav-Afrique. It was the only anti-venom that has been proven safe and effective to treat envenoming from different types of snakes across Sub-Saharan Africa. The serum neutralizes the venom 10 of Africa's most

dangerous snakes. The last batch of antidote expired in June 2016. The antidote has saved many people from bites by deadly species such as the carpet viper (*Echis ocellatus*), common in West Africa and the black mamba (*Dendroaspis polylepis*), found across the sub-Saharan region. But the high costs — US$250–500 per person put it out of reach of most African snake bite victims as it represents at least 4 years' salary for the average African.

Image 4. One of the last batches of Fav-Afrique antivenom

The reasons for cessation of production of Fav Afrique were purely financial.[5] By 2010 Sanofi's share of the market had fallen to 1% -despite being the best product available many buyers switched to cheaper products by competitors, which may not work against bites from African snake species. In 2010, 90% of sales were for two low-cost Indian products of dubious efficacy against African snakes :ASNA-C: manufactured by Baharat serums and vaccines and VINS Pan African.[3,6] Lack of efficacy of these products reduced confidence in antivenoms leading to further lack of demand.

Underlying causes

The African antivenom crisis is both a supply crisis and a demand crisis.

1. There is neglect of snakebite victims who are mainly rural impoverished populations with little political voice (farmers and herders). If victims are invisible the disease becomes invisible as well. Snakebite fatalities have been rising over the past decade in the Central African Republic, Ghana and Chad[2] yet the burden is vastly hidden. The manufacturers of antivenom may feel there is no market but there are definitely unmet needs. Demand for antivenom could be stimulated if quality products were provided at the right price similar to the provision of anti-retroviral drugs.

2. There is poor understanding of cost effectiveness. Quality antivenoms are highly cost effective products. It is an unknown fact that antivenom is one of the most cost-effective interventions. In 2015 Habib showed that antivenom therapy (EchiTabG/EchiTabPlus) was highly cost-effective in a study in Nigeria: cost per Disability-Adjusted-Life-Years (DALY) US$100, cost per death averted: US$2,330. The cost-effectiveness ratio was better than ART and rotavirus vaccination and equivalent to HPV vaccination.[7] There is a need for similar studies with other products in different settings and also for purchasers such as Ministers of Health to understand that low-cost ineffective products are not cost-effective.

3. The high cost of antivenoms makes them unaffordable to the majority of victims. There is virtually no donor support and antivenoms are not listed as a priority by any funding agency.[8] Victims are often incapable of rapidly mobilizing the $100- $200 required for treatment and may not even seek treatment. For fear that antivenom may expire before being sold small rural hospitals may prefer not to stock antivenoms. It has been clearly demonstrated that when quality antivenom products are given free to a rural population treatment seeking behavior improves and outcomes from snake bite are excellent.[4] However, the current situation in Africa is unfortunately a vicious circle of victims that can't pay, no donor support and Ministers of Health that don't take financial risk to purchase products or opt for low-cost ineffective products which all leads to lower the demand for antivenom.

4. There has been no independent quality control for antivenom which may have been prepared from venom of snakes from other parts of the world, and have limited efficacy in Africa. In other words, the quality of products offered is unlikely to have been verified. Confidence among health care providers and patients with respect to antivenom products has therefore declined. Although WHO has established clear norms to evaluate the quality of antivenom products it has had no resources to evaluate antivenom serums (i.e. no bank of reference venoms, no Good Manufacturing Practice audits). As such there is no framework to push producers to comply with quality norms. It was only in December 2015, as a response to recent concerns about the antivenom supply crisis becoming critical that WHO has put out a call to manufacturers of antivenoms intended for use in sub-Saharan Africa to submit an expression of interest in product assessment by WHO.[9] This will consist of a desk review by a panel of experts followed possibly by laboratory investigation to assign a risk/benefit for each product. While this is helpful it falls short of robust clinical trials urgently needed to find a replacement for Fav-Afrique.

