Penicillin resistant Streptococcus pneumoniae (PRSP)

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Streptococcus pneumoniae is the major pathogen causing community acquired infections such as acute otitis media, pneumonia, bacteraemia and meningitis. The rapid increase in resistance to penicillin and other antibiotics is witnessed in both developed and developing countries affecting all age groups and warrant our close attention

Definition of resistance

According to NCCLS (National committee of clinical laboratory service) guideline, it is defined as penicillin sensitive, intermediate and resistant when the MIC is <=*0.*006.0.1-1, and >=2ug/ml respectively. This breakpoint is chosen based on the efficacy of penicillin in treating pneumococcal meningitis. The clinical implication in non-meningeal infection for intermediate and resistant group have been questioned since higher concentration of penicillin can be attained at the site of infection by increasing the dose of antibiotic and clinical response usually occurs.

Prevalence

Clinical isolate with intermediate sensitivity was first reported in 1967. South Africa reported cases of pneumococcus highly resistant to penicillin and multiresistant to other antibiotics in 1977 and 1978. Since then, penicillin nonsusceptible pneumococcus have been reported with increasing frequency in some countries e.g. Spain 57.8%(1988-9). In 1990s, many countries have reported increasing prevalence of penicillin resistance (intermediate and resistant) especially in Asian countries. The rate of nonsusceptibility are 80% in Korea, 65% in Japan, 61% in Vietnam and 58% in Thailand based on ANSORP (Asian Net-work for Surveillance of Resistant Pathogens) study in 1996-7. Hong Kong had the first report in 1988. In the 1990s, the rate jumped from less than 10% to almost 80% nowadays.

Resistance problem

The resistance to penicillin arises from mosaic mutation of penicillin binding protein (PBP) genes due to interspecies recombination of homologous genes. The penicillin resistant pneumococcus is usually also resistant to other common antibiotic such as macrolide, tetracycline, co-trimoxazole, chloramphenicol and clindamycin making choice of antibiotic limited to 3rd generation cephalosporin, vancomycin together with rifampicin in case of critical infection such as meningitis. The recent case report of vancomycin tolerance is a worrying new development.

Fluoroquinolone resistance is emerging in Hong Kong where the resistance rates climb from 0.5% - 5% to around 10% nowadays which is rarely seen in other countries. The risk factors associated with levofloxacin resistance have been identified in a case control study to include chronic obstructive pulmonary disease, hospitalisation, residence in nursing home and exposure to Fluoroquinolone.

Epidemiology

The prevalence of PRSP is higher in isolates from hospitalised patients versus outpatients and higher in children compared with adults. Resistant strains are confined to a limited number of serogroups notably 23F, 19F, 14, 6 which account for more than 90% of PRSP. Evidence from other molecular typing methods such as pulse field gel electrophoresis (PFGE), fingerprinting of amplicons of PBP genes also support the view that the current resistance rate is due to wide dissemination of a few clones of pneumococcus which is related to Spanish strains which are widely circulating in other countries.

Control and management

Prudent use of antibiotics is essential particularly in children and elderly patients where viral infection and chronic obstructive pulmonary disease are common and misuse of antibiotics are prevalent. Some studies have shown that nasopharyngeal carriage of resistant pneumococcus among children attending day care centres are common presumably due to frequent antibiotic exposure and easy transmission of micro-organisms in this setting. The resistant strains will replace the sensitive strains in the presence of antibiotic selective pressure and dominate the colonizing flora. Treatment problem will arise if these strains cause infection subsequently. Vaccination of at risk patients is another option that is not fully utilized. The resistant strains are fully covered in the 23 valent polysaccharide vaccine which has good efficacy in adults and children above 2 years of age. Conjugate vaccine which is immunogenic in those below 2 years of age is now available. There is evidence that it can decrease the carriage of resistant strains belonging to the restricted serogroups in the vaccinated children.

Streptococcus pneumoniae should be closely monitored because the resistance problem is evolving rapidly locally and globally. A network of surveillance centres is now established to monitor these important pathogens in each region.

