Is pertussis re-emerging in Hong Kong?

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Whooping cough (pertussis) is still an uncommon disease, but an increased number of cases have been seen in Hong Kong in recent years despite almost 100% vaccine uptake. In the period of January to May 2002, 13 cases of whooping cough were reported to the Department of Health, as compared to 15 in 2001, 11 in 2000, 5 in 1999, and 3 in 1998.

Pertussis is caused by the bacterium Bordetella pertussis. A milder disease may be caused by the related bacterium Bordetella parapertussis (causing parapertussis). The initial illness (the coryzal phase) is followed by the paroxysmal phase, which is prolonged. The cough paroxysm consists of a series of short expiratory bursts, followed by an inspiratory gasp, which can result in the typical whoop. The paroxysmal phase may last for 1 - 2 months or longer. Complications of pertussis may include pneumonia, haemorrhages and encephalopathy with seizures. Reported disease is seen mostly in children < 5 years old. In the modern vaccine era, most cases are seen in children < 1 year of age. Disease in adults is often atypical and is probably usually missed. Transmission is by contact with discharges of respiratory mucous membranes and respiratory droplets. The incubation period is 7 - 20 days. Erythromycin has been shown to reduce the severity and duration of disease, and is thus the drug of choice. When treated with erythromycin, patients are regarded as non-infectious after 5 days of therapy. Laboratory diagnosis is usually by culture of specimens from the nasopharynx, either by pernasal swab or nasopharyngeal aspirate. The usual culture medium used in the laboratory is freshly prepared Bordet-Gengou medium supplemented with penicillin or cephalexin. Bordetella sp. are slow growing and may take 5 - 7 days to show the typical "split pearl" appearance.

Pertussis was a major cause of morbidity and mortality in infants and children until the mid-20th century when the introduction of whole cell pertussis vaccines led to dramatic declines in incidence. In the 1970s, concerns about adverse reactions to the vaccine, particularly neurological toxicity, led to reductions in vaccine uptake in some

countries (particularly the United Kingdom) and other countries had problems of poor efficacy vaccines (Canada, Sweden). Countries which stopped vaccination programmes saw outbreaks of pertussis. Some countries (e.g. USA, Sweden) have now adopted acellular pertussis vaccines which have been shown to be less reactogenic than whole cell vaccines. However, the current problem is that a number of countries with high vaccine uptake are now seeing increasing numbers of pertussis cases, particularly in young infants. Studies undertaken in the Netherlands suggest that antigenic divergence has occurred in clinical isolates as compared to the vaccine strains, in particular for the surface associated protein pertactin and pertussis toxin, and this adaptation may allow B. pertussis strains to circulate despite high levels of vaccine uptake. Since vaccine induced immunity is thought to last no more than 10 years, newborn infants are not now protected by maternal antibody, and young infants are now prominent in clinically evident cases of whooping cough (cases were predominantly in older infants in the pre-vaccine era). Surveillance data is also likely to underestimate the incidence of disease since disease in well-vaccinated communities is often mild, and may not be clinically suspected. Even when the disease is suspected, standard laboratory techniques such as culture may be insensitive. Newer diagnostic techniques such as PCR have been shown to increase the diagnostic yield, but are not yet available in many regions.

Another issue which has come to light in recent years is the apparently high incidence of pertussis in older children and adults, groups who were previously thought to be infected rarely. One recent study from the USA suggested that up to 25% adult patients with chronic cough had pertussis. The predicted annual incidence of pertussis in adolescents in another study was estimated at 1.2 - 8.2%. The apparent shift of pertussis incidence to the susceptible adult population has led to the consideration of pertussis booster vaccinations in adolescents and adults. Pertussis is now also realised to spread fairly readily in the hospital setting, and may affect staff in contact with pertussis cases. Some authorities recommend macrolide prophylaxis for healthcare workers in close contact with the secretions of pertussis cases. It remains controversial whether the increased numbers of cases being reported in some regions represents enhanced surveillance, cyclical trends in incidence, or a

genuine re-emergence of the disease. It is clear however, that continued careful surveillance of trends in this disease is essential, and newer molecular technologies should help to improve the accuracy of laboratory techniques in the future.

