Bulletin of the Hong Kong Society for Infectious Diseases

Vol. 12, no. 4 **December 2008**

Contents

Laboratory diagnosis of bacterial sexually transmitted diseases

K M Kam, Public Health Laboratory Centre, Centre for Health Protection, Department of Health, Hong Kong

In order to effectively address sexually transmitted diseases (STDs), practitioners should be aware of the prevalent epidemiological patterns, the available laboratory testing facilities, as well as the clinical manifestations of each specific STD. This article attempts to summarize some of the current concerns in each of these areas.

Syndromic approach with laboratory testng

The syndromic approach to the management of STDs is probably the most convenient and appropriate to use in a general practice setting. This involves recognition of the groups of signs and symptoms, and then postulating the possible etiologies. From that point, proper specimen(s) collection and testings start and the corresponding results give indication of the next steps to take [1].

As an example: cervicitis in females can exhibit as mucopurulent cervical discharge, cervical friability, vaginal discharge or strawberry cervix. The possible causes include *N. gonorrhoeae, C. trachomatis, T. vaginalis, Herpes simplex* virus. Microscopy results may show, on Gram stain, presence of ≥ 20 polymorphs per high power field with mucopurulent discharge and/ or cervical friability. Depending on whether facilities exist to further investigate and confirm a chlamydial infection, chemotherapy will

likely include an anti- gonococcal agent as well as one that covers for chlamydiae. Although Gram stain may not be a sensitive test, it may be helpful in assessing the inflammatory status, predominant bacterial flora within the specimen as well as specific pathogens.

It is useful to bear in mind that the "usual" tests in the bacteriological laboratory does not look for the STD pathogens *(viz. N. gonorrhoeae, C. trachomatis*) unless the attending physicians specifically request to look for these. The reason is because most of these are fastidious organisms that require specialized culture media or other methods e.g. enzyme immunoassay, polymerase chain reaction (PCR) for detection.

Re-emergence of syphilis

More recently, there has been a rise in proportion of syphilis cases amongst STDs locally, such that it has replaced herpes genitalis as the fourth commonest STI in Social Hygiene Clinics (SHCs) since 2004 [2]. The number of early (infectious) syphilis, including primary and secondary syphilis, seen at SHCs increased slightly from 90 (85 males and 5 females) in 2006 to 108 (95 males and 13 females) in 2007.

In order to more efficiently detect syphilis amongst suspect cases, the Public Health Laboratory Centre in the Centre for Health Protection, Department of Health, has adopted enzyme immunoassay as screening test for treponemal antibodies which can be present for current as well as past infections [3]. This contrasts with long standing practice of using VDRL or RPR tests which are relatively insensitive and only screen for active untreated disease [4]. Experiences on the initial use of these in the United Kingdom [5], and elsewhere can be found in various publications [6]. In general, nontreponemal tests also are used to monitor responses to treatment or to indicate new infections. False-positive nontreponemal tests occur in 1%–2% of the population, and have been associated with multiple conditions, including pregnancy, human immunodeficiency virus (HIV) infection, intravenous drug use, tuberculosis, and disorders of immunoglobulin production [7]. Both treponemal and nontreponemal tests can be nonreactive when infection has been acquired recently; approximately 20% of test results may be negative when patients have primary syphilis.

When results are reactive to both treponemal and VDRL/ RPR tests, persons should in general be considered to have untreated syphilis unless it can be confidently ruled out by treatment history and negative exposure. Persons who were treated in the past are considered to have a new/ reinfection if quantitative VDRL/ RPR test reveals a four fold or greater increase in titer. When results are reactive to the treponemal test but nonreactive to the VDRL/ RPR test, persons with a history of previous adequate treatment and negative exposure require no further management. If a second treponemal test is also reactive, the possibility of infection should be discussed and then treatment offered to patients who have not been previously treated. Of point to note, diagnosis of neurosyphilis is still dependent on VDRL tests on blood and CSF specimens. Practitioners should be aware of these limitations when interpreting tests results during management of syphilis patients so that optimal care can be given.

More recently, molecular methods have enhanced traditional detection methods. Amongst these, those that are clinically more relevant are the line probe assays which enable dissection of patient's antibody response and assist in resolving difficult cases. A direct PCR test and molecular subtyping have both been successfully applied in a limited number of situations [9, 10]. For the astute venereologist, it would very much be of interest to keep these in view.

Mycoplasmas and ureaplasmas

A number of laboratory methods had been developed for detecting mycoplasmas and ureaplasmas. These include: culture (difficult in culturing various *Mycoplasma* and *Ureaplasma* spp.), antigen/ antibody detection (difficult due to lack of humoral immune response in most patients), DNA probes (16S rRNA gene), and PCR (can be multiplexed to detect more than one pathogen). Amongst the many mycoplasmas and ureaplasmas, *M. hominis, M. genitalium, U. parvum* and *U. urealyticum* are the etiological microorganisms of non- gonococcal urethritis (NGU), postpartum fever, infertility, and pelvic inflammatory disease. However, when there is lack of proper quality control in laboratory procedures, the empirical detection of these must be interpreted with caution and correlated with clinical findings.

