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Editorial Board

Antimicrobial resistance — the local scenario

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Introduction

Bacteria resistant to antibiotics began to appear soon after the introduction of mass-scale production of penicillin in the 1940s. As new classes of antibiotics were introduced, bacteria found ways to resist these antibiotics, either through mutations or acquisition of resistant gene determinants that encode resistance mechanism to specific target sites on different bacteria. These resistant strains become selected out in the presence of antibiotic exposure and become dominant. Some of these resistant bacteria are listed in Table 1.

Antibiotic resistance makes infections more difficult to treat; increases the length of hospitalisation and severity of illness; and lengthens the period of infectivity. This translates to increase in direct and indirect costs and a higher morbidity and mortality.

Methicillin-resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important nosocomial pathogen and prevalent among hospitals in Hong Kong and in the Asia Pacific region [2-3]. Worldwide, there are concerns with the emergence of MRSA in the community setting (CA-MRSA) [4] and also the development of vancomycin resistance in MRSA [5-6]. The CA-MRSA isolates are characterised by two unique genes: the type IVa SCC*mec* cassette and the panton-valentine leukocidin (PVL) locus [4]. These strains characteristically cause necrotising lesions in skin and soft tissues.

The contemporary MRSA causing bacteraemia in four major Hong Kong hospitals belong to three clonal complexes CC5, CC45 and CC239 [7]. The most prevalent clonal complex, CC239, included isolates with a few major pulsotypes, as previously identified as PFGE types A-E, and H [7]. These isolates belonged to SCCmec type III, had multi-locus sequence type (MLST) ST239; and were multidrug-resistant to tetracycline, erythromycin, clindamycin, gentamicin, tobramycin, and ciprofloxacin. This clone was characterised by a number of surface adhesions/proteins, namely, leukocidin E, fibrinogen, fibronectin binding protein B, and hyaluronidase. MRSA that belonged to CC239 had been suggested to be widespread in many countries in SE Asia. This lineage included numerous clones of the British epidemic MRSA (eMRSA1,-4,-7,-9,-11), Brazilian, Portuguese, and Viennese clones. The next prevalent MRSA belonged to PFGE type F and G (ST 45 and 45 respectively) and these have resistance profiles of TEGToCi and TECi respectively. These PFGE type strains carry exotoxin genes to enterotoxins C, G, I, the toxic shock syndrome toxin (TSST-1) and enterotoxins G, I, and J, respectively. The presence of these genes may thus reflect their different propensity to colonise or cause invasive disease by toxin production.

Lastly, a unique PFGE type I with ST398 has SCC*mec* type 4a, typical to that of CA-MRSA. The only published case report of CA-MRSA in Hong Kong was in 2004 from a case of MRSA belonging to ST80 [8]. Although, MRSA with ST80 was not present in the bacteraemic study, a small number of isolates with SCC*mec* IVa, resistant to oxacillin and fusidic acid only, with unique MLST sequence types, dated back in 2000/1, were identified. Screening of the MRSA by Scc*mec* typing and MLST may be necessary to indicate the extent of CA-MRSA in our locality [9].

Fluoroquinolone-resistant *Streptococcus pneumoniae*

Fluoroquinolone is an important class of antibiotics and in western countries, has been incorporated in guidelines for the empiric treatment of community-acquired pneumonia [10].

High prevalence of levofloxacin nonsusceptibility (MIC, ≥4.0 μg/ml) of 13% has been documented in Hong Kong in 2001 [11] and its spread hypothesised to be a result of clonal dissemination of the Spain 23F.

The level of fluoroquinolone resistance increases as more amino acids are substituted by stepwise mutations in the quinolone resistance-determining regions (QRDRs) of the genes encoding the A and B subunits of DNA gyrase and topoisomerase IV, *parC* and *gyrA* genes. Recently, a rapid method, using PCR, restriction fragment length and single strand conformation polymorphism (SSCP), was applied to screen for mutations of fluoroquinolone-resistance determinants from Hong Kong isolates of *Streptococcus pneumoniae* [12]. It was shown that the commonest SSCP profile included 40% strains with 2 amino acid substitutions in ParC (Lys-137-Asn) and ParE (Ile-460-Val) genes, whilst 10% (10) of these isolates which were clearly resistant to levofloxacin with MIC ≥16 μg/ml, and had amino acid substitutions at GyrA and ParE (± ParC) genes. This indicated that the majority of our isolates only require a second mutation (at QRDR of *Gyr*A) to become resistant to levofloxacin, and the majority of these strains were also penicillin-nonsusceptible, and belong to the prevalent Spanish-23F-1 clone.

Local Antibiotic Susceptibilities of Bacterial Isolates from Community

Antibiotics are frequently prescribed and administered before the knowledge of the bacterial culture and antibiotic susceptibility results. Local surveillance data on the organisms involved and their susceptibility patterns are essential to guide the best choice of treatment.