CMV infection: treat if there is 'disease'

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Scenario 1: A leukaemic patient presented with jaundice 4 weeks after chemotherapy; liver biopsy showed hepatitis and no viral inclusion. CMV pp65 antigenaemia test however was positive (3 cells per 2 x 105). Serum CMV-DNA was also detected by PCR for 2 consecutive weeks. Is this CMV hepatitis? Should we start antiviral therapy?

Scenario 2: A patient with ulcerative colitis underwent another colonoscopy because of refractory symptoms. Biopsy interestingly showed CMV inclusion bodies among inflamed tissues. CMV pp65 antigenaemia testing was negative. Should we treat?

Diagnostic criteria for Cytomegalovirus (CMV) end-organ disease were recently summarised and updated.[1] In essence, 1) presence of symptoms and signs and/or laboratory evidence of organ dysfunction, 2) histological evidence of tissue inflammation, 3) demonstration of CMV (by staining inclusion bodies, viral culture, immunohistochemical analysis or in situ hybridisation), and 4) exclusion of other pathogens are required for the diagnosis of CMV disease. Viraemia as suggested by a positive pp65 antigenaemia test or peripheral blood CMV-DNA PCR assay is not included as part of the definition. Moreover, CMV-DNA PCR assay of tissue or body fluid specimen alone is not sufficient for diagnosing CMV disease; as a positive test may simply represent transient viraemia. These definitions apply to post-transplant (solid organ or haemopoietic stem cell) and most other immunocompromised patients; their use in HIV infected patients however, remains controversial.

CMV end-organ disease results from both viral reactivation and its complex interaction with the immune system.[2] While CMV esophagitis and colitis are mainly consequences of a directly cytopathic effect, the development of pneumonitis in the post-marrow engraftment period or retinitis post-HAART (Highly Active Anti-Retroviral Therapy) are compounded by immunoreconstitution.

Besides, CMV disease is associated with an increased risk of superimposed opportunistic infections like aspergillosis or pneumocystis carinii pneumonia, which is possibly related to the additional immunosuppressive effect caused by CMV itself (e.g. suppressed HLA expression). Co-infection and/ or induction of other herpetic viruses like EBV, HHV-6, and HHV-7 are also well recognised indirect effect of CMV disease. Increased incidence of allograft dysfunction, rejection, and reduced survival had been documented.

Interesting, different end-organ disease tends to occur in different clinical settings.[2] Recognising such disease pattern is helpful in making a diagnosis. For instance, CMV pneumonitis more commonly develops in haemopoietic stem cell transplant patients during the post-engraftment period. Those who received anti-lymphocyte globulin for the treatment of GVHD (Graft-versus Host Disease) are at particular risk. The successful management of such patients with IVIG together with an antiviral reflected the immunopathogenesis of this disease as mentioned. CMV retinitis seldom occurs in this patient group.

On the other hand, although > 90% of HIV infected persons were co-infected with CMV, and up to 44% of patients develop CMV disease in the pre-HAART era, retinitis and gastrointestinal tract disease are the more common manifestations. Pneumonitis seldom occurs. In post-renal transplant patients, the observations are similar with gastrointestinal disease predominates. In other solid-organ transplant, disease frequently corresponds to the organ transplanted: e.g. CMV hepatitis develops in the liver allograft. Worth mentioning, CMV hepatitis also occurs in severe primary infection; and an abnormal liver function pattern may be present in > 50% of systemic CMV infections which does not necessarily represent hepatitis/disease. In other immunocompromised patients, e.g. end-stage renal failure or those with underlying malignancy, colitis is probably the commonest manifestation.[3] CMV colitis is also reported in patients with steroid refractory inflammatory bowel disease because of depressed mucosal immunity.[4] Treatment of such infection allows reduction of immunosuppressive therapy.

