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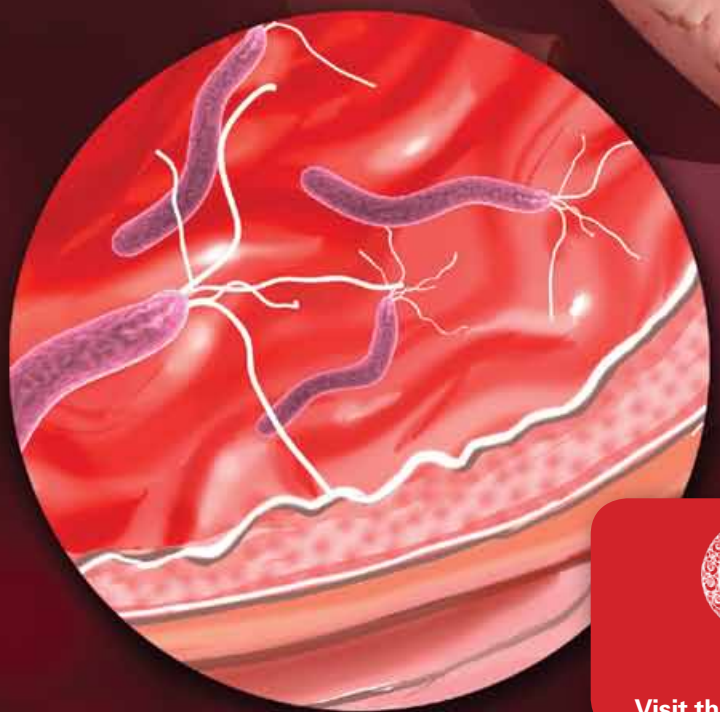

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Editorial

The Nobel Prize for Medicine was awarded to the discovery of *Helicobacter pylori* in 2005 by Dr Robin Warren and Dr Barry Marshall. As the bacterium was classified as a carcinogen by the International Agency for Research on Cancer, the general public was much aware of the consequences. Five years down the road, we saw great improvements in diagnosis and treatment of the infection. Unfortunately, we are still waiting for a vaccine to be developed, if it will ever be successful.

The prevalence of the infection is decreasing in Hong Kong, but remains high in most parts of China. In Hong Kong, we are fortunate to note that the success rate of standard treatment for *Helicobacter pylori* infection is still high, as opposed to some other countries. The standard regimes are still the most cost-effective regimes up to now. Careful monitoring of the prevalence of drug resistance of *Helicobacter pylori* in Hong Kong is important to ensure we are using the right drug for the infection.

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Update on Management of *Helicobacter pylori* Infection

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Helicobacter pylori (幽門螺旋菌), treatment (治療方案)

Introduction

In 2 years' time we shall celebrate the 30th anniversary of the rediscovery of *Helicobacter pylori*. During the past 28 years, there has been a monumental growth of research on *H pylori*, but the interest is somehow diminishing in recent years. The major reasons include both the natural declining prevalence of *H pylori* infection around the world, as well as the availability of numerous tests and treatment approaches for our patients. This paper tries to summarize some of the up-to-date issues related to *H pylori* infection.

Diagnosis

Although most doctors are familiar with the diagnostic methods for *H pylori* infection, there are still a lot of mistakes. In essence, the choice of tests for pre-treated or never-treated patients consists of noninvasive tests and invasive tests. The noninvasive tests include carbon-13 urea breath test, serology for anti-*H pylori* antibody, stool for *H pylori* antigen, and urine for anti-*H pylori* antibody. The invasive tests used during an upper endoscopy and biopsy include rapid urease test, histology, culture, and polymerase chain reaction, with the later two being rarely performed.