In a study performed by Ling et al., 2003 [13], her group examined 4741 specimens obtained from 3977 patients by 89 general practitioners during a sixteen-months' period from July 2000 in Hong Kong. Specimens were collected from patients suspected of infection and the organisms' antimicrobial susceptibility patterns were determined. Update data for 2006 is available from the Antibiotic Resistance Surveillance initiated in July 1999 by the Department of Health, and is published on the website: http://www.chp.gov.hk/datad09e.html?lang=en&cat=4&dns_sumID=84&id=45&pid=26&ppid=10.

In contrast, a multicentre antimicrobial susceptibility survey of 2,099 gram-negative bacilli from patients with community-acquired infections in China and Hong Kong in 2002-2003 showed alarming resistance rates to ciprofloxacin of 40.8%, 32.3% for gentamicin, and 14.7% for cefotaxime [14]. The rates of extended-spectrum B-lactamase (ESBL) production were 16% for *Escherichia coli* and 17% for *Klebsiella sp.* It is likely that the Ctx-M-3 and Ctx-M-14 ESBL genes, which are widely disseminated in Asia [15], also account for the spread of ESBL resistance in community gram negative isolates.

Mechanisms of Resistance to Carbapenems in *Pseudomonas aeruginosa* and *Acinetobacters*

Although the antimicrobial resistance among community isolates of *Pseudomonas aeruginosa* is low [13], multidrug resistant *Pseudomonas aeruginosa* (MRPA) has been a concern in some hospitals in Hong Kong. Carbapenem resistance in *Pseudomonas aeruginosa* has been elucidated [16] and their mechanisms of resistance complex. A combination of mechanisms may be involved (Table 2).

Likewise, *Acinetobacter spp.* especially, *A. baumanii,* is intrinsically resistant to ampicillin, first and second generation cephalosporins, and can become multi-drug resistant. Often, the drugs of choice for treatment include ampicillin-sulbactam, fluoroquinolones, aminoglycosides and carbapenems. However, in a recent study that compared the antibiotic

susceptibilities of these isolates in Hong Kong and Shanghai [17], resistance rates ranged between 13.5% for ampicillin sulbactam to 69.1% to both ampicillin-sulbactam and ciprofloxacin among Shanghai isolates. Carbapenam resistance was as high as 6.3% in this study. In the United Kingdom, multi-resistant *Acinetobacter spp.*, such as the carbapenemase-producing OXA-23 clones, had been widespread in Southern England [18]. Strains of these clones are often susceptible only to minocycline, or polymyxins, and variably to amikacin. These carbapenem-and multi-resistant strains pose a real challenge to treatment, especially in the intensive care units, requiring combinations of minocycline, colistin, or nebulised, polymyxins, and rifampicin.

The development of antimicrobial resistance is inevitable when antimicrobials are used. The aim is to minimise the selective environment for these bacterial pathogens to develop resistance by optimising the antimicrobial usage (with appropriate dosing and maximise eradication) and reducing the potential for any genetic variability and spread of these organisms.

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Table 1 Emergence of Antibiotic Resistance [1]

Year	Resistant Organism
1961	Penicillin-resistant *Staphylococcus aureus*
1965	Ampicillin-resistant *E. coli*
1967	Penicillin-resistant *Streptococcus pneumoniae*

1980s Methicillin-resistant *Staphylococcus aureus* (MRSA)
1983 Extended-spectrum B-lactamase *E. coli*
1988 Vancomycin-resistant enterococci (VRE)
1993 Multi-resistant *Vibrio cholerae*
1998 Vancomycin-resistant *Staphylococcus aureus* (VRSA)
1999 Community-acquired MRSA
2001 Carbapenem-resistant *E. coli*
2002 Fluoroquinolone-resistant *Streptococcus pneumoniae*

Table 2 Mechanisms of Resistance to Carbapenems in *Pseudomonas aeruginosa*

- ↓ Porin expression, OprD
- ↑ Chromosomal AmpC cephalosporinases
- Efflux pumps

	Substrates*	**Not substrate**
MexAB-OprM	FQs, Tet, C, β- lactams (Pip/Fep/Mer/Azt/Caz)	Imp
MexCD-OprJ	FQs, β- lactams (Pip/Fep/Mer)	Imp/Caz/Azt
MexEF-OprN	FQs, Trimethoprim, C	
MexXY-OprM	FQs, Aminoglycosides, β- lactams (Pip/Fep/Mer)	Imp/Caz

- Carbapenemases, eg. IMP, VIM, SPM, GIM

*Abbreviations for fluoroquinolones (FQs), tetracycline (Tet), chloramphenicol (C), piperacillin (Pip), imipenam (Imp), meropenam (Mer), cefepime (Fep), ceftazidime (Caz), and aztreonam (Azt)

Pulmonary hypertension in an HIV-infected patient

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Case presentation

A 38-year old Thai lady presented with exertional shortness of breath and ankle oedema and was admitted to a local hospital. She was born in Thailand and came to Hong Kong 5 years prior to admission. Her past health was unremarkable and she did not smoke regularly or use any illicit drugs.