In addition, the risk of CMV disease varies with the type of transplant and its HLA and CMV serostatus matching; the type, intensity and duration of immuno-suppressants used; and in AIDS patients, the CD4 cell counts. Briefly, the use of anti-thymocyte/ anti-lymphocyte globulin and OKT3 is associated with the highest risk; high dose mycophenolate (MMF), azathioprine, cyclosporine, tacrolimus (FK506) and steroid follow in that order. Typically, CMV disease occurs 1-4 months post-transplant, unless the patient is heavily immunosuppressed for GVHD or graft rejection. In AIDS patients, CMV disease seldom occurs if the CD4 cell count is more than 50-100 mm3.

According to the fore-mentioned diagnostic criteria, tissue biopsy is the most useful strategy for the diagnosis of CMV disease. However, if typical viral inclusion bodies are not seen, immunohistochemical analysis could be considered. It involves the use of mono- or poly-clonal antibodies directed against CMV early antigens and thus has increased sensitivity. In one study involving biopsy specimens of liver allograft, the sensitivity and specificity of the test is 84% and 97% respectively.[2] However, false negatives do occur because of multi-focal nature of the disease. In-situ hybridisation involves the use of complementary DNA probes; it has the advantages of being highly sensitive and semi-quantitative. However, its accuracy varies between different reports and is therefore only recommended in selected cases.

Although a positive CMV pp65 antigenaemia test does not prove or disprove CMV disease (since viremia can occur in asymptomatic patients and CMV disease can develop without viraemia), it does predict future development of disease. This is based on the fact that circulating infected leukocytes or viraemia heralds the onset of clinical disease. This had been verified in various post-transplant settings and leading to the concept of pre-emptive therapy. Detection of early expressed antigen pp65 (a lower matrix-protein encoded by genomic region UL 83) on leukocytes using immunofluorescent technique is associated with a higher risk of CMV disease developing 5-14 days ahead. Moreover, quantification or estimation of viral burden becomes possible. Since its level correlates with disease severity, it is obviously helpful in monitoring therapeutic response to antivirals. Nonetheless, interpretation of result is sometimes difficult. For

haemopoietic stem cell transplant patients, > 1 - 2 positive cells per 2 x 105 cells might be considered significant, while > 10 and > 100 cells are significant in post-kidney transplant/AIDS and liver transplant patients respectively.[5] Therefore although its sensitivity is > 90% for CMV end-organ disease (and a specificity of 76 - 90%), its positive predictive value (PPV) ranges only from 60 - 70% depending on the cut-off value chosen and the prevalence of disease in that particular clinical setting.[2,5] Generally speaking, positive predictive value increases with higher circulating antigen level. Its negative predictive value for future CMV disease however, is greater than 90%.[2] Although not diagnostic, where clinical features are compatible, a highly positive CMV pp65 antigenaemia test may prompt clinicians to search for CMV disease more vigorously.

CMV PCR or 'target amplification' of the genomic region UL 54 which encodes the polymerase gene is a highly sensitive technique to detect the presence of the virus in various body fluids and tissue specimens. As mentioned, diagnosis of CMV disease cannot be based on PCR alone as a positive test may simply represent transient viraemia. Nevertheless, CMV PCR of the peripheral blood had been successfully applied in different pre-emptive therapy programs. A positive test can herald the development of CMV disease by > 17 days. Its sensitivity and specificity approaches 100% and its negative predictive value for disease is high. The positive predictive value, on the other hand is less impressive, because a positive DNAemia may not associate with disease (e.g. CMV retinitis in AIDS patients: PPV of CMV PCR = 60% vs 89% CMV pp65Ag testing).[2] In many programs, therapy is initiated when PCR becomes positive for 2 consecutive weeks. Tests involving the use of serum instead of whole blood or leukocyte may have a higher PPV; since viral DNA 'overflows' from leukocytes to serum during active viral replication. To solve this problem, multiple studies now demonstrate that quantitative or real-time PCR is superior to qualitative tests. A higher viral load is more predictive of disease; and obviously it can be employed to monitor treatment response. However up to this point, there had been no universally accepted 'breakpoint as data only arise from isolated reports; and techniques involved are often not standardised. For instance, in HIV-infected patients (CD4 < 50 mm3), a breakpoint of > 3000 copies/ml had been associated with a PPV of 78% for CMV disease; while for liver or kidney transplant patients, >

