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Appropriate use of antibiotics in common clinical settings

RWH Yung, PCS Lo, H Chen, Infection Control Branch, Centre for Health Protection

Appropriate antibiotic use has long been the concern of medical practitioners and the society. The decision to prescribe an antibiotic falls on both clinical judgement as well as laboratory information. This article is going to provide some suggestions on the appropriate use of antibiotics in common clinical settings.

Upper Respiratory tract infection (URTI)

URTI can include non-specific infections, acute pharyngitis, acute sinusitis and acute otitis media. It is the most common diagnosis in all consultations in primary care [1]. Among all URTIs, 80-90% of them are of viral causes. The most common causative agents are rhinovirus, respiratory syncytial virus, influenza virus, parainfluenza virus, adenovirus and coronavirus. Judging from clinical signs and symptoms, it may not be possible to differentiate whether the patient is suffering from bacterial or viral infection. This makes the proper use of antibiotics difficult.

In a survey conducted in Singapore, only 7.9% of the respondents knew that URTI was mainly caused by viruses. Moreover, over 60% thought that antibiotics would help to relieve their problems faster. The survey also revealed that if the patient knew that URTI would resolve on its own, there would be more appropriate antibiotic recognition and health-seeking behaviour [2]. That is, in such a civilised city similar to Hong Kong, proper health knowledge on antibiotic usage is still insufficient. On the other hand, in Hong Kong, Dickinson et al revealed that among all consultations by family doctors, 25% of patients with URTI, 40% of patients with throat symptoms, and 80% of patients with tonsillitis were prescribed antibiotics [3].

Usually, the doctors would be more likely to prescribe antibiotic if there is a request from the patient, if the patient is a smoker, of old age, having sinusitis, purulent sputum, purulent nasal discharge or imminent overseas travel [4].

The followings are common clinical settings in which antibiotic prescription might be necessary.

1) Acute pharyngitis

90% of acute pharyngitis cases are of viral causes [1]. The Centor criteria can help clinician to decide whether antibiotic prescriptions are necessary in cases of acute pharyngitis (tonsillar exudates, tender anterior cervical lymphadenopathy, absence of cough and history of fever). However, one local study reported that the positive predictive value of having Group Aβ-hemolytic streptococci (GABHS) isolated from throat cultures was only 41.1%, even when all criteria were present [5]. In ideal situation, antibiotic should be reserved for those with confirmed diagnosis of GABHS to prevent subsequent development of acute rheumatic fever, shorten the clinical course of illness, prevent suppurative complications and prevent spread of the organism to others.

To confirm the GABHS infection, we may perform rapid antigen test (80-90% sensitive), which allows us to have the result in minutes. Culture will lead to an even more accurate result with >90% sensitivity, but it can only be available in 24-48 hours, and may delay treatment. Therefore one can consider treatment when GABHS is suspected, and

treatment may be stopped when GABHS has been excluded by a reliable microbiological test.

	Classic Streptococcal	**Viral**
Age	Peak 5-11 year	All
Symptoms	Sudden onset	Variable
	Sore throat, may be severe	Often mild
	Fever	Variable
	Headache	Myalgia, arthralgia
	Abdominal pain, nausea, vomiting	Variable
Signs	Pharyngeal erythema and exudates	Usually no exudates, ulcerative lesions in some
	Tender, enlarged anterior cervical lymph nodes	Generally minor, non-tender
	Palatal petechiae	
	Tonsillar hypertrophy	Variable
	Scarlet fever rash	
	Absence of cough, rhinitis, hoarseness, conjunctivitis and diarrhoea	Often

Adopted from Tanz RR et al [6]

The preferred first line antibiotic treatment for GABHS infection is still penicillin, with erythromycin reserved for those with penicillin allergy. The suggested dose of penicillin V is 250mg (bd for children and qid for adult) for 10 days [1]. Cephalosporins are also effective against GABHS. However, cost-effectiveness and antibiotic resistance development should be taken into account when considering the prescription of cephalosporins for this condition. In fact, Casey et al has pointed out that one needs to treat 19 adults with cephalosporin to get one additional bacteriologic cure, compared with penicillin [7].