Her chest radiography showed prominent bilateral hilar widening and cardiac enlargement. Electrocardiogram revealed normal sinus rhythm, right axis deviation with no ischaemic change. A subsequent computerised tomographic scan of thorax did not identify any evidence of pulmonary embolism. However, her right atrium and right ventricle were found to be dilated under transthoracic echocardiogram. Moderate tricuspid regurgitation was also noticed. Her right ventricular systolic pressure was significantly elevated to 62 mmHg with no intracardiac shunt. Cardiac catheterisation showed pulmonary vascular resistance of 277 dyne and grossly elevated pulmonary arterial pressure (82 mmHg systolic & 29 mmHg diastolic). Secondary causes for pulmonary hypertension including autoimmune, endocrine, thromboasthenic, malignancy-related and respiratory causes were screened and were not found. Her family history and drug history were unremarkable. A diagnosis of idiopathic pulmonary hypertension (PH) was coined for her.

She was given warfarin, calcium channel blocker, digoxin and loop diuretics. Sildenafil was also added later for symptomatic control. Balloon atrial septostomy was performed 9 months later because of persistent elevated pulmonary arterial pressure and desaturation. Despite all these treatment, she had minimal symptomatic improvement. Her 6-minute walking distance was only 286 meters and her functional class was III according to New York Heart Association (NYHA) classification. Because of poor oxygen saturation and severe symptoms, she remained basically home-bound and required long term oxygen therapy. She developed an episode of herpes zoster during admission for septostomy and responded to acyclovir therapy.

She was readmitted for symptoms of fever, cough and increasing breathlessness about one year after the initial presentation. Chest radiography showed bilateral lower zone haziness. Sputum for microscopy, acid-fast staining and culture were all negative. Because of poor response to co-amoxiclav, levofloxacin, sulperazone and cefepime, a bronchoscopy with bronchoalveolar lavage was performed which confirmed *Pneumocystis jirovecii* infection. She responded to a course of trimethoprim-sulfamethoxazole. She also presented with herpes simplex skin lesion and buccal candidiasis. Her HIV status was then checked for the first time and was positive. Her initial CD4 T-cell count was only 10 cells/ml and her serum HIV RNA levels was 110,000 copies/ml. She was commenced on highly active anti-retroviral therapy (HAART) comprising lamivudine, kaletra and stavudine.

Her CD4 cell count rose to 178 cells/ml 2 months after HAART and her HIV viral load was undetectable. She was admitted once after the commencement of HAART for cytomegalovirus retinitis and responded to a course of ganciclovir. Otherwise, her clinical status was much improved. She did not require oxygen therapy after the HAART. Her oxygen saturation and mobility were satisfactory. Sildenafil was stopped and she continued to take warfarin, digoxin and calcium channel blocker. Subsequent 6-minute walking distance was

significantly improved to over 400 meters and her NYHA functional class improved to I.

Discussion

Pulmonary hypertension is a rare disease entity. The estimated annual incidence of PH is 1-2 cases per million per year in the general population [1]. However, studies showed that the incidence of PH in HIV-infected population could be as high as 1 case per 200 individuals [2]. HIV is a “definite” association with PH according to World Health Organisation classification [3], indicating that existing evidence is quite strong to support such claim. The prevalence of HIV-infected population in Hong Kong is still considered low (<0.05% in general population). However, the number of newly HIV-infected cases surged dramatically to over 300 in 2005 [4]. Since the introduction of HAART, the longevity of HIV-infected patients is similar to that of non-infected individuals. Therefore the total number of HIV-infected population will be expected to rise. With a HIV-infected population of 3004 cases by 30 June 2006 in Hong Kong [4], the estimated number of PH would be about 15.

The diagnosis of PH is not difficult since by definition a sustained elevation of pulmonary arterial pressure to more than 25 mm Hg at rest or to more than 30 mm Hg with exercise, with a mean pulmonary-capillary wedge pressure and left ventricular end-diastolic pressure of less than 15 mmHg, is diagnostic [5]. An extensive search for secondary causes for PH is mandatory since some of them are potentially reversible. Algorithm has been proposed to facilitate this search (Figure 1) [1]. HIV test should always be on the agenda for screening. However, especially in area of low HIV prevalence, it may sometimes be neglected. Our patient had the diagnosis of HIV infection one year after her initial presentation when she was admitted for opportunistic infection.