1000 copies/100,000 WBC or a specific viral load increment is said to be predictive.[5] Lastly, PCR assay targeting for pp67 mRNA (NASBA-Nuclisens) is believed to be more predictive of disease since the expression of this 'late antigen' reflects active viral replication; a positive test had preceded disease by 3-28 days in post-kidney and liver transplant patients that was associated with a PPV near 100%.[5] Further studies are clearly necessary to evaluate the clinical use of these new techniques. Nonetheless, CMV-PCR may have greater advantage over pp65 antigenaemia assay in haemopoietic stem cell transplant settings because of the low sensitivity of the latter in patients with profound leukopenia. Moreover, according to experience gathered from post-transplant patients, a negative peripheral blood CMV-PCR may indicate better virus control than a negative pp65 antigenaemia assay, which allows antiviral therapy to be terminated safely. Again controlled clinical trials are needed for its evaluation.

In conclusion, diagnosis of CMV end-organ disease and thus decision for its treatment should be based on fore-mentioned criteria. With advanced laboratory techniques, diagnosis of difficult cases, and even prediction of future disease and thus pre-emptive therapy is becoming possible.

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Update Lectures on Clinical Infectious Diseases: Fifth Annual Management Review for the Practising Physician 2002

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These update lectures highlighted a large numbers of frontier topics in the field of infectious diseases. This review, not only gave the Infectious Disease (ID) physician a summary of what they had learnt, but also a lot of new information that might be of paramount importance in their future practice. This meeting was held in the heart of the New York City, Manhattan during the period 14-17 March 2002.

MRSA

Methicillin resistant Staphylococcus aureus (MRSA) is a problem for many ID physicians. Nowadays, the treatment of choice for MRSA is still vancomycin, which targets the cell wall of the organism. However, the clinical efficacy of vancomycin is about 74% and the microbiological success is about 63%. Because of this shortcoming, new generation of medications targeting protein synthesis has emerged. Linezolid and Quinupristin/dalfopristin (Synercid) have already entered the market. Daptomycin is undergoing phase III trial.

FDA-approved indications for linezolid include invasive vancomycin resistant enterococcal and MRSA/MRSE infections (with documented failure of vancomycin or allergic/intolerance to alternative drugs). Although linezolid is bacteriostatic, its efficacy is comparable to that of vancomycin. The clinical and microbiological success rates of linezolid are 77% and 59% respectively. It demonstrates synergy with rifampicin in experimental animals but not with vancomycin. The numbers of documented clinical resistant isolates of both MRSA and vancomycin resistant enterococcus (VRE) are on their rise. It has also been demonstrated that a single mutation in the 23S rRNA of

the 50S portion of ribosome can result in enterococcal resistance. Moreover, it has significant drug interactions since it is a weak non-selective reversible inhibitor of monoamine oxidase. Therefore, foods rich in tyramine should be avoided and co-administration of drugs like pseudoephedrine and phenylpropanolamine or selective serotonin receptor inhibitors (SSRIs) should be used with care.

Synercid is only available in intravenous (IV) form and has no activity against Enterococcus faecalis. Details of Synercid as compared to linezolid are outlined in the table 1.

Table 1: Comparison of selected features of Synercid and linezolid

Feature	Synercid	Linezolid
Spectrum	E. faecium Penicillin-resistant Streptococcus pneumoniae (PRSP)	E. faecium & E. faecalis PRSP MRSA (bacteriostatic)
Administration	Central IV line	IV/PO
Drug interaction	Cyclosporin Midazolam Nifedipine	Pseudoephedrine Phenylpropanolamine SSRIs
Dose Adjustment	Hepatic failure	No adjustment in renal or liver failure
Dose-limiting toxicity	Myalgia/arthralgia (3-8%)	Bone marrow suppression Thrombocytopenia (after 21 days) Neutropenia