The noninvasive tests of choice include urea breath test and stool antigen test. Serology tests rely on the accuracy of the test kit, and not all test kits perform with the same accuracy. These tests are based on enzyme-linked immunosorbent assay (ELISA) that requires the use of antigen epitopes from *H pylori* during production. Unfortunately, *H pylori* from different countries or races have very diverse genomic variation. Thus, some of the tests manufactured in USA or Europe, which are based on Caucasian *H pylori* strains, yield a very low accuracy for testing in Hong Kong.[1,2] The other form of serology test is the whole blood near patient test. The test uses only one drop of blood for placement onto the test kit, and the doctor can read the result within minutes in the office. It has the same principle as serology test, and the accuracy must be locally validated.

The invasive tests of choice include the rapid urease test and histology. Since the density of *H pylori* in the gastric antrum is generally the highest in patients without drug use, an antral biopsy is usually taken. However, in patients on proton pump inhibitors (PPIs), the density of *H pylori* is reduced in the antrum and increased in the body and fundus. Therefore, patients on PPIs should have biopsy from both the antrum and body of the stomach to increase the accuracy of testing.

Before performing the tests, patients should be asked about the recent intake of PPIs and antibiotics. False negative tests may result from these drugs that suppress bacterial growth. Nowadays, more and more patients are already receiving long-term PPI therapy that cannot be withheld for various reasons. In this case, all tests except the serology and urine tests will not be accurate. A locally validated serology test should be used.

Post-treatment testing is generally performed 4 to 8 weeks after stopping all PPIs and antibiotics, the longer the better. Hence, if there is no urgent need to perform the test, the author would recommend testing at 8 weeks after stopping the treatment. For patients who have used both bismuth and PPIs in the treatment regime, which is most common in second-line treatment of *H pylori* infection, the author would recommend testing 8 to 12 weeks after stopping the

treatment, preferably at 12 weeks. Serology test is never to be used in post-treatment testing, as the antibody level will only be decreasing slowly despite successful treatment. In post-treatment testing for patients who require long-term PPI therapy, we still should not use serology test for the above-mentioned reason. There is no single best method for these patients, and clinical judgement is required in each scenario.

Treatment

For years, triple therapy has been the gold standard for first-line treatment of *H pylori* infection. There are several recent guidelines with detailed description of the different regimens.[3-5] In principle, the eradication rate with any first-line regimen should be above 90%.

The antibiotics used in the first-line regimens will be any two out of these three: amoxicillin, clarithromycin and metronidazole. With a high prevalence of metronidazole resistance in most parts of the world, the agent is usually not used in first-line treatment. Hence, the best regimen is probably PPI plus amoxicillin plus clarithromycin. However, prescription of clarithromycin for mostly respiratory tract infections has increased rapidly in Europe, leading to a rapid drop in eradication rate with clarithromycin-containing regimens to below 80%. Hence, some studies are now exploring the use of other antibiotics such as levofloxacin in place of clarithromycin. However, in a large local study recently conducted by the author and colleagues, the combination of PPI plus amoxicillin plus clarithromycin is still found to be the best regimen with an eradication rate of 92.7%. The use of PPI plus amoxicillin plus levofloxacin 500 mg daily showed an eradication rate of 85.3% only ($p<0.05$).[6]

For second-line treatment of *H pylori* infection, the classical quadruple therapy is still the regimen of choice. Our local study showed that the classical quadruple therapy with PPI, bismuth subcitrate 240 mg bid, metronidazole 400 mg tds and tetracycline 500 mg qds has an eradication rate of 88%. The use of PPI plus bismuth plus amoxicillin 1,000 mg bid and levofloxacin 500 mg bid has an eradication rate of only 73% ($p<0.05$).[7] It is fortunate that our rates of resistance to the commonly used antibiotics are not that high, so that our classical first- and second-line regimens are still in good use.

In this regard, it is of importance to emphasize good compliance during both first- and second-line treatment. Most cases of treatment discontinuation are usually due to minor adverse effects such as loose stool, altered taste, etc. It is important to encourage patients to complete the whole course of treatment, and reassure them that these minor adverse effects are tolerable and will disappear after completing the regimen. It is still important to be on the alert for pseudo-membranous colitis due to the use of amoxicillin. Patients should be reminded to contact the physician urgently if there is profuse watery diarrhoea during the course of treatment.