The next question is whether the early diagnosis of HIV infection would make a difference in patients with PH. Conventional therapy including oral anticoagulant, diuretics and oxygen is the standard initial treatment for patient presenting with NYHA functional class III or IV [6]. Calcium channel blocker would be the next treatment of choice for further symptomatic control [6]. The next step-up therapy would include endothelin-receptor antagonists (e.g. bosentan), phosphodiesterase type 5 inhibitor (e.g. sildenafil) and prostacyclin derivatives (e.g. epoprostenol) [6]. Anecdotal reports have also demonstrated that these medications are efficacious in HIV-infected individuals [7-9]. Unfortunately our patient had no improvement despite the combination of conventional therapy, calcium channel blocker and sildenafil. Atrial septostomy is considered a palliative treatment in patients with advanced PH based on its potential to decompress the failing right ventricle and increase cardiac index. Fifteen to 58% of patients undergoing the operation had improvement in cardiac index immediately following the procedure. However, this procedure carries a mortality of 5-50% [10]. Despite survival after the procedure, the functional status of our patient remained poor.

Since the introduction of HAART in the mid-nineties, HIV-infected patients live longer and they suffered less from opportunistic infections. Studies have also demonstrated that HAART will improve symptoms related to PH. In the Swiss HIV cohort, 14 patients who received HAART had their right ventricular systolic pressure over right atrial pressure gradient significantly decreased by a median of 21 mmHg, while there was an increase by a median of 25 mm Hg in 9 patients who had not received anti-retroviral therapy at all [11]. HAART also decreased mortality due to PH in this group of patients [11]. The underlying mechanism for this improvement remains elusive. Although HIV or its proteins could not be demonstrated in pulmonary vasculature or endothelial cells in patients with PH, HIV-activated macrophage may release abnormal amount of cytokines (endothelin-1, IL-1a, IL-6, and platelet-derived growth factor) that could lead to enhanced leukocyte adherence, growth factor secretion, and endothelial proliferation, leading to PH [11]. HAART may reverse these processes by

down-regulation of viral replication and hence immune stimulation that underlies PH. Our patient had a jump of CD4 T-cell from a nadir of 10 cells/ml to 178 cells/ml in 2 months time. It is conceivable that her immune recovery may help to lower the pulmonary arterial pressure.

In conclusion, PH is more common in HIV-infected individuals than in general population. Investigation for the underlying aetiology for PH should include HIV testing. The optimal therapy for HIV-associated PH is still evolving. HAART may help in reversing the pathogenic process underlying PH.

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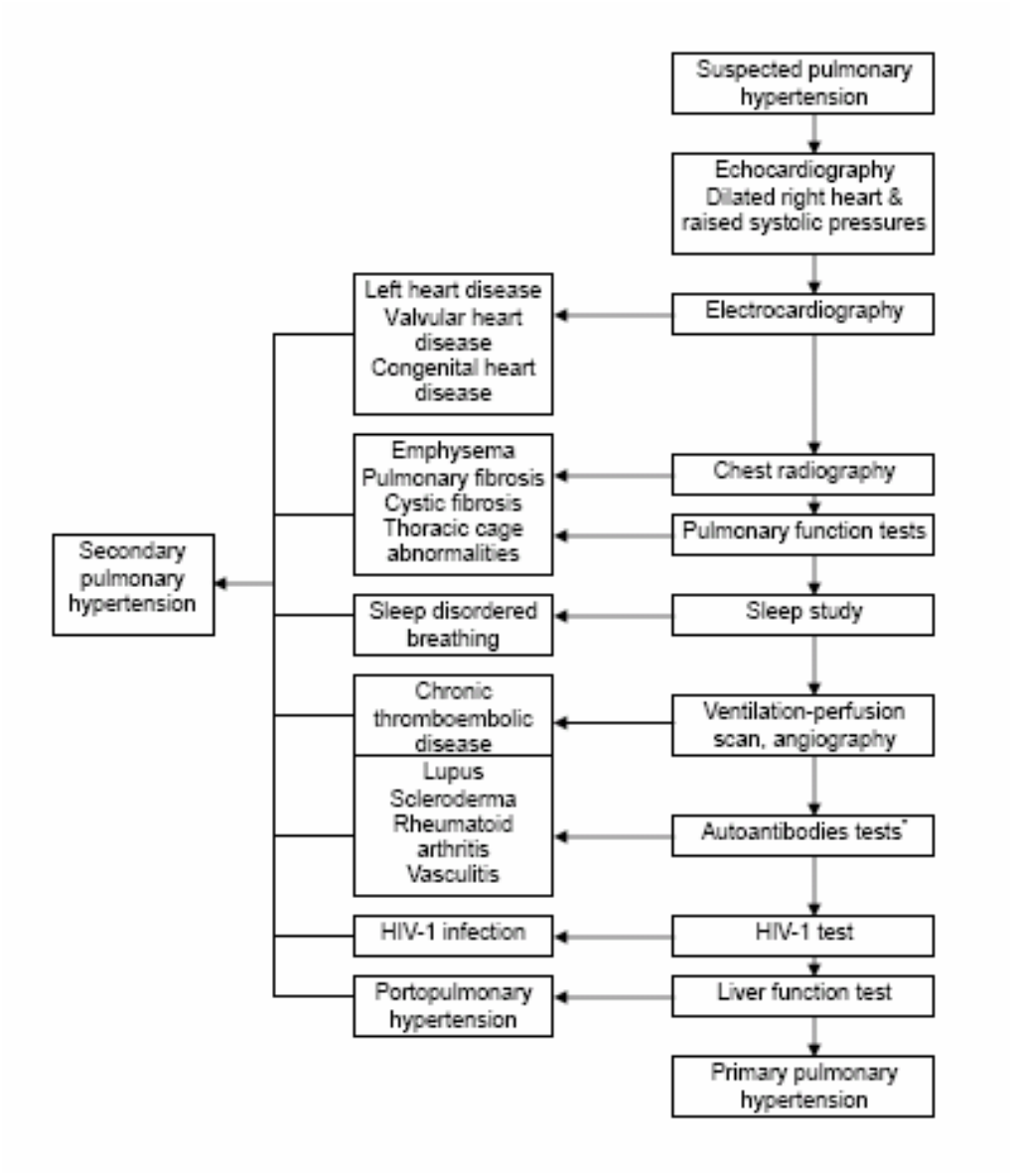