2) Acute sinusitis

Acute infectious sinusitis can result from viral and bacterial etiology. After all, only 0.5-13% of all clinical sinusitis are bacterial in origin [8,9]. In fact, cases of acute bacterial sinusitis commonly follow viral upper respiratory infections. Common causative bacterial agents include *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.*

The clinical indicators of acute bacterial sinusitis include “double-sickening” (patient starts with a cold and begins to improve, then has the congestion and discomfort returned), unilateral pain above or below the eyes on leaning forward, maxillary toothache, purulent rhinorrhea or secretion and tenderness over sinuses [10]. The response towards decongestants or antihistamines is poor. However, these classical signs may not be found in young children.

Clinical diagnosis of acute bacterial sinusitis is made when there is persistent non-specific upper respiratory signs and symptoms (>10-14 days) or severe upper

respiratory tract signs and symptoms including fever greater than 39℃, facial swelling and facial pain. A randomised controlled trial showed that acute bacterial sinusitis should be treated with antibiotics as they were significantly more effective than placebo alone [11]. For children with persistent nasal discharge or older children with radiographically confirmed sinusitis, antibiotics given for 10 days will reduce the probability of persistent infection in short to medium term (NNT=8, 95% CI 5-29), but no long term benefits have been documented [12].

Acute infectious sinusitis will often resolve even without antimicrobial therapy. Therefore, only those with protracted symptoms (>8-10 days) suggestive of bacterial infection merit antibiotic therapy. Amoxicillin is the preferred first line treatment. For recurrent infections or inpatients showing no response after 48-72 hours, we may use amoxicillin-clavulanic acid or β-lactamase-stable cephalosporins, which are active against pneumococcus. We may also consider an agent against penicillin-resistant pneumococci e.g. clindamycin or high-dose amoxicillin [1,13].

3) Acute otitis media (AOM)

AOM is common in children, especially for those with age between 6 and 15. Symptoms include fever, pain and discharging ear, but it can also present non-specifically in children. Therefore, clinicians should have a high index of suspicion in children. Organisms commonly causing AOM include *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* [1]. There has been a global trend of emergence of penicillin resistance among strains of *S. pneumoniae* [13]. Hong Kong is one of the regions with the highest prevalence. For *S. pneumoniae* isolates obtained from all regions of Hong Kong in the year 2000, 39.4% of 180 isolates were susceptible to penicillin, 11.7% were intermediate and 48.9% were resistant [14]. β-lactamase production occurs in a relatively high proportion of isolates of *H. influenzae* (0-37.1%) and *M. catarrhalis* (>90%), and their susceptibilities to amoxicillin and cefaclor are relatively low. The susceptibility of *H. influenzae* to macrolide is also low [15,16].

The management of pain is important in AOM. Antibiotics may be considered for groups with specific risk factors [1]. Risk factors include children younger than 2 years old, history of chronic or recurrent otitis media, presence of perforated tympanic membrane, attendance of day care, as well as undue parental anxiety. The parents of the children should be given information about the benefits and risks of antimicrobial therapy, and a shared decision-making approach to antimicrobial therapy can then be followed.

Of the available oral agents, amoxicillin has the greatest in vitro activity against pneumococci. It also has a long history of safety and clinical efficacy when used to treat AOM. Because of the high prevalence of resistant *S. pneumoniae*, a higher dose of amoxicillin (80-90mg/kg/day in divided doses) becomes the first-line therapy. For children smaller than 2 years old or those patients with severe disease, the antibiotic should be continued for 10 days. For patients greater than 6 years or those with mild to moderate disease only, 5 to 7-day course is enough. Amoxicillin-clavulanate, clindamycin and ceftriaxone may be considered if condition does not improve after 2-3 days [1,17,18].

Urinary Tract Infection (UTI)

In outpatient setting, apart from upper respiratory tract infection, urinary tract infection is also not uncommonly seen.

The most common causative agent of UTI is *Escherichia coli*. Other common agents include Klebsiella and Proteus species, as well as *Staphylococcus saprophyticus*, which predominantly affect young, sexually active ladies. Clinically the classical presentations are frequency, urgency and dysuria. Dipstick test may be used to identify pyuria and bacteriuria. The antibiotic resistance surveillance by the Department of Health revealed that resistance of *E. coli* towards nalidixic acid and co-trimoxazole were 60% and 38% respectively in 2005. In fact, the emergence of ESBL-producing strain of *E. coli* leads us to reconsider the proper antibiotic treatment of UTI [1].