5. Medical workers are often ignorant of how to use antivenom correctly and manage the side effects and may fear using the product leading to underuse of antivenom and compounding a lack of experience. In 2009 snakebite was given the status of a Neglected Tropical Disease (NTD) by WHO but unlike the other 17 NTDs it has no formal programme for improving treatment by training medical workers, advising ministries or educating communities. This is despite snakebites causing more deaths than all 17 diseases put together.[2]

Measures to address market failure and improve access

The solution to the crisis must address the root cause of the problem, which is a vicious circle that limits access to all antivenoms, not just Fav-Afrique. The shortage results from inadequate product production, distribution, training, and funding at the local level in Africa.[5]

The strategy recommended by the African Society of Toxinology,[10] founded 3 years ago, addresses three basic points:

1. Better region-specific antivenom development and distribution needs accurate epidemiological studies.
2. Medical staff need training to optimise product selection and use.
3. Purchasing support programmes should standardise charges on behalf of stakeholders (governments and private employers, especially agricultural firms, health insurance providers, etc) to mutualise the costs equitably.

At an MSF Access Campaign Meeting at Fondation Mérieux, January 2015 the following solutions were recommended[(3)]:

Short term

1. Produce another batch of Fav-Afrique to address shortage.
2. Finalise technology transfer for continued production of Fav-Afrique
3. Open a new WHO position on access to antivenoms and snakebite management.
4. Conduct pre-clinical and clinical studies to compare existing African antivenoms.

Medium term

1. Conduct more cost-effectiveness studies to guide policy-making.
2. Support suppliers of hyperimmune equine serums to increase global production capacity.
3. Finance WHO-PQP for quality control of antivenoms.
4. Support purchase and procurement to meet needs in African countries with obligation to buy only WHO-PQed products.

This crisis will not be overcome in laboratories or in universities, but in rural communities alongside health workers and victims of snake bites.[5]

Continued on page 21…

MAKING USE OF MOBILE PHONES IN HEALTH EDUCATION

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KEY WORDS

Mobile phones, cell phones, health education, resource poor areas, traditional healers, health workers

The use of mobile (cell) phones for many aspects of education, access to information, contact with help, job seeking and poverty alleviation is on the increase in all parts of the world. Mobile phone network providers are constantly improving mobile phone coverage and there is now the ability to recharge phones by various mechanisms.

While current epidemics like HIV AIDS require education of whole populations through ancient techniques such as indigenous traditional story telling, songs and music, various aspects of theatre and dance and the use or radio and public addressing systems and village meetings, they do not provide the individual health information which today can be attained through mobile/smart phones and the use of *Apps*. The last few years many hundreds of millions of smartphones have been produced and are used throughout urban, peri-urban and rural areas, and asRyan et al(2011)) have indicated in publications about traditional health practices, even witch doctors have mobile phones. Thus, the management of snake bites still finds the traditional healer first on call but instead of looking for evil spirits in the form of the snake, using a tourniquet and scarifying the bite, the traditional healer can photograph the snake using a mobile phone and make contact with an anti-venom centre. As likely or not , no anti-venom will be needed and the appropriate treatment, which is immobilisation, to prevent lymphatic spread, is preferred to a bumpy journey to an anti-venom centre many miles away.

Health publications can be summarised in a *what's app* message and shared with millions of people all over the world, in just a few seconds. More and more useful *apps* are being developed, mostly free or very low cost. The development of the internet is now accessed most commonly by the mobile phone. http://www.mhealthevidence.org.states,'mhealth is the use of mobile information and communication technologies for improving health. It can be used for a wide range of purposes, including health promotion and illness prevention, health care delivery, training and supervision, electronic payments ,and information systems.

www.mhealthevidence.org brings together the world's literature on mHealth effectiveness, cost effectiveness, and programme efficiency, to make it easier for soft ware developers, researcher, program managers, funders and other key decision –makers to quickly get up speed on the current state-of-the- art. It includes more than 6,500 peer-reviewed and grey literature records from high-middle-and low resource setting.' It has been most used for promoting maternal and child health. but because of the visual natural of dermatological disease, it is very appropriate for diagnosing and managing skin disease. It has been observed that most health workers rapidly use and become comfortable with touch screen devices and only limited technical support is needed. Unrestricted use of smart phones generates a strong sense of ownership and empowerment among health workers. (BMJ 2013;347:f6009 http://www.bmj.com/content/347/bmj.f6009).