Conclusion

Although several new regimens have been proposed for the treatment of *H pylori* infection, the classical triple and quadruple therapy are still the best for first- and second-line treatment, respectively. It is important to ensure patient compliance to achieve high eradication rate.

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The Use of Laser and Light Source for the Treatment of Freckles and Lentigo in Asians

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Key words:
Asian (亞洲人), lentigo (斑痣), treatment (治療)

Introduction

Photoageing in Asians differ from that in Caucasians in that pigmentary changes tend to occur with a higher incidence than skin wrinkling in Asians. Chung recently found both pigmentary changes and wrinkling to be major features of photoageing in Asians.[1] However, moderate to severe wrinkling becomes apparent only at about 50 years of age, which is a decade or two later than age-matched Caucasians. Acquired pigmentary conditions such as freckles and lentigo are two of the most common cosmetic conditions encountered in any dermatology practice in Asia.

Lasers and light sources have been used for the treatment of freckles and lentigo in the last several decades. However, in Asians, there is a higher epidermal melanin content, and the risk of postinflammatory hyperpigmentation (PIH) is the main concern.

The objective of this article is to review basic light and tissue interaction, and the use of laser and light source for the treatment of these two common pigmentary conditions in Asians.

Light Radiation and Tissue Interaction: Concept of Selective Photothermolysis

The interaction of light radiation with skin is determined by the optical properties of skin constituents and the wavelength of the incident light.[2] Melanin, haemoglobin and water are the three main chromophores (targets of light radiation) in skin, and different chromophores absorb radiation of specific wavelengths. Melanin absorbs radiation with wavelengths between 320 nm and 1,000 nm. Water is the dominant chromophore for radiation of higher wavelengths (>1,000 nm), and haemoglobin is the main chromophore for green and yellow light. Selective tissue damage can be achieved using laser light with wavelengths that match those of the skin chromophores.[3]

"Pigmentary changes tend to occur with a higher incidence than skin wrinkling in Asians"

Laser light can produce photothermal and photomechanical reactions in skin. Photothermal interactions are derived directly from heat that is generated by laser light. The extent of thermal damage is directly proportional to the amount of heat that is dissipated from the target site to the surrounding tissue. As it requires time for heat to diffuse outward and cause thermal damage, the extent of that damage depends upon the rate of heating. If the exposure time is shorter than the target's thermal relaxation time (defined as the time required for a target to cool from the temperature achieved immediately after laser irradiation to half of that temperature), then heat will not be able to diffuse. This limits the thermal damage to the target site. Tissue damage can be

Table 1. Laser vs IPL

Laser	IPL
• Monochromatic (fixed wavelength) • Collimated (coherent) • More specific • Fewer treatment sessions • Associated with down time • More expensive	• Polychromatic (fixed spectrum of wavelengths) • Divergent (incoherent) • Less specific and acts on several targets at the same time • Penetrates different depths • More treatment sessions necessary • No down time • Less expensive • Larger spot size

IPL = intense pulsed light

Table 2. Lasers and light source for the treatment of freckles and lentigo

- QS/long pulsed 532 nm Nd:YAG laser
- Long pulsed 532 nm KTP
- Long pulsed 595 nm pulsed dye laser
- QS/long pulsed ruby laser
- QS/long pulsed Alexandrite laser
- QS/long pulsed 1064 nm Nd:YAG laser
- Intense pulsed light
- Fractional resurfacing

restricted to the target site by using a laser with a wavelength that is specifically absorbed by the target tissue, where it is converted to heat, resulting in thermal injury. As the thermal relaxation time of an object is inversely related to its size, lasers with ultrashort pulses that emit high energy have been developed. For example, in the case of melanin, nanosecond pulses are needed to rupture the melanosomes. This concept of selective photothermolysis has revolutionized the treatment of skin conditions.[3] In photomechanical interactions, high-energy pulsed lasers disperse the target tissue by rapid thermal expansion and local vaporization. As the laser pulse duration is shorter than the thermal relaxation time of the target, a temperature gradient is created between the target and its surrounding tissue. When the temperature gradient collapses, it generates localized shockwaves that cause the fragmentation of its targets.