Clinical issues on the management of MRSA

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Resistant gram-positive pathogens now pose serious therapeutic and infection control challenges both in the hospital and community. Methicillin-resistant *staphylococcus aureus* (MRSA) probably represents the problem in its largest scale and the successful control of which are of paramount importance as methicillin-resistant *coagulase-negative staphylococci* (MRCNS), glycopeptide intermediately resistant S. *aureus* (GISA) and vancomycin-resistant *enterococci* (VRE) actually emerge in the same context.

The incidence of MRSA infection is increasing worldwide and had been associated with worse clinical outcome. Apart from being endemic in hospitals, community infections are also recognized. Molecular studies have demonstrated its horizontal spread both inside and between institutions; and transient colonization of hands of health care personnel efficiently transmits the pathogen. Stringent infection control measures should therefore be implemented.

MRSAs are prevalent in local hospitals (Table 1). They constitute more than fifty percent of all S. *aureus and are* common isolates in wound/catheter sites, drainage fluid, respiratory secretions and even blood cultures. However, differentiation between infection and colonization must be made clinically.

Table 1: MRSA isolates in PMH 1999

Number of MRSA isolates		% of all isolates
Wound	854	9.3
Respiratory	813	8.8
PDF	87	13.6
Blood (HAI)	108	12.8
Blood (CAI)	16	2.8
Others	162	
Total	2040	

Sensitivity: *Co-trimoxazole* 86-94%, *Vancomycin* 100%, *Fusidic acid* 91 %

Over 90% of S. *aureus* are now resistant to penicillin because of beta-lactamase production. Methicillin-sensitive S. *aureus* (MSSA) are susceptible to the oxacillin group or fl-lactam/inhibitor combinations like co-amoxiclav. Sometimes, a β-lactamase hyper-producing strain can mimic MRSA phenotypically, of which

higher doses of S-lactam/inhibitor combinations should be useful. For *true* MRSA, acquisition and de-repression of the *mecA* gene lead to an altered penicillin binding protein (PBP 2'a) and thus methicillin/β-lactam resistance. Initial heterogeneous clones become homogenously resistant after further exposure to β-lactams. Other genes (6/a or *fern),* and environmental conditions (e.g. presence of biofilms) can also affect the expression of methicillin resistance. Vancomycin or teicoplanin are useful, but it must be emphasized that co-resistance to other groups of antibiotics are common (e.g. quinolones, macrolides etc.). GISA with vancomycin MIC 8-16 ug/ml (c.f. vancomycin sensitive strains: MIC = or < 4 ug/ml) emerge as a result of prolonged exposure to the drug. It is possibly resulted from marked thickening of cell wall with increased impedance to vancomycin, and mutations causing altered cell wall metabolism are involved. Patients with underlying medical conditions (e.g. chronic renal failure), indwelling catheters (e.g. Tenckhoff), nosocomial MRSA infections (e.g. in ICUs) and prolonged vancomycin therapy (e.g. 6 - 18 weeks) are at risk. GISA isolated during therapy resulted in treatment failure. Fortunately no highly resistant strains had been encountered clinically. The widespread use of vancomycin also led to VRE, but the mechanism of resistance is different.

The best treatment for MSSA is the oxacillin group. Cefazolin or β-lactam/inhibitor combinations are good alternatives. If patient is allergic to beta-lactams, vancomycin can be used but it is actually bacteriostatic and less effective. Therefore detail description of the "allergic event" is essential, as it may not always preclude the use of alternatives.

Table 2

Potential therapies for MRSA
glycopeptides: vancomycin / teicoplanin
Co-trimoxazole / minocycline
rifampicin / aminoglycosides / fusidic acid
streptogramins (quinupristin-dalfopristin)
Oxazolidinones e.g. linezolid
daptomycin
new carbapenems e.g. L-695
quinolones e.g. trovafloxacin

Potential antibacterial therapies for MRSA are summarized in Table 2. As all listed antibiotics are not completely effective and are associated with development of resistance as well as significant toxicity, the following principles should be observed: (1) treat only true / invasive infections and not colonizers (2) differentiate b-lactamase hyper-producing MSSA from true MRSA by *mecA* gene detection is sometimes required (3) request sensitivity testing to multiple agents

(4) repeat cultures regularly if prolonged therapy is contemplated (5) consider combination therapy in difficult or severe infections (e.g. IE); gentamicin, rifampicin or fusidic acid can be useful adjuncts (though efficacy not well proven), however they are prone to develop resistance if used alone (6) surgical means (e.g. line removal, drainage of abscess, debridement) are extremely helpful (7) strict infection control measures should be implemented to prevent outbreaks (8) consider newer drug groups.