Figs 1, 2. A patient in South India affected by lymphatic filariasis transmits an image of his foot using a mobile phone. Courtesy of IAD India.

In general it is necessary to employ a mix of established and newer communication technologies to the benefit of both literate and non-literate users. Of course, it must be multi-lingual and stick to the simplest of messages. The user does not have to be highly educated, and one must note, that in countries like Ethiopia, health extension workers are recruited by the thousands. They are often young women who have recently left high school, who are sent out to rural areas with only the mobile phone for support. The phone can be linked to centrally placed doctors, to answer their questions from the field. There is no longer a lack of technical know-how but there is a need for more support of the system.

It is important to remember that mobile phones are quickly becoming exploited as a channel for misinformation, for commercial or ideological interest. The pharmaceutical industry is already spending $373,000,000 (US) per year worldwide on mobile phone advertising. We are all too

familiar with the availability of agents for the skin which do harm, such as skin lightening creams. WHO and public health organisations are aware of the problems and keen to eliminate information which may be harmful but there are now a number of approved public health educational videos. Regulatory bodies include the US Food and Drug Administration and it is a responsibility of governments to ensure that health information is never hard to find and is safe and reliable, *Health Care Information for All* HIFA@dgroups.org being an example. Recent studies have shown that each health worker made on average 160 minutes of health related calls and downloaded 37MB of data per month and that India has 125,000,000 smart phone users of a total population of more than a billion and this number is growing rapidly. One problem is the use of the phone for non-medical use, such as Bollywood films available for less than half the cost of a movie hall ticket, and inexpensive links to a new age video lending library. In 2014 the number of mobile devices overtook the global population and it is expected to grow tenfold in the next five years, especially in the Middle East and Africa.

The health profession can learn from the teaching profession who have struggled with differing policies on mobile phones in different schools. In those countries where more than 75% of the children have mobile phones, aggressively removing phones from classrooms has eliminated the use of the phone as an educational tool(www.bbc.co.uk/newsround/18015984) . Mobile phones are a severe disruption to learning when used inappropriately, however, when fewer dollars are available for classroom supplies, mobile phones that are currently tucked into students' backpacks can be used to obtain useful information. Phones should be visible rather than banned so they can be used to obtain encyclopaedic information, organise data collection, gather information or accurately convert metric measurements. William M Ferriter (@plugusin on Twitter),who teaches 6th grade language arts and social studies in Raleigh, North Carolina, blogs enthusiastically about the benefits of mobile phones in teaching.

'Store and forward' teledermatology, can help health care professionals to access distant help about complicated cases with the use of smartphone images attached to an email or through a group messaging service such as *WhatsApp*. The educational benefits of this type of teledermatology are obvious. Taking dermoscopic images is more difficult but, if sent with other images, can add value to the teledermatology referral. This is particularly helpful for the diagnosis of skin lesions (Figs 1,2). Dermoscopy can be very useful in differentiating malignant and benign skin tumours. Non-contact dermoscopy is especially useful in diagnosing some infectious conditions such as scabies. If the local practitioner has diagnostic doubt images can be shared via mobile phone to a panel of helpful experts instantaneously, anywhere on the globe, eg www.dermoscopy-ids.org.

In the future it may be possible to expand telemedicine to help with distant reporting of histopathology specimens. Images taken down a microscope could be emailed via the mobile phone for discussion with experts.

There is of course a well known illegal trade hovering in the background. Using a mobile phone, one can buy partners, obtain illegal drugs and receive many things free which rightly should be paid for. The rules and regulation differ from one country to another, for example, advice on AIDS HIV epidemic may not fit with every Government's view on sexuality. There are pros and cons and users should at least learn the rules of the game. Though helpful with dermatological diagnosis ,misdiagnosis is still possible. A patient's clinical details exposed to view on the internet requires confidentiality and informed consent.