Currently, for treatment of uncomplicated UTI in adult, we may use nitrofurantoin, amoxicillin-clavulanate or ofloxacin. In children, we may use cefuroxime or co-trimoxazole as the first line treatment. Co-trimoxazole, nitrofurantoin and nalidixic acid are not recommended for infants younger than 3 months of age. Moreover, we need to consider antibiotics prophylaxis after curative treatment if the patient is younger than 3 years old [1,19,20].

Local guidelines on antibiotic use

The Department of Health has published the "Guideline for antimicrobial use in primary health care clinic" in 2002. Recently the University of Hong Kong, Centre for Health Protection, Hospital Authority and other collaborators have also updated the "IMPACT (Interhospital Multidisciplinary Programme on Antimicrobial ChemoTherapy) guidelines" to promulgate a proper attitude among medical staff towards prescription of antimicrobial chemotherapy. With the guidance of these local references, we hope to enhance doctors' antibiotic prescription and thus ameliorate the situation of emerging antibiotic resistance.

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Pharmacological considerations in optimising antibiotic prescription

Raymond WM Mak, Department of Pharmacy, Queen Mary Hospital

Introduction

In the clinical development of drugs including antibiotics through different stages of clinical trials, the determination of the "best" dosage regimen is often decided in the early phase I or II trials. The initial choice of dosage regimen was often rather empirical, based upon the likely minimum inhibitory concentration (MIC) of pathogens targeted, preliminary pharmacokinetic data, as well as dosage regimens that provided plasma drug concentrations which usually far exceeded the MIC of the target organisms. The dosage regimens that afforded efficacy data from the early trials are carried forward into phase III trials, and could eventually become the dosage regimen licensed. In the early phase, the case numbers involved in dose-finding trials were often small, and with such limitation little real difference in efficacy can be ascertained [1], let alone having any reassurance that the dosage regimen employed was ideal.

A closer study of a drug's pharmacology, in particular the recent research on pharmacokinetics (PK) and pharmacodynamics (PD) on antibiotics would allow exploration into whether an antibiotic's therapeutic potential has been fully exploited. Pharmacokinetics refers to the study of how our body handles a particular drug, i.e. its absorption, distribution, metabolism and elimination. On the other hand, pharmacodynamics is the study of a drug's biochemical and physiological actions, such as the mechanism of action and the MIC of the target organism.

Drawbacks of MIC

In the management of infections, the MIC figure is often referred to for a given pair of antibiotic and pathogen. It is a measure of how 'sensitive' a micro-organism is to an antibiotic, or how 'potent' an antibiotic is against a micro-organism. It is a very useful tool because it provides guidance on the selection of antibiotics. However, when used alone, it is not perfect because it does not provide a full picture of everything that occurs during antibiotic treatment. For example, it gives no information as to whether there is persistent antimicrobial effect when the drug levels fall below the MIC; it does not tell us whether an antibiotic exhibits concentration-dependent or time-dependent killing kinetics; and, worst of all, it does not take into account the factor of drug exposure of the organism involved.

For a given pair of antibiotic and pathogen (Figure 1), the MIC of the organism is largely fixed; and similarly the pharmacokinetics (PK) of the drug (or how our body handles the drug) usually remains fairly constant. However, by changing the dosage regimen, the degree of drug exposure or the concentration-time profile may be altered. Since changes in drug exposure, for example bigger/smaller doses and more/less frequent dosing, do have an impact on the antibiotic treatment outcome, various means of linking drug exposure (pharmacokinetics) with drug effects (pharmacodynamics) have been studied.