The best anti-microbial therapy for MRSA is still vancomycin in terms of clinical and microbiological response. Teicoplanin, a closely related glycopeptide, has no therapeutic advantage over vancomycin, although renal toxicity is probably less. Reports describing treatment failure and development of resistance during therapy are recognized. Moreover, cross-sensitivity with vancomycin do occur. In contrast, it is useful in treating van B and van C strains of VRE.

The newer drug group streptogramin (e.g. quinupristin-dalfopristin) is effective against a range of resistant gram-positive pathogens like MRSA and VRE (*E. faecium* only and not *faecalis) as* well as anaerobes. For treatment of MRSA, clinical success rate is *64-71%.* However, constitutive erythromycin resistance affects its activity. Moreover, only parental route is possible and significant side effects or drug interactions due to inhibition of cytochrome P450 have limited their usefulness. Nevertheless it offers an effective alternative in serious infections involving these resistant organisms.

Linezolid belongs to another new drug group oxazolidinone. Its unique mechanism of inhibiting ribosomal initiation of protein synthesis precludes cross-resistance to other groups of antibiotics. It is effective against MRSA, VRE, penicillin-resistant S. *pneumoniae* (PRSP) and anaerobes. In general it is not active against gram-negative bacteria with *H. influenzae, M. catarrhalis,* and *Legionella* species being the exception. It produces only mild gastrointestinal side effects and no dose adjustment is necessary in mild to moderate liver or renal diseases. Clinical studies showed that linezolid achieves over 94% cure rate for community-acquired pneumonia. As therapy for MRSA, linezolid 600mg twice daily (oral/parental) has similar clinical efficacy to vancomycin in treating pneumonia, bacteraemia, urinary or soft tissue infections. One study demonstrated its superiority in MRSA eradication by 15%. It may also have the advantage of shorter treatment duration by 4-8 days, and "step down" therapy from intravenous to oral administration is certainly possible. Despite earlier claims that linezolid resistance is uncommon, clinical failure (in VRE treatment) is now being reported.

Rapid emergence of resistance had limited the usefulness of ciprofloxacin; however quinolones of newer generations e.g. trovafloxacin demonstrated therapeutic efficacy in animal models which warrants clinical confirmation. Daptomycin, an experimental drug, seems to offer greatest bactericidal activity in vitro. There are also isolated reports on the success of various combination

therapy involving vancomycin plus rifampicin / co-trimoxazole/ high dose cloxacillin/ beta-lactamase inhibitors to treat severe MRSA or GISA infections like endocarditis, promoting clearance of bacteraemia.

In addition to standard infection control practice, elimination of colonizers during outbreaks seems to reduce the rate of MRSA infection in surgical, dialysis or other special units; but its *routine use is still controversial.* Topical agents like mupirocin 2% ointment applied twice daily to nares and wounds for 1-2 weeks eliminated 95% of MRSA colonizers. However, 40% of cases relapsed and 11% of isolates become resistant. Concomitant oral therapy with minocycline, rifampicin, co-trimoxazole or ciprofloxacin had been tried with various success as well as other topical agents like ramoplanin, fusidic acid, bacitracin and chlorhexidine soap bath.

In order to prevent the emergence of resistant gram-positive pathogens, use of glycopeptides should be restricted and closely monitored. Practical guidelines published by the CDC *{with elaborated recommendations)* are summarized as follows:

Indications for using glycopeptides:

1. Serious infections caused by B-lactam resistant gram-positive organisms confirmed by culture
2. Infections due to gram-positive organisms in patients severely allergic to R-lactams
3. Life-threatening clostridium-difficile colitis or treatment failure with metronidazole
4. Prophylaxis against infective endocarditis for high-risk patients e.g. prosthetic heart valves, vascular shunts or past history of endocarditis (or those with recent exposure / hypersensitive to penicillin)
5. Surgical prophylaxis during prosthetic device insertion e.g. artificial heart valve, hip (esp. patients previously colonized with MRSA)
6. Suspected infective endocarditis affecting prosthetic device
7. Empirical treatment for ICU / febrile neutropenic patients if there is evidence of central line infection or gram-positive cocci revealed by smear from blood or other appropriate specimens (otherwise consider cloxacillin)
8. As an adjuvant antibiotic in the empirical treatment of presumed pneumococcal meningitis