Figure 1: Algorithm for investigation of suspected pulmonary hypertension
* Antinuclear antibody, anti-neutrophilic cytoplasmic antibody, rheumatoid factor

Multiple relapses of *Plasmodium vivax* malaria after primaquine prophylaxis

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Introduction

Plasmodium vivax malaria constitutes 41% of malaria cases worldwide [1]; and it accounts for most of the cases acquired outside Africa [2]. In Hong Kong, there were 40 cases of malaria in 2006 [3]. The diagnosis and treatment are usually straightforward; however, we encounter a case of multiple relapses of *P. vivax*.

Case report

A 41-year old businessman had fever, chills, rigor and bone pain 3 weeks after returning from Myanmar. He also had history of diabetes mellitus and hyperlipidaemia. He had taken unknown medications bought in Yunnan, China (2 tablets, once per month) for malaria prophylaxis. He was diagnosed to have malaria in Shenzhen and was treated with artesunate and chloroquine for 7 days. However, fever recurred 3 days later and he was given oral chloroquine for 3 days. Although fever was down, he complained of vomiting, abdominal pain, haematuria and passing bloody stool and was then admitted. On examination, he was febrile with a temperature of 38^{o}C. Urinalysis revealed 3+ red cells. Otherwise, physical examination was unremarkable. Laboratory tests showed the following: platelet count 69 x 10^9/L, serum albumin level 28g/L, serum total bilirubin 43 umol/L and serum lactate dehydrogenase 494 U/L. Peripheral blood smear revealed *P. falciparum* with a parasitaemia level of 0.1%.

The serum glucose-6-phosphate dehydrogenase (G6PD) level of the patient was normal. He was given a standard course of oral quinine 600 mg every 8 hours and doxycycline 100 mg every 12 hours for 7 days and then primaquine 45 mg for 1 dose. Repeated blood smear at the end of treatment revealed no parasite. The symptoms resolved completely with the normalisation of laboratory tests.

He was admitted again for fever, chills and bone pain 39 days after the first presentation. He only had travelled to Shenzhen in between. On admission, he did not have fever, but blood pressure was on low side, 92/67 mmHg. Physical examination was unremarkable. Laboratory tests showed that platelet was 82 x 10^9/L, serum albumin was 32 g/L and serum total bilirubin was 44 umol/L. Peripheral blood smear revealed *P. vivax* with a parasitaemia level of > 0.1% this time. He was given oral mefloquine 750 mg followed by 500 mg 12 hours later, then primaquine 15 mg daily for 14 days. Repeated peripheral blood smear 1 day after mefloquine showed that parasitaemia level had dropped to 0.1%, and became undetectable 3 days later. Again the symptoms resolved with normalisation of laboratory tests.