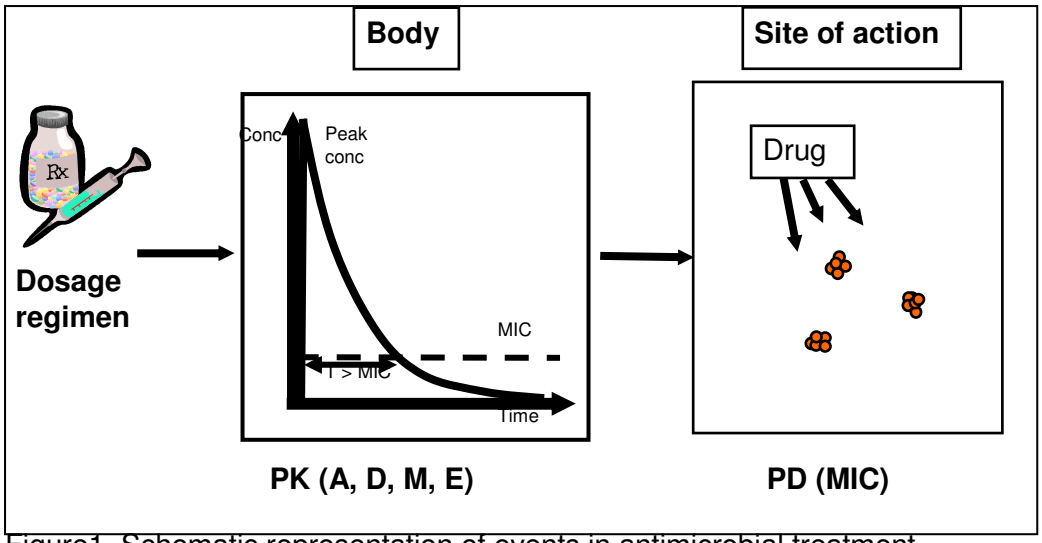

Figure1. Schematic representation of events in antimicrobial treatment

The PK/PD parameters and their importance

In order to correlate drug exposure with drug effects, different features of drug exposure such as the peak concentration (Peak), area under the curve over 24 hours (AUC_{24}) and the time (T) above the MIC of the concentration-time graph, have been linked to the MIC in the form of ratios. Such ratios are: the time above the MIC (T>MIC), area under the curve to MIC (AUC_{24}/MIC) and the peak concentration to MIC (Peak/MIC). These ratios are useful tools for a number of reasons: (1) they are ratios that link pharmacokinetics with pharmacodynamics, (2) they are amenable to manipulation through changes in the dosage regimen, and if that is possible then (3) research may be conducted to find out whether any target drug levels will give rise to favourable treatment outcome. Recent studies have shown that, provided that we could achieve certain drug targets, these PK/PD parameters may become important predictors of clinical and/or microbiological treatment outcome, as well as the likelihood of emergence of drug resistance [2].

Magnitudes of PK/PD parameters associated with favourable outcomes

For antibiotics exhibiting time-dependent killing, studies have shown that significant efficacy (i.e. > 80% bacterial eradication) is associated with a T>MIC of at least 40-50% of the dosing intervals [3-5]. Examples of antibiotics with efficacies predicted by this parameter would include the penicillins, cephalosporins, carbapenems, as well as the monobactams. The T>MIC target for favourable outcome is in fact the same whether for penicillin-sensitive, penicillin-intermediate or penicillin-resistant strains [5]; although with the higher MICs of more resistant strains, the PK/PD target would be harder if not impossible to achieve with regular dosing.

For antibiotics exhibiting concentration-dependent killing, a Peak/MIC ratio of at least 8-10 is associated with clinical efficacy and reduced development of resistance [6,7]. Examples of such antibiotics include the aminoglycosides, fluoroquinolones and ketolides. The association of efficacy with the target Peak/MIC level has been demonstrated in patients with nosocomial pneumonia, treated with aminoglycosides, mostly in combination with β-lactam antibiotics. Following treatment by day 7, an aminoglycoside Peak/MIC ratio of 10 was associated with a nearly 90% chance of temperature resolution by day 7 of treatment [6]. The association of Peak/MIC ratio with reduced emergence of resistance had been demonstrated in patients with nosocomial pneumonia treated with ciprofloxacin monotherapy. For patients given regimens resulting in Peak/MIC levels of <8, the likelihood of emergence of resistance were as high as 80%, whereas for those with Peak/MIC levels of >8, the corresponding rate was

only 10% [8].