Glycopeptide is not advised for:

1. Initial treatment of neutropenic fever (unless clinically unstable)
2. Only one blood culture is positive for *coagulase-negative staphylococcus, Bacillus* or *Diphtheroid species*
3. Continue empiric treatment if cultures yield no R-lactam-resistant gram-positive microbe *(after 48 hrs)*

4. Treatment of β-lactam-sensitive microbes in dialysis patients for convenience
5. Routine prophylaxis for general surgery, central line or dialysis catheter insertion
6. Eradication of MRSA from colonized surfaces e.g. superficial wound swab, exit sites of catheter, drain fluid

Clostridium difficile associated disease – diagnosis and infection control

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Clostridium difficile associated disease (CDAD) is the most common cause of nosocomial diarrhea. It should be suspected in those with diarrhea who have received antibiotics within the previous 2 months or whose diarrhea begins >= 72 hours after hospitalisation.

In the prospective case-control study by Wilcox and colleagues, CDAD prolonged hospital stay by 21 days per case and increased financial cost by 4107 per case. It would not be uncommon to see at least 100 cases per year per general hospital. Therefore, in a general hospital, CDAD would lead to an additional cost of about 400,000 per year.[1]

Pathogenesis

There are 4 steps in the pathogenesis of CDAD: 1) normal colonic flora disruption, 2) colonic colonisation with C. difficile, 3) toxin production and 4) colonic mucosal injury.

The normal colonic flora confers resistance to C. difficile colonisation and its disruption is a prerequisite for establishing CDAD. The most common offending agents are antibiotics, especially cephalosporins. Cytotoxics are also implicated.

There are two main sources: the infected / colonised human gut and the contaminated hospital environment. C. difficile or its spores are transmitted to the susceptible host by ingestion through contact with infected patients, contaminated hands of healthcare workers, surfaces or formites or by direct inoculation into the 01 tract through any procedures using contaminated equipment, such as nasogastric tube insertion or bowel enema.

Whereas most vegetative cells are killed by gastric acid, the spores germinate after exposure to bile acid and the organisms colonise throughout the colonic lumen rather than attach to specific receptors.

Two exotoxins are produced. Toxin A is an enterotoxin whereas toxin B is a cytotoxin. They cause recruitment of immune cells and release of proinflammatory mediators, leading to mucosal injury: colitis and pseudomembrane formation.

Most cases occur in those older than 60 years of age but rarely in children and infants. This age-related susceptibility is explained by the hypothesis that there are few or no toxin receptors in the gut of children and infants. Lewis I, X and Y antigens are implicated as toxin A receptors whereas toxin B receptors have not yet been identified.

Microbiological diagnosis

There are two approaches: C. difficile stool culture and C. difficile toxin detection in stool.

1. C. difficile stool culture

To isolate C. difficile in stool, cycloserine cefoxitin fructose agar (CCFA) is used. After 48 hours of anaerobic incubation at 37C, C. difficile colonies are 4-6 mm in diameter, yellowish and with rhizoid margin. Another distinctive characteristic is the horse dung odor.

After isolation, further tests are required to confirm the identity, including gas liquid chromatography and biochemical characteristics.

C. difficile stool culture is highly sensitive, being able to detect as few as 2000 C. difficile organisms in the presence of 6 x 10'colony-forming-units of bowel flora per gram of wet stool. Also, it allows antimicrobial susceptibility testing which is important as metronidazole resistant strains are becoming more common. Since culture cannot differentiate non-toxigenic strains from toxigenic strains, toxin detection in stool or from the stool culture isolate is advised.

2. C. difficile toxin detection in stool

The clinical specimen should be a fresh, non-formed stool. The toxin denatures at room temperature. Whenever processing is expected to be delayed, the stool should be stored at low temperature, preferably - 70C, and processed not later than 3 days after receipt.

Rectal swab is not a suitable specimen.

2a. Cytotoxin (toxin B) detection using cell culture neutralisation assay

It is regarded as the gold standard for C. difficile toxin detection. The commonly used cell line is the Vero cell line. The cytopathic effect of cytotoxin should be confirmed by neutralisation with C. difficile-specific antitoxin.