About 3 months after the last episode (about 6 months after the initial episode), the patient experienced fever and chills again. On admission, he did not run a fever, but blood pressure was low, 90/62 mmHg. He had a platelet count of 58 x 10^9/L, serum creatinine 127 umol/L, albumin 29 g/L and total bilirubin 48 umol/L. Peripheral blood smear showed *P. vivax*. He was given oral quinine 600 mg every 8 hours and doxycycline 100 mg every 12 hours for 3 days. Blood smear became negative 1 day later. He was given primaquine 22.5 mg daily for 14 days afterwards. Repeated blood smear 4 days and 23 days later were negative.

He remained asymptomatic for an additional 19 days after finishing the course of treatment; nevertheless, he complained of fever and chills again while having a trip to Beijing. Peripheral blood smear revealed *P. vivax* with a parasitaemia level of 0.01%. White cell count was 3.8 x 10^9/L, haemoglobin was 12 g/dL, platelet count was 58 x 10^9/L and serum total bilirubin was 62 umol/L. Therapy with chloroquine was initiated (600mg followed by 300 mg 6 hours later) but was switched to quinine for 4 days and doxycycline for 7 days. Repeated blood smear 3

days later was negative. In view of his large body weight (82 kg), he was given primaquine 22.5 kg every 12 hours for 14 days. He was followed up 2 days after finishing the course of primaquine and was asymptomatic. Blood smear was negative and laboratory tests were normal.

Discussion

Malaria is a parasitic infection caused by the protozoa *Plasmodium.* Human infection results from the bite of an infected female *Anopheles* mosquito, during which the sporozoites are injected into the bloodstream. The sporozoites then enter the parenchymal cells of the liver — primary exoerythrocytic phase. Subsequently numerous asexual merozoites enter the bloodstream, infecting the erythrocytes. Some might differentiate to gametocytes, completing the life cycle. Parasites in the red cells multiply and are released from the host cells synchronously — erythrocytic cycle. For *P. vivax*, the release of parasites typically occurs every 48 hours, which co-incides with the cytokine release and fever. *P. vivax* parasites can persist in the liver as hypnozoites which can cause relapse.

P. vivax has an incubation period of 12-17 days. It preferentially invades reticulocytes, causing anaemia. It is less virulent as it does not reach high parasite densities and does not sequester in capillaries and venules. Common clinical manifestations include fever, chills, nausea, vomiting and myalgia. Rarely, it can result in cerebral malaria, severe anaemia, jaundice, acute respiratory distress syndrome, splenic rupture, acute renal failure, severe thrombocytopenia and pancytopenia.

The gold standard of diagnosis of malaria is still by peripheral blood smear. Thick smear concentrates the parasites and permits detection of as little as 10-20 parasites/uL of blood. Thin smear is essential for species differentiation. Amoeboid trophozoites and cytoplasmic Schuffner's dots are typically found in *P. vivax* infection. Antigen detection can allow rapid diagnosis in places with no access to microscope. It employs a dipstick or test strip with monoclonal antibodies against target parasite antigens e.g. histidine-rich protein 2 or *plasmodium* LDH. However, *plasmodium* species other than *P. falciparum* cannot be differentiated and the sensitivity of the test is inferior to that of blood smear if parasite density is less than 500 parasites/uL of blood [4].

Treatment should aim at both the blood and liver stages of the parasite — so called the radical cure. Chloroquine was shown to achieve parasite clearance in the blood within 100 hours [5]. It is considered the standard treatment. The total dose is 25 mg/kg, divided into either four doses (given as 10mg stat, 5mg at 6hrs, 24 hrs and 48 hrs) or three doses (given as 10mg stat, at 48 hrs and 72 hrs). A hypnozoiticidal agent, primaquine, should also be given afterwards after G6PD deficiency has been ruled out. The total dose given is the main determinant of treatment success. The standard dosage would be 15 mg for 14 days (or 0.25 mg/kg/day). For patients with mild G6PD deficiency, a dose of 0.75 mg/kg once a week for 8 weeks can be given [6].

Persistent parasitaemia, however, is not uncommon. It can be due to re-infection, recrudescence and relapse. Recrudescence is the incomplete killing of blood stage schizonts, usually happens within 16 days of treatment; while relapse is the activation of liver stage hypnozoites, which typically occurs after 28 days of initiation of treatment. For persistent parasitaemia developed between 16 to 28 days, the two situations cannot be differentiated. In Southeast Asia, about 50-60% of *P .vivax* infections relapse; whereas in Indonesia and Indian subcontinent the frequency is lower at 30% and 15-20% respectively [7]. Relapses may occur 1-4 times after radical treatment, any time after day 16 and up to 4 years after primary infection. Nonetheless, treatment failure is not equivalent to resistance. It can also be due to

misdiagnosis, incorrect dosing, non-compliance, emesis, poor drug quality and drug interactions. For in vivo assessment of chloroquine resistance of *P. vivax*, a follow-up period of 35 days is recommended, and this should be accompanied by measurement of whole blood chloroquine and desethychloroquine levels. If the concentrations exceed 100 ng/ml, i.e. suppressive, the strain causing persistent parasitaemia is resistant [8-10]. For in vitro tests, parasites obtained from blood are placed in microtitre wells, exposed to known concentrations of a drug and examined for the inhibition of maturation into schizont parasite stages. However, the test is laborious and is not routinely available.