While lasers have been used for the treatment of cutaneous lesions, intense pulsed light (IPL) source has gained much popularity in recent years. Unlike laser which is fixed wavelength radiation, IPL consists of a fixed spectrum of wavelengths and can target different chromophobes. Details of their differences are listed in Table 1.

Freckles and Lentigines

Many lasers and light sources can be used for the treatment of freckles and lentigo. (Table 2) Q-switched (QS) lasers employ quality switching, which refers to the use of techniques such as an electromagnetic switch to stop the laser from abruptly passing through the cavity. The blockage is then suddenly removed, allowing the production of pulses with short durations (in the nanosecond range) and high energy (1,000,000 W/cm^2).

QS lasers can be most effective for the treatment of freckles and lentigines especially in light-skinned patients. Complete or near complete clearance can be achieved after even one treatment. The main disadvantage associated with QS lasers is the down time, with redness and swelling lasting 1 to 2 days and crusting that can persist for about a week. Furthermore, PIH can occur among Asians as QS lasers produce not just a photothermal effect, but also photomechanical injury, leading to an excessive degree of inflammation and therefore subsequent PIH. A previous study indicated such risk to be higher among patients with lentigo as compared to those with mainly freckles.[4]

IPL has been used to reduce the down time and potential complication associated with the use of QS lasers; it can be most effective especially when patients want to improve other components of their skin, such as pore size and facial

Figure 1. With good contrast, significant lightening after one IPL treatment session

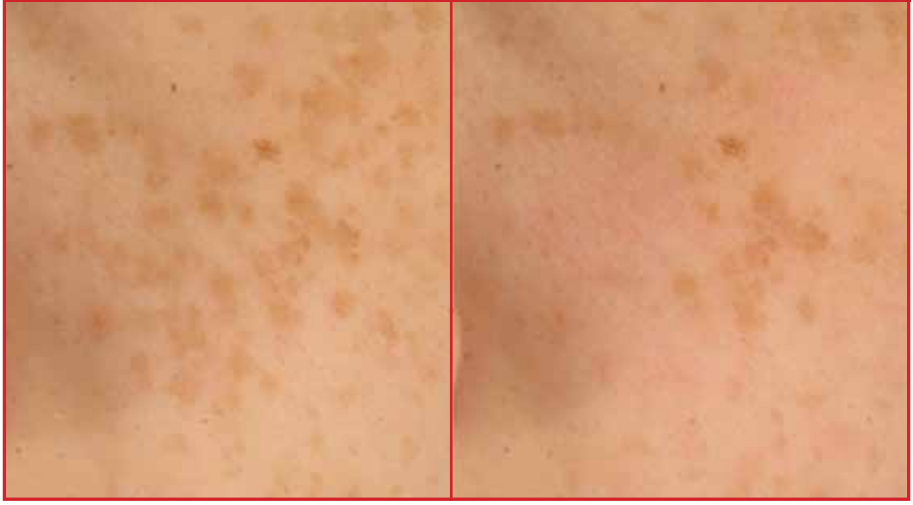
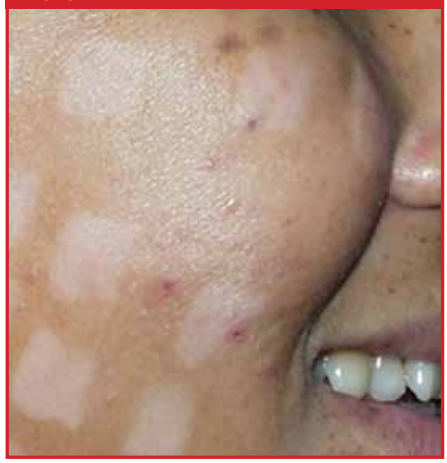


Figure 2. Low contrast leads to above-threshold injury and development of hypopigmentation



telangiectasia.[5] However, for dark-skinned patients, the lesser contrast between the normal and lesional skin implies that care should be taken to avoid potential complication such as hypo- or hyperpigmentation. (Figures 1 and 2) If the contrast is low (light-coloured lentigines in dark-skinned patients), it would be best to choose a small spot size pigmented laser over IPL to avoid unnecessary injury to the surrounding normal skin.