For those antibiotics with treatment efficacies predicted by AUC_{24}/MIC, the target ratios will depend on the type of micro-organisms to be tackled. With Gram-negative bacteria, a ratio of at least 100-125 is associated with efficacy [2,9]; whereas for Gram-positive bacteria, a lower ratio of 30-35 would suffice for non-neutropenic patients [10]. In terms of emergence of resistance, in patients receiving ciprofloxacin with or without a β-lactam for primarily Gram-negative nosocomial pneumonia, an AUC_{24}/MIC ratio of <100 was associated with resistance emergence rate of 82%, whereas the rate dropped to 9% when a ratio of $\geqq$100 was achieved [11]. The treatment efficacies of many groups of antibiotics are predicted by the AUC_{24}/MIC parameter (Table 1). In summary, for β-lactam antibiotics, treatment outcomes are best predicted by T>MIC whereas for the aminoglycosides, fluoroquinolones and ketolides, the Peak/MIC (or AUC_{24}/MIC) appears to be a better predictor of efficacy. The efficacies of most other antibiotic groups are best predicted by the AUC_{24}/MIC ratio.

T > MIC	**AUC_{24}/MIC**	**Peak/MIC (or AUC_{24}/MIC)**
Penicillins	Macrolides	Aminoglycosides
Cephalosporins	Clindamycin	Fluoroquinolones
Carbapenems	Tetracyclines	Ketolides
Monobactams	Streptogramins	
	Glycopeptides	
	Oxazolidinones	

Table 1. Association between PK/PD parameters and antibiotic groups

Association between predictive parameters and antibiotics

For antibiotics exhibiting concentration-dependent killing (e.g. aminoglycosides, fluoroquinolones or ketolides), it is not difficult to understand why the Peak/MIC ratio should predict treatment outcome. However, for antibiotics with time-dependent killing characteristics, it is not immediately apparent why for some antibiotics, their efficacies would be predicted by T>MIC, while for others the AUC_{24}/MIC ratio would be the preferred parameter. To better understand this phenomenon, it is necessary to consider another characteristic of antibiotics, namely the ability to suppress the growth of bacteria when drug levels fall below the MIC i.e. the post-antibiotic effect (PAE).

The β-lactam group of antibiotics generally possess minimal to no PAE [12], whereas the other antibiotic groups possess moderate to prolonged PAE. As the β-lactam antibiotics possess minimal to no PAE, it is therefore sensible to maintain the drug levels above the MIC for as long as possible, and hence it is not surprising that T>MIC should predict the treatment outcome for these agents. For the other time-dependent killing agents, maintaining the drug levels above the MIC is less critical, and for them a PK/PD ratio that represents total drug exposure over time (i.e. AUC_{24}/MIC) seems to best predict their treatment efficacies. For the concentration-dependent killing agents, the fact that they demonstrate moderate to prolonged PAE would imply that they could be dosed less frequently.

It is possible that the treatment efficacy of some antibiotics may be predicted by more than one predictive parameter. This is largely due to the fact that the peak concentration, the time above the MIC, and the area under the curve are different but inter-related parameters on the same concentration-time graph. The predictive parameter to use for a given antibiotic group would be the parameter that shows the best correlation with bacterial eradication.

Strategies for antibiotic dosing according to best predictive parameter

It is generally neither necessary nor routinely practical to dose an antibiotic to a pre-defined PK/PD target. However, knowing which PK/PD parameter best predicts favourable treatment outcome for an antibiotic is useful as it provides information on how best to devise the dosage regimen for optimal/favourable outcome (Table 2).

T > MIC	AUC_{24}/MIC	Peak/MIC
More frequent dosing (continuous infusion or bigger doses?)	Bigger doses or More frequent dosing or Both	Bigger doses (± less frequent dosing)