2b. Enzyme immunoassay

There are many commercial kits available. Most of them detect enterotoxin (toxin A) only. They have the advantage of good specificity, acceptable sensitivity, short turnaround time and are less expensive.

Comparison of microbiological methods in diagnosing CDAD, evaluated using both clinical and laboratory data[2]

Methods	Sensitivity (%)	Specificity (%)	Utility
C. difficile stool culture	89 – 100	84 - 99	highly sensitive ; toxigenicity confirmation optimal
cytotoxin detection using cell culture neutralisation assay	67 – 100	85 - 100	with clinical data, diagnostic of CDAD
enzyme immunoassay	63 – 99	75 - 100	with clinical data, diagnostic of CDAD
endoscopy	51	100	diagnostic of PMC

Laboratory practice

The recommended laboratory practice in diagnosing CDAD by the Society for Healthcare Epidemiology of America (SHEA) is a combination of C. difficile stool culture and cytotoxin detection using the cell culture neutralisation assay, the former being sensitive and the latter being specific.[2] But it is costly and time-consuming.

The common practice in many hospitals is to use EIA and clinical findings. In most cases, one stool specimen is enough for diagnosing CDAD. In the study by Renshaw et al. in 1996, repeated assays within 7 days accounted for 36 % of all assays but provided clinically useful information in only 1 %.3 In the study by Manabe et al. in 1995, negative predictive value for the first stool specimen was 97 %.[4] In the study by Aronsson et al. in 1984, testing 3 stool specimens could increase the likelihood of a positive result by 10% only and thus was not cost-effective for routine practice.[5]

Hospital infection control

The most important is antibiotic restriction, i.e. reduction in the use of antibiotics associated with CDAD. In the study by Brown et al. in 1990, a rise in CDAD from 0.02 % in 1982 to 1.47 % in 1987 coincided with an increase in third-generation

cephalosporin use[6]. McNulty et al. in 1997 showed that by changing cefuroxime to penicillin and trimethoprim, CDAD cases fell by > 50 % (37 cases in 252 patients before and 16 in 234 after).[7]

Contact precautions are also important. Single room isolation is optimal but often not available and thus cohort isolation is an alternative. Protective barriers such as gloves should be worn when handling excreta of CDAD patients.

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Guidelines for the management of acute upper respiratory tract infections

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Recently, different societies have published new guidelines for the management of upper respiratory tract infections. The main reason being that resistant organisms are becoming more prevalent particularly Streptococcus pneumoniae and the urgent need to optimise the use of antimicrobials in such infections. The objective is to guide physicians in using antibiotics appropriately and hopefully in the long run decrease the spread of antibiotic resistance.

Pharyngitis

Pharyngitis, nasopharyngitis and tonsillopharyngitis are common manifestations of acute upper respiratory tract infections (URI). The average person may experience 2 – 6 attacks per year. The etiology is mainly viral with rhinovirus accounting for 30 - 40% of the cases. Influenza, parainfluenza and respiratory syncytial virus account for 10- 15%. Beta-haemolytic streptococcus accounts for not more than 5-10% of all cases. The major differential diagnoses include Epstein Barr virus infection, adenovirus infection, herpangina, herpes simplex pharyngitis, gonococcal pharyngitis, Arcanobacterium haemolyticum infection, mycoplasma and Chlamydia pneumoniae infection. In HIV-infected patients, Candida esophagitis sometimes may give rise to sore throat.

Since beta-haemolytic streptococcus accounts for less than 10% of all cases of sore throat, the use of penicillin is infrequently needed if a good history and examination have been carried out.

Clinical features suggestive of strep. pharyngitis in older children and adults include fever of more than 38C, pharyngeal erythema and exudate, tender anterior cervical nodes and absence of rhinorrhea, cough, sinusitis or red eyes. Studies have been carried out utilising such clinical signs and symptoms as guidelines for diagnosis and use of antibiotics. A point is awarded each for documented temperature of 1C above normal, absence of cough, tender cervical nodes, tonsillar swelling or exudate and age of 18 years or under. One point is deducted if the patient is older than 45 years old. According to the scoring system no treatment or culture need to be done if the patient has 1 point or less. When the patient has a score of 4 points, treatment (with or without culture) with penicillin is indicated. This approach has been found to be reasonably sensitive in a Canadian study and has cut down the use of antibiotics by about 50%. Patients with scores between 2 - 3 can be handled by close clinical observation, have a swab taken for latex agglutination or a swab sent for culture. Patients can be treated empirically with penicillin or treatment can be deferred until culture results are available. It has been shown that a reasonable delay in treatment did not result in treatment failure, relapse or increase in rate of complication.