For the first episode of treatment failure, the cause is probably misdiagnosis. Actually in patients presenting with falciparum malaria, 30% of them have cryptic mixed infection by *P. vivax* [5]. The patient might acquire both *P. falciparum* and *P. vivax* infection during the journey to Myanmar. Yet the first blood smear might be overwhelmed by *P. falciparum*, which usually has a higher level of parasitaemia. For patient diagnosed to have *falciparum* malaria acquired from places like South America, Southeast Asia and Indian subcontinent, one might also need to consider the possibility of cryptic mixed infection.

For the first relapse, probably the dosing of primaquine was inadequate (15mg daily for 14 days). As the patient has a large body weight (82kg), the standard dosage should be at least 20.5 mg for 14 days instead (0.25mg/kg x 82 kg = 20.5 mg).

Since the third episode of parasitaemia occurred between 16 to 28 days after last treatment, it could be either recrudescence or relapse. The patient was given quinine and doxycycline to clear the parasite in the blood. This should be appropriate even for chloroquine resistant strain. Actually chloroquine resistance had been reported in Brazil, Colombia, Ethiopia, Guatemala, Guyana, India, Republic of Korea, Myanmar, Solomon Islands, Thailand and Turkey [11]. Apart from quinine, alternatives like amodiaquine (30 mg/kg over 3 days), artemisinin-based therapy (except artesunate plus sulfadoxine-pyrimethamine due to resistance to sulfadoxine-pyrimethamine) and mefloquine (15mg/kg once) [11] can be considered. However, our patient was only given 3 days of quinine, while the standard duration of treatment is 7 days. This may account for the recrudescence as quinine has a shorter half-life compared with chloroquine (16 hours versus 30 days). Yet our patient could still have a relapse as primaquine tolerance was possible. There are case series reported that the relative risk of relapse is lower for patients treated with a higher total dose of primaquine (ranged from 315 mg to 420 mg) than those treated with a lower total dose (210 mg) in places like New Guinea, Southeast Asia, Indonesia and in the Oceania. The relative risk ratio of higher dose to lower dose was reported to be 0.11 [12]. In our patient, the total dose of primaquine given was 315 mg, which may still be inadequate for his rather large body weight if the strain was tolerant. Therefore, in the last admission, he was given 630 mg primaquine in total (0.5 mg/kg for 14 days). However, the optimal dose remains unclear in patients of heavy body weight [13], and such a large dose can potentially result in leukopenia, agranulocytosis, gastrointestinal symptoms (can be decreased if taken with meal), haemolytic anaemia, methaemoglobinaemia with cyanosis [12]. These did not happen in our patient, though.

The patient remained asymptomatic for at least a month since last presentation. He did not report any vomiting during the course of treatment and he reported strict adherence to treatment. Therefore, the absorption of the drug should be considered adequate. If relapse still happens, then primaquine resistance is possible. Nevertheless, laboratory proof of resistance is difficult because the parasite cannot be propagated in vitro and the pharmokinetics are poorly understood. Rarely should resistance happen, suppressive chloroquine therapy 300 mg/week for 4 months had been reported to be successful [14].

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Journal review

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Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet. 2007; 369: 643-56.
Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007; 369: 657-66.

Male circumcision has been widely suggested as a method to reduce the risk for HIV transmission; removal of the foreskin presumably eliminates from the body a large number of potential HIV target cells present in this body structure. Recently the efficacy and safety of circumcision have been assessed in two randomised trials. Both studies were terminated early after interim analyses showed substantial benefit of circumcision.

In Kisumu, Kenya, more than 2700 HIV-negative, sexually active young men (median age, 20) were randomised to receive circumcision or delayed circumcision. Participants received HIV counseling and periodic testing and were followed up for over 24 months. During the study, 22 in the circumcision group and 47 in the control group seroconverted, which corresponded to a 2-year HIV-infection incidence of 2.1% (95% CI, 1.2-3.0) and 4.2% (95% CI, 3.0-5.4), respectively. Risk for HIV acquisition was reduced by more than 50% in the circumcision group. Adverse events occurred in up to 1.5% of circumcised participants and none was severe. It was noteworthy that these results were obtained despite the fact that subjects in the control group actually decreased their HIV-risk behaviors more than those in the circumcision group.