Apart from QS lasers, long pulsed (LP) pigmented lasers can also be used for the treatment of freckles and lentigines. While the pulse duration of QS lasers (nanosecond) matches the thermal relaxation time of the melanosomes, the pulse duration of LP lasers is much longer (millisecond), which matches the thermal relaxation time of the epidermis. With a longer pulse duration, LP pigmented lasers generate mainly a photothermal effect but not photomechanical effect. As a result, it is particularly effective for the treatment of freckles and lentigo among Asians, with previous studies indicating a lower risk of PIH than QS lasers.[6] It is also associated with less down time, but several treatment sessions are required to achieve complete or near complete clearance. Compression of the skin surface by the flat glass window on the handpiece leads to emptying of blood vessels and, therefore, reduces the risks of dermal vascular damage by laser and subsequent bruising and PIH.[7]

In a recent retrospective study of 40 patients with freckles and lentigo treated with four different lasers, small spot size LP 532 nm KTP laser with compression was associated with better efficacy and lower complication risk than large spot size LP 595 pulsed dye laser with compression, which in turn performed better than QS 532 nm Nd:YAG laser and large spot size 755 LP Alexandrite lasers without compression.[8] Similar to any other retrospective study, there are limitations associated with such findings. Nonetheless, this study provided data indicating the type of optimal device to be considered in the treatment of freckles and lentigo in Asians.

In conclusion, by using the appropriate device and parameters, freckles and lentigo can be effectively treated among Asians.

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Case Study: A 75-year-old Gentleman With Recurrent Palpitation

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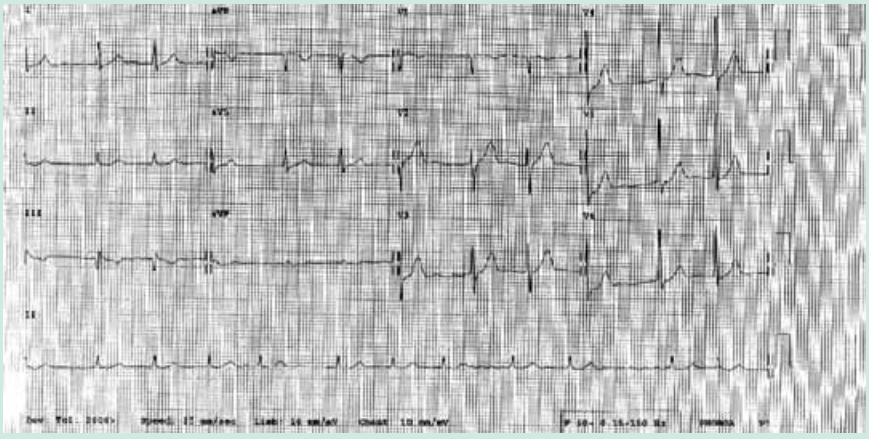
Key words:
Atrial fibrillation (AF) (心房纖顫), embolism (栓塞), anticoagulation agent (抗凝血藥物)

A 75-year-old gentleman is seen by his family doctor for recurrent palpitations in the past year. The palpitations are not associated with chest pain or syncope. The patient has a history of hypertension and diabetes mellitus. Thyroid function tests and echocardiogram are normal. His doctor suggests that he should be treated with warfarin. You are seen to provide a second opinion on the role of warfarin.

The ECG tracing is shown.