For parents who insist on receiving drugs for sore throat secondary to viral infection, it would be reasonable to recommend zinc acetate lozenges every 1 - 2 hours. Recent studies indicate that zinc acetate lozenges may decrease the severity and duration of sore throat related to cold symptoms. The action may be related to decrease in proinflammatory cytokine levels.

Otitis media

Acute otitis media (AOM) is a very common paediatric infection. However it is wrong to assume that every child with earache and URI symptoms is suffering from AOM. Clinical diagnosis can be made by otoscopic examination. Tympanocentesis, microscopical examination, Gram smear and culture of middle ear fluid may need to be done confirm the clinical suspicion of bacterial infection.

Use of antibiotics in AOM is still controversial. Multiple meta-analyses showed universal and marginal advantage with the use of antibiotics. However most of these studies were done in the early 1990s, that is, before the era of high incidence of resistant pneumococcus.

Pneumococcus accounts for 40 - 50% of all AOM. Approximately 15 - 20% of such cases would resolve spontaneously. Treatment failure is high with penicillin non-susceptible Strep. pneumoniae. In spite of this ampicillin or amoxicillin is still the first drug of choice for AOM. Taking into consideration the spontaneous recovery rate and the incidence of resistant pneumococci in the community, the use of ampicillin as the first drug of choice would carry a failure rate of 10%.

The risk of harbouring resistant pneumococci is higher in patients under two years old, have acquired infection in day care setting or have received antibiotics in the preceding 1 – 3 months. The usual dosage of 40-45 mg per kg per day of ampicillin may not be adequate for this group. Doubling the dosage to 80-90 mg per kg per day will yield middle ear fluid level of ampicillin about 3 - 8 ug/ml and should be adequate for most patients. Pneumococcal resistance is related to penicillin binding protein problems. Thus adding clavulanic acid will not solve the problem of penicillin resistance unless the dose of the amoxicillin is increased. However, the use of augmentin (amoxicillin with clavulanic acid) may help by eradicating concomitant Haemophilus influenzae or Moraxella species. Many commonly prescribed oral cephalosporins for AOM usually have very poor efficacy as the minimal inhibitory concentration (MIC) of the pathogen is high and the middle ear fluid concentration of these antibiotics is low for Strep. pneumoniae. This includes cefixime, cefaclor, loracabef and cefbid. Cefuroxime, clindamycin or ceftriaxone may be needed for more resistant cases.

Sinusitis

More than 80% of sinus problems are treated by primary care physicians. It is important to recognise that 90% of patients with colds have rhinosinusitis

symptoms. 25% of such patients may have symptoms lasting for more than two weeks. Only 0.5 - 5% of rhinosinusitis patients have actual bacterial infection. Of the pathogens isolated pneumococcus accounts for 20 - 41%, H. influenzae 6 - 50%, anaerobes 0- 10% and M. catarrhalis 2 - 4%. 30 - 50% of sinus aspirates actually show no pathogen.

60% of patients with bacterial sinusitis may respond spontaneously without antibiotics. The result is better with the use of decongestants. For clinical practice acute sinusitis is generally a clinical diagnosis. Radiography is rarely used for confirmation. Some of the symptoms commonly associated with acute sinusitis actually are poor predictors of infection. These include sore throat, itchy eyes and constitutional symptoms. On the other hand, a biphasic illness, maxillary toothache, paranasal tenderness, abnormal transillumination of the sinus and a sedimentation rate of more than 10 mm/hour are good predictors of infection. Usually the more symptoms and signs are present the higher the likelihood of bacterial sinusitis.

The first line antibiotics for treatment of acute sinusitis are amoxil-clavulanate (Augmentin), amoxil-cefpodoxime proxetil, and cefuroxime axetil. Depending on the sensitivity pattern of the isolates in a particular locality, trimethoprim-sulfamethoxazole may also be helpful.