To conclude, there is an issue of balance as described by Nand Wadhwani, in African Strategies for Health Project's New Resource - http://www.k4health.org/toolkit/mhealth/mhealth-compendium-edition-two - produced by the African Strategies for Health Project - (http://www.msh.org/our-work/projects/african-strategies-for-health) in June 2013. It contains twenty-seven cases which document a range of mHealth applications being implemented mainly throughout Africa, but also in other regions. It is an example of the highest technology becoming everyone's property but not without the need for regulations which everyone should understand and follow.

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Miltefosine for the Treatment of Leishmaniasis *continued from p16*

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COMMENT: Antivenom Crisis in Africa *continued from p18*

While we are waiting for clinical trials to bring replacements for Fav-Afrique to the market, the keys to reducing the risk of snakebite are education and preventive measures — such as wearing proper shoes, using a light when walking home from the fields and sleeping above ground level, beneath a mosquito net.[2]

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GENTIAN VIOLET

Gentian violet is an effective and inexpensive but somewhat forgotten topical therapy. It is especially useful in treating pyodermas, candidiasis and infected eczemas in resource-poor settings.

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KEY WORDS
crystal violet, pyoderma, candidiasis, antiseptic, triphenylmethane dye

Introduction

Gentian violet (hereafter GV), is a triphenylmethane dye used as an antiseptic since 1912. It is the basis of the Gram stain for microorganisms. Synonyms used for GV include crystal violet, methylrosaniline chloride and basic violet[3].

As an antiseptic GV has a potent bacteriostatic and bactericidal effect, especially for gram positive organisms. It is also a highly effective anticandidal agent. Unlike topical antibiotics, it is unlikely to produce resistance and it has been shown to be effective against methicillin resistant staphylococcus aureus. The drying and astringent action of GV, its ability to permeate and stain tissues as well as a possible action to reduce extravascular fluid extravasation, all contribute to its effect on microorganisms.

GV is cheap and relatively easy to prepare from powder which is stable and easily transportable in tropical environments. When the powder. is kept dry in sealed containers it has a long shelf life which is an advantage in humid environments. Side-effects are uncommon except for, usually temporary, staining of the skin.

Formulation and Dose

Details of the preparation and storage of GV are given in Bakker.[1]

GV is a powder that is sparingly soluble in water. It can also be made as a cream, ointment or alcohol based solution. The aqueous solution is most often used at 0.5%. It can be made in very high dilutions, such as 0.01%, in which case it may not stain.

Concentrations of 1% or 2% have been long used but are more likely to irritate. Some recommend 0.1% for extensive areas. In the United Kingdom it is recommended that GV not be applied to broken skin or mucous membranes, although the risk of a significant side-effect in these situations is extremely low.

Dosing regimens are variable. For pyoderma the solution can be applied twice a day for 3 days, or until the condition has markedly improved. It may be applied less frequently, for example once a week by a health care worker. Long term use, for weeks or months, may be necessary as for leg ulcers or burns.

Uses

1. Pyodermas

The term pyoderma is applied to ulcers or lesions of the skin which produce pus and this includes impetigo, ecthyma, bacterial folliculitis and staphylococcal scalded skin syndrome. Secondary pyodermas include especially impetiginized eczema.

Impetigo in children is an under-recognised disease, especially in tropical, poorly resourced contexts. It is estimated that at any one point in time there are in excess of 162 million cases of pyoderma, especially impetigo, in the world[2] and this is a cause of significant morbidity.

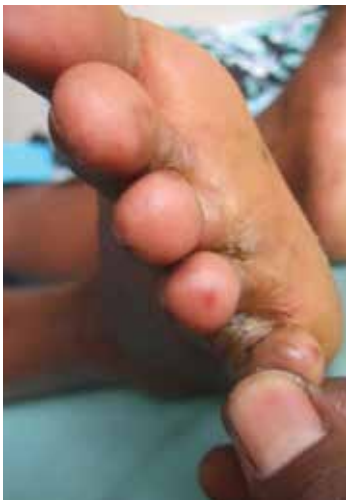

Fig 1. "Athlete's Foot" type tinea pedis – maceration, bacterial, fungal, overgrowth for Gentian violet solution daily (courtesy of Dr Edward Ogwang).