1. **What is the absolute risk of stroke without warfarin (% per year)?**
   A. 3% B. 5% C. 7% D.9%
2. **What is the percent risk reduction of stroke while on warfarin (relative benefit)?**
   A. 20% B. 40% C. 60% D. 80%
3. **Which of the following information is helpful for calculating the risk of bleeding?**
   A. Presence of hepatic disease B. Presence of anaemia
   C. Prior stroke D. Reduced platelet count E. All of the above



Answers: The ECG tracing shows atrial fibrillation. 1. B 2. C 3. E

Atrial fibrillation (AF) is a common arrhythmia which carries significant mortality and morbidity. The lifetime risk for the development of AF is 1 in 4 for men and women 40 years of age or older. Systemic embolization, especially ischaemic stroke, is the most dreadful complication. AF-related strokes tend to be especially severe and disabling, with 1-year mortality of about 50%. Long-term antithrombotic therapy with either anticoagulants (eg, warfarin) or antiplatelet agents (eg, aspirin) helps lower the risk. Anticoagulant therapy is far more effective and is therefore the preferred option in most but the lowest-risk patients. However, anticoagulant therapy may also cause significant bleeding. The risk and benefit of antithrombotic therapy should be carefully assessed, and the choice of therapy should be individualized.

Table 1. $CHADS_2$ score for assessment of risk of stroke and effect of warfarin

$CHADS_2$ score	% stroke/year with warfarin	% stroke/year without warfarin	% reduction with warfarin
0	0.25	0.49	49
1	0.72	1.52	53
2	1.27	2.50	49
3	2.2	5.27	58
4	2.35	6.02	61
5 or 6	4.6	6.88	33

Adapted from references 1 and 2.

The $CHADS_2$ score is used to assess the absolute risk of stroke and the effect of warfarin in patients with nonvalvular AF.[1,2] (Table 1) The $CHADS_2$ is formed by assigning 1 point each for the presence of **c**ongestive heart failure, **h**ypertension, **a**ge 75 years or older, and **d**iabetes mellitus, and by assigning 2 points for history of stroke or transient ischaemic attack. Patients are considered to be at low risk with a score of 0, at intermediate risk with a score of 1 or 2, and at high risk with a score ≥3.

The patient has a score of 3 (age, hypertension, and diabetes mellitus). Thus, his risk of stroke will be 5.27% per year without warfarin. The risk will be reduced to 2.2% per year with warfarin. The percentage risk reduction is 58%.

Treatment with warfarin may carry a risk of major bleeding of about 2.2% per year. The risk will depend on an individual's risk factors. The risk of major bleeding while on warfarin can be calculated by the $HEMORR_2HAGES$ score.[3] (Table 2) Risk factors included in the score are **h**epatic or renal disease, **e**thanol use, **m**alignancy, **o**lder age (age >75 years), **r**educed platelet count or function, **r**e-bleeding, **h**ypertension (uncontrolled), **a**naemia, **g**enetic factors, **e**levated risk of fall, and **s**troke. The score assigns 2 points for a prior bleed and 1 point for each of the other risk factors.

Table 2. $HEMORR_2HAGES$ score for assessment of risk of major bleeding while on warfarin

$HEMORR_2HAGES$ score	% bleeding per year while on warfarin
0	1.9
1	2.5
2	5.3
3	8.4
4	10.4
≥5	12.3

Adapted from reference 3.

The following points are explained to the patient:

1. The ECG shows AF.
2. The estimated risk of stroke is about 5% per year. Warfarin with a target International Normalized Ratio (INR) of 2 to 3 cuts down the risk to about 2% per year. The therapeutic effects of anticoagulation are optimized only within a very narrow INR range of 2 to 3.
3. The need for regular blood monitoring and the awareness of food-drugs interactions are emphasized.

The patient requests for alternative choices to substitute warfarin.

What are the roles of the following options?