Acute bronchitis

Acute bronchitis is mostly caused by viral agents including influenza, parainfluenza, adenovirus, rhinovirus and RSV. Atypical pneumonia including Mycoplasma pneumoniae or Chlamydia pneumoniae and Bordetella should be included in the differential diagnosis. Antibiotic is justified when Bordetella is suspected or when the patient has symptoms lasting for more than 7-10 days. Atypical pneumonia may respond to macrolides and tetracyclines.

Highlights from Asia Pacific Post-graduate Forum: Evolving strategies in HIV management 23 - 25 March 2001 Hanoi, Vietnam

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It has been more than 5 years since combination of antiretroviral agents are used to treat HIV. Highly active antiretroviral therapy (HAART) has led to remarkable decrease in rate of hospitalization and improving morbidity and mortality among HIV-infected patients. With time, HIV physicians are now facing challenges more than maintaining an elevated CD4 count and a suppressed HIV RNA viral load. Issues on long term toxicity, adherence, and salvage of failed regimens are the main theme of the forum and will remain to be important in the years to come.

We are now almost certain that, with the present available antiretroviral agents, HAART will have to be continued for life. There are a host of different adverse events associated with each of the antiretroviral therapies that needs to be considered when initiating therapy. With regards to metabolic disorders, elevated cholesterol and triglycerides and effects on glucose metabolism vary between antiretroviral agents. Lipodystrophy is a multifactorial syndrome, the etiology of which is as yet unknown. However, new evidence suggests that the nucleoside reverse transcriptase inhibitors like zidovudine and stavudine contribute to many of the body-form changes associated with lipodystrophy and appear to play a major role in mitochondrial toxicity. Factors other than medication may also be contributing to the cause of lipodystrophy. Hence it appears unfair to attribute lipodystrophy solely to protease inhibitors as once thought.

Another important consideration in comparing antiretroviral therapy is the variable rate of nausea, vomiting, diarrhoea, rash and liver toxicity. These are becoming increasingly important factors in patient quality of life and adherence to treatment regimens. Regimens complexity (for example, three times versus two times daily), pill burden, food restrictions and special requirement (e.g. fatty food to increase absorption of some drugs and fasted state for others) have also been correlated with adherence rates.

With these considerations in mind, one evolving strategy is dual protease inhibitors combination in which a 'baby dose' of ritonavir twice daily is added to standard protease inhibitor (PI) containing regimens. Ritonavir is a potent inhibitor of the cytochrome P450 system and significantly boosts blood levels of other PI (s). The combination of indinavir with ritonavir has been shown to yield high plasma levels of indinavir. With ritonavir 100mg twice daily, indinavir 800mg can be given twice instead of three times daily and this favours adherence without food and mealtime restriction.

In the events of salvage, a significant number of patients who have previously failed multiple Pi-based regimens have responded favourably to indinavir (800mg bid) plus ritonavir (200mg bid) based salvage regimens. Indinavir trough levels are well in excess of the IC95 of most indinavir-resistant strains of HIV -1. Such combination has been shown to be able to suppress isolates that have been shown to have genotypic and phenotypic resistance to Pl(s). It has been shown that the only factor that does play a role in determining which patients respond to such therapy is adherence to the salvage regimen.

The other strategy in current HIV management is to spare PI in the initial HAART regimen. This is made possible by the availability of potent PI sparing triple therapy regimens which contain either 1 NNRTI and 2 NRTIs or 3 NRTIs. Compared to PI containing regimens, equipotent Pi-sparing regimens may have several advantages including more convenient dosing, lower tablet volume, fewer drug interactions, better central nervous system penetration and the maintenance of PIs as an option for second line therapy. Tolerability with the 3 leading Pi-sparing approaches (regimens containing Efavirenz, Neviparine or Abacavir plus 2 nucleoside analogues) appears generally good with few individuals discontinuing in clinical studies due to adverse drug events. The majority of adverse events with Efavirenz and Neviparine occur within the first month, and are predictable and manageable without therapy interruption. Similarly, apart from a rare (3%) hypersensitivity reaction, which requires therapy cessation without rechallenge, Abacavir adverse effects are uncommon. Of the three regimens, Efavirenz-containing one is the most potent.