GV is a cheap, safe and effective treatment for impetigo and ecthyma. For limited disease, it may be used alone, but for more extensive disease it can be combined with oral antibiotics. Its action is not completely understood; multiple mechanisms have been proposed including the inhibition of reactive oxygen and specific effects on mitochondrial function in microorganisms. As a water soluble dye, its ability to penetrate and stain tissue seems to give it a long lasting effect not seen with other antiseptics which are inactivated by organic materials. GV's drying and astringent properties also contribute to its effectiveness.

Pyodermas are due to Gram positive organisms, namely staphylococcus aureus and streptococcus pyogenes. The ability of GV to penetrate bacterial cell wall and bind to DNA is the basis of its action against these organisms. GV has been shown to be effective against methicillin resistant staphylococcus aureus (MRSA) and bacterial resistance does not seem to occur with this agent. The lipids surrounding the cell wall of gram negative organisms and mycobacteria provide a barrier to this water soluble agent, but increasing the pH results in a more potent antibacterial action.

GV may have other benefits in the treatment of pyodermas. Studies have shown that by blocking the activation of endothelial angiopoietin[2] it reduces bacterial activation of vascular leak into the 'third space'[3]. As a result these infections may be associated with less swelling and fluid exudate and, if used, systemic antibiotics will be less diluted in tissues.

2. Candidiasis (Thrush)

GV topically has long been used to treat candidiasis of the skin, mouth and vagina. Even very dilute concentrations will inhibit the growth of candida; for example a dilution of 0.00165% has been shown to maintain a potent antifungal effect without staining of tissues.[4]

Oral candidiasis in HIV positive patients can be painful and may lead to reduced food intake further compromising an already ill patient. Oral

Fig 2. Gentian violet solution for impetiginized lesions in prurigo simplex (papular urticaria)

fluconazole, although effective, is expensive especially for long-term use and resistance may develop. In resource poor settings GV is useful and studies have shown it to be more effective than nystatin and equally effective to clotrimazole and oral ketoconazole.[5]

GV solution (0.5% or less) can be applied directly to the affected areas or 5ml of solution can be used as a 2 minute rinse in the mouth, twice daily for 14 days.

3. Leg Ulcers

GV application can be used to stabilise eschars and scabs in superficial wounds. In addition to its antibacterial action, it discourages granulation tissue formation and seals the wound. This simplifies wound care and reduces the need for bulky and expensive dressings. A study of 111 wounds in a geriatric population treated with 1% GV solution daily, reported complete healing in 103 without complications.[6]

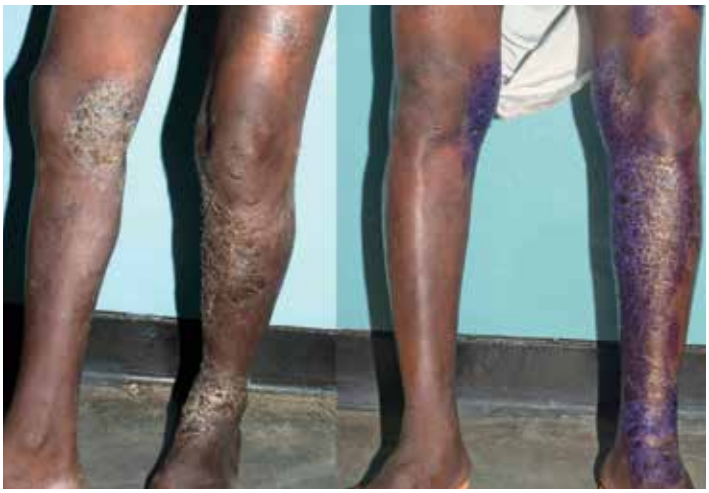

Fig 3. Infected eczema before and after Gentian violet solution applied daily for 1 week

4. Burns

GV has been used extensively in the management of burns during the pre- antibiotic era. It still has a significant role in resource poor settings. A study from Bilaspur, India was conducted in a randomised prospective controlled manner on 400 patients. Healing occurred in 6-8 weeks without severe sepsis or the need for skin grafting.[7]

5. Infected eczema

GV solution may be used to treat infective eczema, either alone or under topical steroids. In addition to its antimicrobial effect, it has been shown in an experimental skin irritation model to produce significant reductions in corneocyte dehydration, barrier damage and irritative erythema.[8]