Table 2. Strategies for antibiotic dosing according to best predictive parameter

For antibiotics with treatment efficacies that are best predicted by T>MIC, one should dose the antibiotic to maintain the drug level above the MIC for as long as possible. There are many ways to achieve a high T>MIC; for an in-patient setting when dose administration is supervised, more frequent dosing would be a good option. An example of this strategy would be ceftazidime. For less severe infections the recommended dose is 1g Q8H to 2g Q12H, and for more severe infections 2g BD to TDS or 3g Q12H; the recommended strategy for ceftazidime which is a β-lactam would be to choose the more frequent dosing regimen, that is, 1g Q8H or 2g Q8H depending on the severity of the infection. For antibiotics with treatment efficacies that are better predicted by Peak/MIC, which also possess moderate to prolonged PAE (such as the fluoroquinolones), their daily doses should always be combined and given once a day (except ciprofloxacin due to its short $t_{1/2}$). For antibiotics with treatment efficacies predicted by AUC_{24}/MIC, a good deal of flexibility exists for the dosing strategy. The ultimate choice of regimen could depend on other considerations, such as bigger doses to enhance penetration to the site of action, more frequent dosing for patients who have compromised immune function or bigger doses plus more frequent dosing should the infection be suspected to be caused by less sensitive target pathogens. It is always worth bearing in mind at all times during the selection of an “optimal” dosage regimen, that the foregoing discussion has not taken into account the issue of antibiotic toxicity or tolerability. While consideration of the PK/PD principles does provide useful suggestions on antibiotic choices, it also dictates that alternatives have to be chosen in cases failing to reach PK/PD targets, or when unacceptable toxicities are encountered as a result of such therapies.

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An uncommon cause of spondylitis in Hong Kong

GCY Lui, Department of Medicine and Therapeutics, Prince of Wales Hospital

A 52- year-old gentleman presented with a 3-day history of lower limb swelling. The swelling was associated with pain and redness over the dorsum of his feet. Since four months prior to admission, he had been experiencing progressive low back pain. The pain also radiated down his right buttock and leg and affected his ambulation. He also complained of weight loss but denied having fever. He had consulted a chiropractor and had received physiotherapy, with only partial improvement in his symptoms. He also had known history of diabetes mellitus, hypertension and gouty arthritis. He had previously worked as a cook, and mainly handled raw pork to prepare for roasted pork (siu mei). He quitted his job 3 months ago due to severe back pain. He had not travelled outside Hong Kong for the past one year, and he had no history of consumption of unpasteurised dairy products.

On admission, he was febrile with a temperature of 39^{o}C. Right hip and knee movements were limited by pain. Lower limb power was otherwise preserved. Straight-leg raising tests were 70^{o} on both sides. Signs of cellulitis were present over the dorsum of both feet. No heart murmur, organomegaly or lymphadenopathy was present.

His haemoglobin was 9.3g/dL, platelet 303x10^{9}/L, white cell count 7.1x10^{9}/L, sodium 134mmol/L, creatinine 58µmol/L, albumin 31g/L, globulin 41g/L, bilirubin 5µmol/L, alkaline phosphatase 178U/L, alanine transaminase 33U/L, erythrocyte sedimentation rate (ESR) 91mm/h, and C reactive protein (CRP) 28.5mg/L. Chest radiograph and ultrasonogram of the abdomen were unremarkable.

A plain radiograph of the lumbar spine showed generalised osteopenia and degenerative scoliosis, with decreased disc space and spondylolisthesis at L3/4, and wedging of T11 and L2 vertebrae. Bone scintigraphy showed multiple active lesions at fourth and fifth lumbar vertebrae, first to third lumbar spinous processes, and right sacroiliac joint, suggestive of spondylitis and septic arthritis respectively. Magnetic resonance imaging (MRI) of the lumbar spine showed T2 hyperintense enhancing signal in L4 and L5 vertebral bodies and pedicles, L4/5 intervertebral disc, and around the right sacroiliac joint; a thick rim of abnormal enhancing soft tissue surrounding the spine from L4 to S1; narrowing of the spinal canal by L4/5 intervertebral disc protrusion; and T11 and L2 vertebral collapse. Such features were compatible with L4/5 spondylodiscitis and right sacroiliitis.

The patient was given an empirical course of ampicillin and cloxacillin for treatment of the cellulitis of his feet. His fever settled and skin changes over his feet also resolved.

Two sets of blood culture taken after admission grew Gram-negative coccobacilli after 3.8 and 5.1 days of incubation. It was later identified as *Brucella* species by 16S RNA sequencing performed at the Public Health Laboratory Services of the Centre for Health Protection. Speciation was being performed at the time of writing. Antibodies for *Brucella abortus* and *melitensis* were both greater than 1:640 on standard tube agglutination test.