Daptomycin (Cidecin) is a novel cyclic lipopeptide antibiotic. It is derived from fermentation of the product of Streptomyces species. Its main action is to disrupt the cytoplasmic membrane function, preventing the synthesis of peptidoglycan and lipiteichoic acid, and alter the membrane potential. It is rapidly cidal against all gram-positive cocci, including glycopeptide-intermediate Staphylococcus aureus (GISA), PRSP and VRE. Its peak antibiotic effect is about 1-6 hours and it manifests concentration-dependent killing. It can have additive or indifferent interaction

with most other antibiotics but there is no antagonism. The $t_{1/2}$ of this antibiotic is 8.5 hours. It is highly protein bound (90-94%) with 80% renal excretion. Its main side effect is dose-dependent muscle toxicity.

Should cephalosporin be avoided in patients with penicillin allergy?

Knowing the allergic history of a patient is important since it can be life threatening, although most patients (80-90%) with history of penicillin allergy are not at risk of an immediate reaction. Moreover, "can patients with a history of penicillin allergy be given cephalosporins?" is another major question since the choice of antibiotics is limited occasionally. Decreased antimicrobial effectiveness, increased cost, and increased antimicrobial resistance (particularly to vancomycin) are potential drawbacks if an antibiotic that does not contain a beta-lactam ring is selected. Penicillin allergy can be classified according to table 2. Besides the penicillin allergy, one should consider the possibility of aminopenicillin rashes which occur in 5-9% of ampicillin treatment. Greater than 50% of patients will have rash when they are infected with Epstein-Barr virus or cytomegalovirus, having acute/ chronic lymphocytic leukaemia or if co-administered with allopurinol. These types of rashes do not constitute permanent allergy. Patients with viral infections (HIV, Enteroviruses or HHV-6) may also have rash independent of the antibiotic treatment. Skin testing for IgE antibody against major and minor penicillin antigenic determinants is an excellent way of sorting out the true risk of IgE-mediated reactions.

Table 2: Classification of Penicillin Reactions

Class	Time of onset	Mediator	Clinical	Comment
Immediate type I	< 1h	IgE Ab	Anaphylaxis Angioedema	↑ risk IV Fatal 1:50,000
Late Type II	> 72 h	IgG, complement	↑ clearance of RBC & platelets	Skin test not helpful
Type III		IgG, IgM	Immune complexes	
Type IV		Cell-mediated	Contact dermatitis	
Other		idiopathic	Morbilliform rash	1-4% of patients

Reactions to cephalosporins can be divided into 5 classes according to their manifestations (Table 3) (1). The frequency of reactions to cephalosporins in patients with a history of penicillin allergy differs among different cephalosporins (Table 4). However, the percentage of reactions to cephalosporins is higher in patients with penicillin allergy than that of the whole group of patients in one study. Therefore, we should be cautious in prescribing cephalosporins in patients with a history of penicillin allergy. This cross reactivity between cephalosporins and other beta-lactams may be explained by the side chain structure similarity; e.g. the side chains of cefamandole and cephalothin are similar to that of penicillin G; cephalexin side chains are identical to that of ampicillin; ceftazidime side chains are identical to that of aztreonam. Unfortunately, there are no cephalosporin skin tests or anti-cephalosporin IgE antibody assays available at the moment.

Table 3: Reactions to cephalosporins

Reaction	Frequency, %	Comment
All types skin reaction	1-3	Urticaria less often than penicillin
+ve direct antiglobulin	1-2	Hemolysis, uncommon
Anaphylaxis	0.0001-0.1	Risk ↑ if penicillin

		allergy
Fever	0.5-0.9	e.g. ceftazidime
Eosinophilia	2-8	Maybe harbinger of rash

Table 4: Frequency of reactions to cephalosporins in patients with a history of penicillin allergy

Drug **Total no of patients** **Allergic reaction (%)**			**History of penicillin allergy**		
			Total No	**Allergy No (%)**	**reaction**
Cephalexin	6573	7(1.1)	69	5(7.2)	
Cephaloridine	10967	92(0.8)	255	20(7.8)	
Cephalothin	1983	21(1.1)	138	8(5.8)	

Therefore, in the absence of skin test reagents for penicillins or cephalosporins, one should avoid all cephalosporins if the IgE penicillin reaction is positive. If the penicillin reaction is mild or non-lgE mediated, and there is strong indication for cephalosporin use, that patient can be given a cephalosporin, provided that he or she is undergoing close monitoring and treatment of any drug reaction is readily available.