In a similar study in Rakai, Uganda, almost 5000 HIV-negative men aged 15-49 were randomised to the same interventions and followed up accordingly. At 24 months, the cumulative HIV-infection incidence per 100 person-years was 0.66 in the circumcision group and 1.33 in the control group, corresponding to a protective efficacy of over 50%. HIV-acquisition rates were lower in the circumcision group than in the control group for all age-groups. Major adverse events related to surgery occurred were uncommon.

Points to note: These studies clearly show that male circumcision can be performed safely in developing countries and that it substantially reduces the risk for HIV infection in males, although clearly this practice should not obviate the need for condoms under these settings. Assuming an efficacy similar to those seen here, other researchers have estimated that large-scale implementation of male circumcision could avert up to 2 million new HIV infections in sub-Saharan Africa over the next decade (for instance, see article by Williams BG, Lloyd-Smith JO, Gouws E et al. The potential impact of male circumcision on HIV in Sub-Saharan Africa. PLoS Med 2006; 3: e262).

Obviously a number of issues remain to be addressed, given the provocative results presented by these studies. For example, can enough practitioners be trained to perform large numbers of circumcisions safely, especially in developing countries? What is the optimal age for males to be circumcised? Will circumcision reduce condom use and increase high-risk sexual behavior? And will it protect the sexual partners of HIV-infected men from disease transmission? Further studies and observations are required before one could give definitive answers to these pressing issues.

Shrestha MP, Scott RM, Joshi DM, et al. Safety and efficacy of a recombinant hepatitis

E vaccine. N Engl J Med. 2007; 356: 895-903.

Hepatitis E virus (HEV) is widely distributed globally and has caused large outbreaks in parts of Asia, with most outbreaks being traced to consumption of faecally contaminated water. Acute infection by HEV does carry significant morbidity and mortality; acute infection can last up to 4 weeks, mortality is 1% to 3% overall and can reach 25% in pregnant women infected during the third trimester. Recently, a group of investigators have reported on their findings in a phase II trial of a recombinant HEV vaccine in the *New England Journal of Medicine*.

A total of 2000 healthy, HEV-susceptible adults from the Nepalese army (99.6% men; mean age, 25) were randomised to receive three doses of recombinant HEV vaccine or placebo injections given over a period of 6 months; they were then followed up until the end of the study for the occurrence of hepatitis E infection (median follow-up, 804 days). Symptomatic HEV infection was confirmed in 3 vaccine-group and 66 control-group participants, for an efficacy of 95.5%. No serious vaccine-related adverse events were identified, with injection-site pain being more commonly reported in the intervention group only. 100% of vaccine recipients had anti-HEV antibody levels considered protective 1 month after receiving the third dose; the proportion dropped to 56.3% by the end of study.

Points to note: Although the vaccine was highly efficacious in preventing clinical hepatitis E, its role in preventing asymptomatic infections is currently unknown. Also, the vaccine's safety and efficacy in women (including, in particular, pregnant women), and the duration of its protection remain to be determined. Even if the vaccine is ultimately proven to be safe and efficacious in these populations, cost considerations could be a potential deterrent to its widespread use among developing country populations where the need is greatest.

Miller EK, Lu X, Erdman DD, et al. Rhinovirus-associated hospitalisations in young children. J Infect Dis. 2007; 195: 773-81.

Rhinoviruses are well-known to cause mild, self-limited upper respiratory illness, but the frequency with which they cause more-severe illness is not known. A group of US investigators has recently evaluated the prevalence of rhinovirus infection among children hospitalised for acute respiratory illness in two counties in Tennessee and New York; they also used these figures to generate population-based rates of rhinovirus-associated hospitalisation.

From October 2000 through September 2001, children (age <5 years) who were hospitalised for acute respiratory symptoms or fever had nasal and throat swabs performed for viral culture and PCR. Of the 592 children enrolled, 61% had at least one virus detected. Rhinoviruses were the most common (26%), followed by respiratory syncytial virus (20%), parainfluenza viruses types 1-3 (7%), influenza viruses types A and B (3%), human metapneumovirus (3%), and enteroviruses (2%). Only slightly over 10% of rhinovirus-infected children were coinfected with another respiratory virus, and only 3 had bacterial coinfections. A multivariate model revealed history of wheezing or asthma to be independently associated with rhinovirus detection (P=0.02). The overall rate (per 1000 children per year) of rhinovirus-associated hospitalisation was 4.8; it was highest among children aged 0-5 months and among children with a history of asthma or wheezing.

Points to note: Despite their association with apparently benign conditions such as the "common cold", rhinoviruses are in fact associated with a large proportion of hospitalisations for acute respiratory illness in young children. The lack of co-pathogens in most infected

children suggests that rhinoviruses likely play a major pathogenic role in their respiratory illnesses. Further studies to confirm these interesting findings are eagerly awaited.