Crusted scabies

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Case 1

An 86-year-old female elderly home resident was admitted to hospital for chest infection. She had been bed-bound for years because of past history of recurrent cerebrovascular accident. Examination of skin revealed keratotic scales on both hands and subungual hyperkeratosis over fingernails. Scratching was not noticed. She was treated as fungal infection but the response was poor. Dermatologist was consulted and a diagnosis of crusted scabies (CS) was made. Microscopic examination of the scales revealed numerous scabietic mites and eggs. She was barrier-nursed and treated with repeated courses of 25% benzyl benzoate emulsion (BBE). The keratotic scales were treated with 3% salicylic acid ointment. The nails were cut short and the subungual keratosis removed. After three weeks of treatment, all the skin lesions resolved and further skin scraping for scabietic mites became negative. Some nursing staffs in the ward also got scabies. Empirical treatment with BBE was given to all contacts.

Case 2

A 56-year-old homosexual man with acquired immunodeficiency syndrome presented with an itchy rash for three months. Examination revealed widespread papular erythema with excoriation and patchy psoriasiform rash on the trunk. Skin scraping revealed scabietic mites, eggs and faeces. Thus, the diagnosis of CS was confirmed. He was treated in the similar way as the first patient.

Discussion

Scabies is a skin infestation caused by the mite Sarcoptes scabies hominis. It frequently affects geriatric and convalescent patients. The diagnosis is confirmed when a mite or a burrow is identified. Scabies is normally transmitted by close skin or sexual contact. CS is a hyperinfestation variant of scabies. Patients usually present with psoriasiform lesion on the hands and feet, erythematous scaly rash that may be generalized, and nail dystrophy. Itching is minimal in most cases. Clinically, it can be misdiagnosed as fungal infection, eczema, psoriasis or Darier's disease because of the hyperkeratotic lesions in skin and nails. Patients with physical debilitation, mental retardation, sensory impairment and immunosuppression are at risk of CS. It is very contagious because of the myriad of mites in the scales and subungual debris, as contrast to cases of conventional scabies where only 10-15 mites would be present. Microscopy of skin scraping in CS can easily reveal mites, eggs or faeces. The key step in making an early diagnosis in CS is a high index of suspicion.

Treatment of CS is more difficult than that of conventional scabies. Strict barrier nursing is necessary to avoid nosocomial transmission. BBE is the first line

scabicide used locally. It is safe, cheap and easily available. However, prolonged application of BBE may cause irritant contact dermatitis. Other topical scabicides include permethrin, allethrin I, malathion and 1 % gamma benzene hexachloride. They are much less stinging than BBE. Neurotoxicity has been reported in gamma benzene hexachloride. Repeated clinical evaluation and microscopic examination is required to monitor the progress. Crotamiton cream is an anti-pruritic agent with mild scabicidal activity. It is commonly used in the treatment of post-scabies pruritus. CS responds more slowly to treatment than conventional scabies because penetration of scabicide is prevented by the hyperkeratotic scales and crust. Repeated courses of scabicides are required, say once weekly; with use of crotamition in between. The keratotic scales should be removed by physical brushing and application of topical keratolytic such as 3% salicylic acid ointment. Nail trimming and scrubbing with scabicide is necessary for those with nail involvement. CS may be complicated by pyoderma, septicaemia and glomerulonephritis.

Systemic treatment with ivermectin has been reported to be very effective in treating CS[1]. It is currently the only oral drug available for scabies. It is also very safe and well tolerated. However, ivermectin is not available locally. Single dose of 200 mcg/kg is commonly used although some authors recommended using two or three repeated doses.

Thousands of mites can be shedded into the environment from a single patient with CS. The adult mites can survive for three days outside human body and the eggs survive up to 10 days. Hence, transmission by fomites is possible and one case of CS could be sufficient to lead to outbreak of conventional scabies in an institution. Thus, treatment of contact and decontamination of environment is also important. Successful treatment of CS depends on a high index of suspicion and the cooperation between physicians, nurses, hospital infection control unit and dermatologist.

Reference

Uwe Paasch, Uwe-Frithjof Haustein. Management of endemic outbreaks of scabies with allethrin, permethrin and ivermectin. Inter J Dermatol 2000; 39: 463-70.