He was given streptomycin and doxycycline for 2 weeks and discharged with doxycycline. ESR and CRP one week after initiation of therapy dropped to 75mm/h and 4.3mg/L respectively. Repeated blood culture 12 days after initiation of antibiotics was negative. He remained afebrile and had partial improvement in back pain 4 weeks after initiation of therapy.

Discussion

Brucellosis is a zoonosis with worldwide distribution and protean clinical manifestations. Osteoarticular manifestations are the most frequent complications of brucellosis [1], occurring in up to 70% of patients in endemic areas [2]. Amongst such complications, sacroiliitis is the most common manifestation in most series, and affects all age groups [2,3]. On the other hand, spondylitis more commonly affects older patients [4] and those with chronic diseases [5].

Animal brucellosis has been declining in China since the 1980s, although the incidence of human brucellosis was observed to be increasing in the recent decade. *B. melitensis* was the predominant strain in mainland China [6]. Brucellosis is uncommon in Hong Kong. Only three laboratory-confirmed cases of brucellosis were reported to the Centre for Health Protection over a 2-year period in 2004 to 2006 [7]. As in other areas with low prevalence, diagnosis of this disease is often delayed due to subtle clinical manifestations early in its course [4].

Although vaccination programmes have been successful in animals, especially in eradicating bovine disease, in many industrialised countries, human brucellosis still evades complete eradication in many parts of the world. Occupational contact, for example by abattoir workers, dairy industry professionals and laboratory staff, remains one of the major sources of infection, especially in developed countries [1,4]. Brucellosis is one of the 51 occupational diseases under the Occupational Safety and Health Ordinance, Schedule 2 (Cap. 509) of the Laws of Hong Kong. Thus, a detailed occupational history will aid clinicians to raise the suspicion of brucellosis in compatible clinical settings.

Blood culture remains an important tool to reach the diagnosis. Bacteraemia, for example, is present in up to 70% of patients with spondylitis [4]. Although traditionally, prolonged incubation and weekly subculture of blood culture are recommended when brucellosis is suspected, automated blood culture systems allow isolation of *Brucella* species in 3 to 5 days [8]. PCR-based tests on blood samples are also emerging as sensitive tools for more rapid identification of the organism [9].

Imaging also plays an important role in the diagnostic process of brucellosis. Radiological changes on plain radiograph may only be evident 2 to 8 weeks after symptom onset. On the other hand, both bone scintigraphy and MRI enjoy the advantage of higher sensitivity in the early stage. The latter modality also allows better delineation of epidural and paravertebral extension, differentiation from other spinal pathologies, including tuberculous infection, and monitoring of response to therapy [10].

Brucella spondylitis classically runs a protracted course and has less optimal outcomes to therapy. Treatment failure and relapses were not uncommonly seen in various series [4]. Although no antibiotic regimen can be demonstrated to be more efficacious in the treatment of spondylitis in a recent review, a prolonged treatment course of at least 3 months is advocated [11]. Duration of therapy may be guided by clinical and radiological progress [12].

Although Hong Kong has a low annual incidence of brucellosis, we are not totally immune from it. Inquiry into relevant epidemiological linkage, performing blood cultures and imaging, together with a high index of suspicion, may aid in early diagnosis and prevent long-term complications of this zoonosis.

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Journal Review

Alan KL Wu, Department of Pathology, Pamela Youde Nethersole Eastern Hospital

Chang DC, Grant GB, O'Donnell K, et al. Multistate outbreak of fusarium keratitis associated with use of a contact lens solution. JAMA. 2006; 296: 53-63.

Microbial keratitis is a well-known risk of contact lens use, although keratitis caused by fungal organisms is uncommonly seen. Thus, an investigation was carried out by the CDC after three cases of contact lens–related fusarium keratitis were reported in March 2006. Notably, similar cases had also occurred at around the same time both in Singapore and Hong Kong.