Infective diarrhoea

The widening array of recognized enteric pathogens and the increasing demand for cost-containment sharpen the need for careful clinical guidelines based on the best evidence currently available. Recommendations regarding the diagnosis and treatment of diarrhoea proposed by the Infectious Diseases Society of America diseases were published last year to address these issues (Table 5) (2).

Inappropriate antibiotic treatment sometimes can worsen the outcome of infective diarrhoea, e.g. the likelihood of hemolytic uraemic syndrome (HUS) in patients with *E coli* 0157:H7 infections may be increased when certain antibiotics are used to treat the initial diarrhoea (3); treatment of salmonellosis with antibiotics can

prolong the carrier state and lead to a higher clinical relapse rate. In addition, antimicrobial therapy can increase susceptibility to other infections, such as infection with a resistant Salmonella species, because of selective pressure that converts silent carriage into overt infection and symptomatic illness. Use of metronidazole or vancomycin for possible C. difficile diarrhoea in hospitals is also a major factor in enhancing colonization with and spread of VRE. However, appropriate antimicrobial therapy can shorten illness and reduce morbidity in some bacterial and parasitic infections, and can be life-saving in invasive infections. Empirical antibiotics are recommended for Traveller's Diarrhoea, in which enterotoxigenic E. coli or other bacterial pathogens are likely causes, and prompt treatment with a fluoroquinolone or, in children, trimethoprim-sulfamethoxazole can reduce the duration of an illness. Some may also consider empirical treatment for diarrhoea associated with *Shigella* and *Campylobacter* species for the same reason. Suspected or documented Shiga toxin-producing Escherichia coli (STEC) infections should not be treated with antimotility agents as it may increase the risk of HUS.

Table 5: Recommendation for infective diarrhoea

Recommendation	Ranking[a]
Initiate rehydration (oral whenever possible)	A-I
Perform a thorough clinical and epidemiological evaluation for any significant diarrheal illness (profuse dehydrating, bloody or febrile diarrhoea, or illness in infants, elderly, or immunocompromised patients). That is, ascertain how the illness began; stool characteristics (frequency and quantity); symptoms or signs of hypovolaemia; travel history; whether the patient attends a day care center; whether the patient has ingested raw or undercooked meat, raw seafood, or raw milk; whether the patient's contacts	A-II

are ill; the patient sexual contacts, medications, and other medical conditions, if any.	
Perform selective faecal studies	B-II
Institute selective therapy for: (1) Traveller's diarrhoea (2) Shigellosis (3) Campylobacter infection	 A- I A- I B- II
Avoid administering antimotility agents with bloody diarrhoea or proven infection with STEC	E-II
Selectively administer available vaccines and, for travellers to (or residents of) areas where typhoid is endemic, administer typhoid vaccine (parenteral Vi or oral Ty21A)	B-II

[a] Letters indicate the strength of the recommendation and Roman numerals indicate the quality of evidence supporting it, respectively

Recurrent Clostridium difficile disease (CDD)

About 70% of the *Clostridium difficile (C. difficile)* infections are hospital associated. Eighty-five to 95% of these infections are preceded by antibiotic usage in the last 2 months. Therapies of these infections comprise cessation of the culprit antibiotic, supportive care, and metronidazole and vancomycin treatment. Unfortunately, about 15 - 50% of infected cases will recur within 4 weeks of the end of successful antibiotic treatment. Some patients may require repeated courses of antibiotics for months and even years in attempts to cure multiple episodes of CDD before C. difficile is finally eradicated. Recurrent episodes of C. difficile infection seem to be due to re-infection rather than relapse, and perhaps some strains are more virulent than others.