A. Aspirin 160 mg daily
B. Aspirin 100 mg daily plus clopidogrel 75 mg daily
C. Aspirin 325 mg daily plus low-dose warfarin 1.25 mg daily or target INR 1.2 to 1.5
D. Dabigatran 110 mg bid
E. Dabigatran 150 mg bid

Two-third of strokes due to AF is preventable with a vitamin K antagonist (VKA) (target INR 2–3). A meta-analysis showed that adjusted-dose warfarin results in a reduction in ischaemic stroke and all-cause mortality.[4] Anticoagulation with a VKA is recommended for medium- and high-risk patients. However, warfarin has a very narrow therapeutic window. While over-anticoagulation increases the risk of bleeding, under-anticoagulation reduces the stroke prevention value. Moreover, even in well-controlled environments such as clinical trials, INR values are within therapeutic range in only 60% to 70% of the time. INR control tends to be much lower in clinical practice.

The patient suffers from nonvalvular AF with a $CHADS_2$ score of 3 (age, hypertension, diabetes mellitus), which indicates he is at high risk of stroke.

An ideal alternative drug will be one with high efficacy, low bleeding risk, no laboratory monitoring required, no drug or dietary interaction, and simple daily dosing. (Table 3)

A. Aspirin 160 mg daily

Aspirin reduces the risk of stroke by one-third, but the risk reduction is mostly limited to minor strokes. The risk of major bleeding is about 1.3% per year. The low efficacy limits its role in patients at high risk of stroke.

B. Aspirin 100 mg daily plus clopidogrel 75 mg daily

When aspirin plus clopidogrel is compared with warfarin, the combination therapy showed inferior efficacy with no better safety profile (similar major bleeding risk).[5] Therefore, in an AF patient for whom oral anticoagulation is contraindicated due to a high risk of bleeding, dual antiplatelet therapy should not be considered as an alternative.

C. Aspirin 325 mg daily plus low-dose warfarin 1.25 mg daily or target INR 1.2 to 1.5

Low-dose warfarin plus aspirin is associated with a much higher morbidity and mortality than adjusted-dose warfarin (low efficacy), with a similar bleeding risk. Therefore, this combination is not optimal for high-risk patients.

D. Dabigatran 110 mg bid

Dabigatran etexilate is a novel, small molecule, reversible, direct thrombin inhibitor. Potent antithrombotic effects are achieved with direct thrombin inhibitors as they specifically block

Table 3. Efficacy and safety of various anticoagulation options		
Options	**Efficacy compared with warfarin**	**Safety compared with warfarin**
Aspirin	Inferior	Superior
Aspirin + clopidogrel	Inferior	Similar
Aspirin + low-dose warfarin	Inferior	Similar
Dabigatran 110 mg bid	Noninferior	Superior
Dabigatran 150 mg bid	Superior	Similar

the activity of thrombin (both free and clot-bound), the central enzyme in the process responsible for clot (thrombus) formation. It has a rapid onset on action, and a predictable and consistent anticoagulant effect. Dabigatran is less susceptible to dietary and drug interactions and to genetic polymorphisms that affect warfarin. Furthermore, neither anticoagulation monitoring nor dose adjustments are necessary with dabigatran.

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, 18,113 patients with AF and a risk of stroke were studied.[6] The median duration of follow-up was 2 years. Dabigatran 110 mg bid met the criteria for noninferiority compared with adjusted-dose warfarin, with a significantly reduced risk of major bleeding.

E. Dabigatran 150 mg bid

The same trial showed that dabigatran 150 mg bid was superior to warfarin in systemic embolism prevention, with a similar major bleeding risk when compared with warfarin.

The patient may consider dabigatran 110 mg bid if he has an increased risk of bleeding (eg, concurrent use of nonsteroidal anti-inflammatory drugs), as it provides similar systemic embolism prevention as warfarin with a lower bleeding risk. If he has an increased risk of thromboembolism (eg, prior embolic event), dabigatran 150 mg bid provides superior protection against systemic embolism without increasing major bleeding risks.