By the end of the investigation, a total of 164 confirmed and 32 suspected cases of fusarium keratitis had been identified in 33 states and 1 U.S. territory, with 55 (34%) of the patients with confirmed infection having undergone or were about to have corneal transplantation as a result of severe keratitis. The only factor significantly associated with fusarium keratitis was use of a specific contact lens solution (ReNu with MoistureLoc) during the month before symptom onset (69% vs. 15%, OR 13.3). Cultures of samples from confirmed patients' contact lens products yielded fusarium species in 1 of 17 opened bottles of ReNu with MoistureLoc and 6 of 11 used contact lens cases; the organism was not detected in unopened solution bottles or in environmental samples from lens solution factory. Molecular typing of fusarium isolates in the outbreak revealed a diversity of species and genotypes. The product was eventually withdrawn from the market in May 2006.

Points to note: These findings are most consistent with the hypothesis that the specific lens solution in question supports growth of fusarium after extrinsic contamination of contact lens solution bottles, lenses, or lens cases. This composition of solution is unusual in that it contained alexidine and polyquarterium 10, as well as a high concentration of the surfactant poloxamer 407. Further investigation of the interaction of these ingredients with fungal pathogens is eagerly awaited.

Dixon WG, Watson K, Lunt M, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006; 54: 2368-76.

Patients who receive anti–tumour necrosis factor (TNF) drugs for treatment of rheumatoid arthritis (RA) are at risk for infectious complications. Using a national registry of RA patients, a group of U.K. researchers recently conducted a study to compare the rates of serious infections in 7664 patients receiving anti-TNF drugs (etanercept [Enbrel], infliximab [Remicade], and adalimumab [Humira]) and 1354 patients receiving only disease-modifying drugs (DMARD; e.g. methotrexate). Serious infections were defined as those that resulted in hospitalisation or death or that required intravenous antibiotics for the patients.

The rate of serious infections was higher in the anti-TNF group (53 vs. 41 events / 1000 person-years) as compared to the DMARD group, with similar rates for each of the three anti-TNF drugs. Skin and soft-tissue infections were significantly more common in the anti-TNF group than in the DMARD group. In addition, nineteen serious intracellular bacterial infections occurred, all in anti-TNF drug recipients: tuberculosis and atypical mycobacterium (11 cases, 7/10 extrapulmonary for those with tuberculosis), salmonella (3), listeria (3), and legionella (2).

Points to note: This study captured a large number of patients in UK who were administered anti-TNF drugs during a defined interval, and the results generated should thus be representative of these patients in general. Important findings are the increased incidence of skin and soft-tissue infections and the infections with intracellular organisms (especially tuberculosis). Further studies involving controls from the general population should be conducted to quantify the excess risk of infections in patients given anti-TNF drugs for RA.

Vong S, Coghlan B, Mardy S, et al. Low frequency of poultry-to-human H5N1 virus transmission, southern Cambodia, 2005. Emerg Infect Dis 2006; 12: 1542-7.

The H5N1 virus continues to spread in avian populations, causing death of poultry and wild birds worldwide. On the other hand, clinically evident human infections have remained relatively infrequent to date. To better understand the epidemiology of transmission of the virus, researchers conducted a seroepidemiologic survey in southern Cambodia, where a 28-year-old man suffered a fatal infection of H5N1 in March 2005 and H5N1 was found in chickens.

In late March 2005, the investigators interviewed residents living within a 1-km radius of the index human case, gathered sick and dead poultry, and randomly collected cloacal swabs from healthy poultry. Of note, over 90% of interviewed households raised chickens, and 31% raised both chickens and ducks. 63% of households reported poultry deaths during the early months of 2005. Specimens from two sick chickens were positive for H5N1 on RT-PCR.

In early June 2005, the investigators interviewed 351 residents from 93 households and obtained blood samples. No villager reported having had a febrile respiratory infection during the time of the poultry outbreaks. All 351 blood samples tested were found to be negative for neutralising antibodies to H5N1. Households that had purchased live poultry during the preceding year were more likely to have had flocks infected with H5N1. Cleaning cages or stalls and cleaning up feathers were associated with a reduced risk for H5N1 infection in the household poultry.

Points to note: These findings seem to suggest that mild and asymptomatic infection with H5N1 was uncommon and that the H5N1 virus present in Cambodia in 2005 was not easily transmitted to humans. Furthermore, they suggest some practices that might reduce the risk of introducing H5N1 into household flocks. Further studies are urgently needed to investigate these important issues, which would have significant bearings on the prevention and control of the disease.