After being exposed to antibiotics and the organism, about 30% of the patients will become colonized with C. difficile. Studies have shown that those colonized individuals who are able to mount an immune response to C. difficile toxin A will not develop CDD. However, about 50% of these colonized patients who cannot

produce immunoglobulin (Ig) G against toxin A will develop diarrhoea. After the CDD, those who respond immunologically will have no relapse, while those who are still not able to produce a satisfactory immune response after the diarrhoeal disease will recur. The odds ratio for recurrence associated with a low concentration of serum IgG against toxin A, measured 12 days after onset of C. difficile diarrhoea, has been 48-0 (95% Cl 3.5-663) (4).

Diarrheal recurrences are usually not due to the development of antimicrobial resistance, and patients typically respond again to the agent used to treat the original episode. A small number of patients develop multiple recurrences; they respond to specific therapy each time but develop recurrent symptoms and have positive stool cytotoxin assays after completion of a course of treatment with metronidazole or vancomycin. A variety of empirical approaches have been used to treat CDD recurrences, including biotherapeutic measures. The rationale of such measures is to avoid further antibiotic therapy and allow the normal colonic flora to re-establish itself. They include administration of *Saccharomyces boulardii* or *Lactobacillus* species, rectal infusion of faeces or a synthetic faecal bacterial flora, and the administration of a nontoxigenic *C. difficile* strain. Other strategies have involved administration of vancomycin and rifampin in combination for 10 days, vancomycin in tapering doses, cholestyramine, and intravenous gamma globulin, whole-bowel irrigation, and withholding of all treatment with careful observation.

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Erysipelothrix rhusiopathiae bacteraemia

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Case report

A 49-year-old male with alcoholic liver disease and a habit of fishing daily, but no recent history of being injured by fish or fishing equipment, was admitted to Yan Chai Hospital in July 2002 because of acute fever and chills for one day with mild respiratory symptoms. He was conscious but had a temperature of 38.6°C. He was haemodynamically stable. No skin lesion was identified. The cardiovascular and other systems were otherwise normal. His peripheral white cell count was increased to 13.0 x 10^9/L and liver function tests mildly deranged. He was put on oral cefuroxime and became afebrile the next day. His blood culture later yielded slender Gram positive rods which produced H_2S in triple sugar iron agar. The organism was sensitive to penicillin, erythromycin and levofloxacin but resistant to vancomycin. It was identified as *Erysipelothrix rhusiopathiae* by the API 20 Coryne System (bioMérieux). In order to exclude infective endocarditis after recognizing the pathogen, the patient had a transthoracic echocardiography done which revealed no vegetations although the aortic valve was not well seen. Repeated blood culture was sterile and his haematological parameters normalised. He recovered well without any complications and was discharged with oral amoxycillin for one more week. The patient at follow-up was in his usual state of health.

Brief review of Erysipelothrix Rhusiopathiae

E. rhusiopathiae, literally 'thread of red skin disease', is a non-motile, non-sporulating, non-acid-fast, slender, non-branching, pleomorphic, facultatively anaerobic Gram-positive rod. It is not a fastidious organism, and traditional cultural methods using non-selective media and standard blood culture media are sufficient for growth. The colonies formed can be haemolytic on blood agar

after 24 h of incubation. It is catalase-negative and produces H^2S in triple sugar iron agar. This organism and its associated infections are worldwide in distribution. It has been found as a commensal or a pathogen in swine, its major reservoir, sheep, cattle, horses, turkeys, birds and rodents. It has greatest economic impact by causing swine erysipelas and is shed by diseased animals in faeces, urine, saliva and nasal secretions which can contaminate food, water, soil and bedding. The maintenance of this organism in nature appears to result from asymptomatic carriage in animals; an average of 20-40% of healthy swine harbour Erysipelothrix in the lymphoid tissue of the alimentary tract, particularly in the tonsils. It causes no known disease in fish, molluscs and crustaceans but can grow for long periods of time in their mucoid exterior slime. It can also be found in decomposing nitrogenous matter and persist in animal tissues, retaining virulence and viability for months. It is even resistant to pickling, smoking and salting. However, it can be killed by moist heat at 53ºC for 15 min.