6. Other uses

Based on its antimicrobial, anti-inflammatory and anti-angiogenic actions, it is proposed that GV may also be used in a number of novel conditions,[9] including:

- MRSA otitis media and nasal carriage (GV applied to external ear canal and nasal skin, not mucosa)
- Oral hairy leucoplakia
- Ulcerated infantile haemangiomas
- Plantar warts
- Prurigo nodules
- Cutaneous melanoma metastases

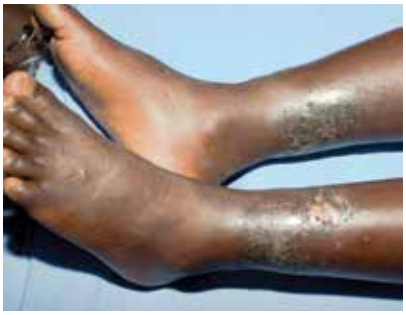

Fig 4. Insect bites – eczematised and impetiginized. For Gentian violet solution daily with a topical steroid over this (if available)

Side-effects

With over 100 years of clinical experience, GV has been shown to be a safe treatment. GV has been applied to the umbilical stumps of millions of newborn babies and added to blood transfusions in hundreds of thousands of South American patients to prevent the transmission of Chagas' disease.

Apart from staining of the skin, observed side-effects are linked to a small number of case reports

1. Staining of skin, bedding and clothing

This has been a major disincentive for the use of this agent. It may, however, be an important part of the antibacterial mechanism and apparent superiority of GV over other antiseptics which are short lasting because of inactivation by blood, pus and other organic materials. The binding of the water soluble dye to tissues may be the reason why a single or infrequent (eg once a week) applications of GV are effective in some situations. Another positive aspect of staining is the measure of treatment compliance. Staining is less obvious in dark skin types. The possibility of tattooing of deeper ulcerated lesions are treated has been described but this seems to be rare.

2. Ulceration and necrosis

Oral and skin ulceration have occasionally been reported. This often reflects inappropriate use, high concentrations of the solution (water may evaporate from open bottles) or undissolved powder.

3. Ototoxicity

Care must be taken when applying GV to the external ear canal to ensure that it does not reach the middle ear. In the event of a perforated tympanic membrane, vestibular damage may occur. If GV accidentally reaches the middle ear, rinsing with normal saline is advised.

4. Ophthalmic toxicity

Care must be taken to avoid contact with the eye, however, very dilute GV may be used to visualise the capsule in cataract surgery.

5. Contact dermatitis

GV is a weak sensitiser and reports of contact allergic dermatitis are few. Irritant reactions may occur, especially with higher concentrations in occluded zones such as the flexures.

6. Carcinogenicity

Some decades ago carcinogenicity was reported in mice which led to reduced use in humans. The banning of such an effective and low cost agent has not found significant support but, unsurprisingly, has been of some concern to various regulatory bodies. Conversely, more recent studies have shown that GV may have antineoplastic effects.[9] In clinical use for over one hundred years and in millions of patients, there have been no reports of carcinogenicity.

Conclusion

GV is a highly effective antibacterial and anti-candidal agent. It also has anti-inflammatory and possibly antineoplastic properties. Because of its low cost and ease of application, its use should be considered in resource poor settings.

Continued overleaf…

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If you have any interest in medical care, whether in well established medical centres or in a rural health centre then the Community Dermatology Journal is for you. It brings up to date, relevant information on the diagnosis and treatment of skin disease and is particularly for health workers in developing countries.

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DERMLINK

Dermlink is the ILDS/IFD scheme that seeks to support applications from member societies to undertake initiatives that help patients with skin disease in underserved parts of the world. Small grants of between $3000-$5000 US are awarded in March/April each year. We welcome applications from anywhere in the world. All these applications need to be supported by an ILDS member society. **Application forms can be found on the IFD website or obtained from admin@ilds.org."**

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Further details from http://www.ifd.org

The British Dermatological Nursing Group (BDNG) have some useful resources available on their website that can be found at /www.bdng.org.uk/resources/ and are open access for whoever wishes to use them.

Gentian Violet *continued from p18*

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