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CME FOR MEDICAL DOCTORS

Oct 3, 2010 SUNDAY SYMPOSIUM 11:00 am – 4:30 pm Lunch 1:00 pm – 2:00 pm

Cardiac Markers
Dr Leung Wai Suen, Ablert（梁偉宣醫生） Specialist in Cardiology
MBBS, MRCP, FHKAM (Med), FHKCP, FRCP (Edin), FRCP (Glasg)

ROMA and the Role of Biomarkers in Diagnosis of Patients with Pelvic Mass – HE4
Dr Jaganathan Sicken MD, MBA Manager, Regional Scientific Affairs, Abbott Laboratories Ltd

NGAL Marker
Dr Tam Kwok Kuen, Vincent（譚國權醫生） Specialist in Nephrology

Personalized Therapy of Lung Cancer
Professor Mok Shu Kam, Tony（莫樹錦教授） Specialist in Medical Oncology

Does DHA Help Improve Cognitive Development in Children?
Does Chelation Work?
Dr Fung Yee Leung, Wilson（馮宜亮醫生） Specialist in Paediatrics

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Advances in Chemotherapy – Knowing more for General Practice
Dr Wong Shun Man, Irene（黃舜雯醫生） Specialist in Clinical Oncology
MB,BS (HK), FRCR (UK), FHKCR, FHKAM (Radiology)

Targeted Therapy – The Basics
Dr Chan Tze Mun（陳子敏醫生） Specialist in Clinical Oncology
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Radiotherapy Revolutionized with Modern Technologies
Dr Cheung Ming Chee, Michael（張明智醫生） Specialist in Clinical Oncology
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Monotherapy or Combination therapy?

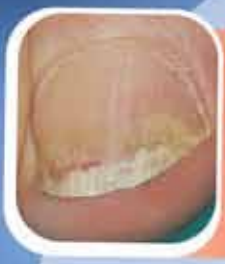
Consensus Guideline on Management of Onychomycosis [1]

Criteria	Topical	Oral	Combination	Nail removal
1. Involvement < 50% nail plate	✓			
2. Minimum number (3 or 4) of nails involved	✓			
3. Unable to swallow pills	✓			
4. No melanonychia	✓			
5. Known drug interaction/allergy	✓			
6. Mycological exam – causative fungi known drug interaction/allergy	✓	✓	✓	
7. >50% nail involvement		✓	✓	
8. Matrix area involvement (25.84% of cases in the recent EUROO study)		✓	✓	
9. Topical drug penetration suboptimal		✓	✓*	✓

*After nail removal

Drug of Choice for Treating Onychomycosis

- Highly efficacious in treating onychomycosis
- Excellent safety profile
- Require no baseline liver function test
- Simple, once-weekly usage

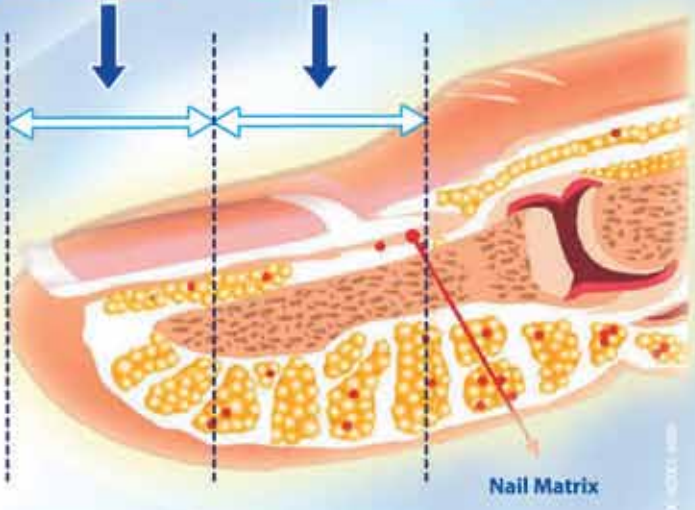


Loceryl Nail Lacquer Monotherapy

Onychomycosis < 50% area of nail plate and without matrix involvement

Loceryl Nail Lacquer + oral antifungal Combination therapy

Onychomycosis > 50% area of nail plate or with matrix involvement



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