Most human cases are related to occupational exposure; butchers, fishermen, fish handlers, abattoir workers, veterinarians, housewives are at greatest risk. Infection is initiated by an injury to the skin with infective materials or by penetration of the skin by the bacteria. Immunocompromised individuals can also acquire the infection by ingestion of contaminated food products [1,2,3]. Person-to-person transmission has not been reported.

There are three main clinical categories. The most common but mild type is erysipeloid of Rosenbach, which is an acute, localized cellulitis, after an incubation of 1-7 days. The lesion is well demarcated, rhomboid shaped, slightly elevated and violaceous. As it spreads peripherally, the central area fades. There may be vesicles but no suppuration. The local swelling is non-pitting. The patient may have intense itching and severe disproportionate burning or throbbing pain. Systemic effects are uncommon; 10% of cases can have low grade fever, arthralgia; 33% can have lymphandenitis and lymphadenopathy. Arthritis can manifest in an adjacent joint. The disease is self-limiting and usually resolves in

3-4 weeks without therapy, although relapses may occur if untreated.

The rare diffuse cutaneous form occurs when the lesion progresses proximally from the initial site or appears at remote areas. Bulla may be present. Systemic symptoms are more frequent and include fever, malaise, arthralgia, myalgia, severe headache and, rarely, polyarthritis. The clinical course is more protracted and recurrence rate is higher.

Septicaemia and endocarditis develop uncommonly from localized infection. About one-third of patients with Erysipelothrix endocarditis have antecedent or concurrent skin lesions. According to some reports, 90% of patients with bacteraemia had endocarditis [4]. According to one study, it was shown that bacteraemia without endocarditis usually occurs in immunocompromised patients, while endocarditis usually occurs in immunocompetent patients [5] although alcohol abuse is believed to be a risk factor. The presentation of endocarditis is often subacute with non-specific manifestations such as low grade fever, malaise and weight loss. Left-sided, particularly the aortic valve, previously normal heart valves are commonly involved. The mortality can be up to 38% with reported complications of congestive heart failure, present in 80% of cases, myocardial abscesses, aortic valve perforation, diffuse glomerular nephritis and meningitis.

Over one-third of patients require valve replacement. Other reported infections caused by this pathogen include intracranial abscess, osseous necrosis of thumb, chronic arthritis and peritonitis [6].

Because the organisms are located in deeper parts of the skin, swabs or aspirates from the lesion would not be rewarding. Rather, biopsies of the entire thickness of the dermis should be considered to isolate the bacteria. Identification is based on Gram's stain, cultural morphology, motility, haemolytic characteristics and H_2S production as described above.

The organism is highly sensitive to penicillin, cephalosporins, clindamycin, imipenem and ciprofloxacin, variably sensitive to chloramphenicol, tetracycline and erythromycin, but resistant to aminoglycosides, trimethoprim-sulfamethoxazole and vancomycin. Oral antibiotics can hasten healing of erysipeloid in 48 h and reduce the chance of relapse. Incision and drainage are usually contraindicated as surgery has been noted to prolong the duration of erysipeloid lesions [7]. Penicillin G at 12-20 MU/day for4-6 weeks is the treatment for endocarditis. Cephalosporins are the most appropriate alternatives.

Discussion

In this case, our patient had a typical history of contact with fish and in alcohol abuse. However, his clinical picture was atypical in that he did not have a skin lesion and his clinical course was very mild without having any complications like endocarditis as a result of bacteraemia. In Hong Kong, the fishing industry is prosperous and there are numerous people who like to go fishing as their interest. The actual prevalence of this infection is nevertheless unknown in this locality. The rarity of successful isolation of this organism may be due to its mild presentation in most of the patients who recover spontaneously without any investigation done or treatment given. In addition, the deep anatomical site, where the pathogen resides and cannot be revealed by simple sampling methods like swabbing or aspiration, may also explain such an observation.

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