Quality Assurance

From the laboratorian perspective, the quality assurance of test procedures as well as results reporting remain of paramount importance. Apart from the pathogens and issues discussed which often have internationally recognized quality assurance programs, antibiotic susceptibilities testing for the gonococci should be undertaken only by clinical microbiology laboratories that have shown proficiency in these tests, including penicillin (plus beta- lactamase production), tetracycline, quinolone and third- generation cepahalosporins. In particular, treatment failures should be correlated with in vitro test results whenever possible. When patient referrals occur, the attending physician should be aware of the problems of cross-comparison of test results (especially quantitatively) obtained from different laboratories.

Bacterial STDs bear the characteristic psychosocial stigma not seen in other non-STD communicable diseases. It is prudent that the attending physician be aware of these implications, as well as possible legal proceedings which can often accompany management of these patients.

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Intestinal Tuberculosis Mimicking Colonic Carcinoma: A Case Report and Review of Literature

Ng Yuk Yung, Department of Medicine and Geriatrics, Tuen Mun Hospital

Case Report

A 40-year-old male patient had history of schizophrenia, compulsive water drinking and mixed vitamin B12 and iron deficiency anaemia on replacement therapies. He was found to have refractory anaemia and was transferred to our hospital for further workup.

He was mute and non-communicable. Physical examination was unremarkable. No fever was documented on admission. Digital examination revealed no melaena or rectal mass.

The laboratory data showed normochromic normocytic anaemia with haemoglobulin level 8.2g/dL (MCV 87.4fL, MCH 29.5pg) and reticulocytosis (reticulocyte count 2.68%). The iron study suggested anaemia of chronic disease [iron 3micromol/L (8-29micromol/L), total iron binding capacity 25micromol/L (44-68micromol/L), iron saturation 12% (20-55%), ferritin 1592pmol/L (67-896pmol/L)] and vitamin B12 was within normal range 460pmol/L (156-698pmol/L). His renal and liver function tests were normal, except hypoalbuminaemia, 29g/L. Faecal occult blood was positive in three specimens.

Oesophagogastroduodenoscopy was performed which did not show any abnormality.

He developed fever on day three of admission. There was no consolidation on chest x-ray. Sepsis workup including blood, sputum and urine culture was negative. Throat swab grew commensals. Nasopharyngeal aspirate for polymerase chain reaction of influenza A and B was negative. Urine for Legionella antigen was not detected. He was treated empirically with Augmentin and Azithromycin.

He was found to have abdominal distension and vomiting with absent bowel sound on day eight of admission. Abdominal x-ray showed small bowel dilatation as evidenced by central location of the dilated bowel and the presence of valvulae conniventes. The abdominal distension was not improved with conservative management. Computerized tomography scan of abdomen was performed and reported a malignant tumour of ascending colon with evidence of local pericolonic infiltration and lymphadenopathy. Partial obstruction resulted with proximal dilatation of the caecum and small bowel. Several ill-defined small nodular opacities and small amount of ground glass opacities were present in bilateral posterior basal region and lingular segment of left upper lobe. Patient's carcinoembryonic antigen was normal (0.3ng/mL). Colonoscopy was not performed because of intestinal obstruction as insufflation of air could increase the risk of perforation in the presence of small bowel and caecal dilatation.

Laparotomy was urgently proceed in

which surgeon found a circumferential obstructing tumour at the caecum causing complete obstruction, stricture of small bowel about 70cm away from ileocaecal valve and mesenteric lymph node involvement. Radical right hemicolectomy and partial small bowel resection was performed Histopathological examination of the resected specimen revealed necrotizing granulomatous inflammation involving full thickness of bowel and lymph nodes. Ziehl-Neelson staining showed scanty acid fast bacilli. There was no evidence of malignancy.

Sputum was negative for acid-fast bacillus. Standard anti-tuberculous drugs (isonazid, rifampicin, pyrazinamide and ethambutol) were given. Fever subsided after the operation and the patient was referred to chest clinic for directly observed therapy on discharge from surgical ward.

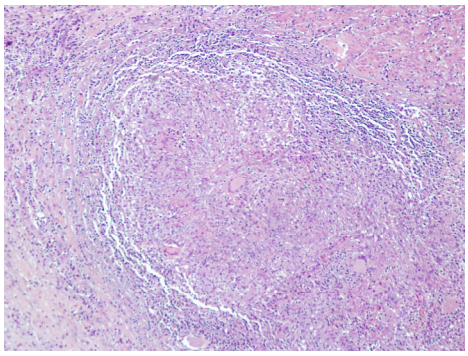

Fig 1. Resected specimen shows caseating epitheloid granuloma and Langhans'giant cells by hematoxylin and eosin staining.

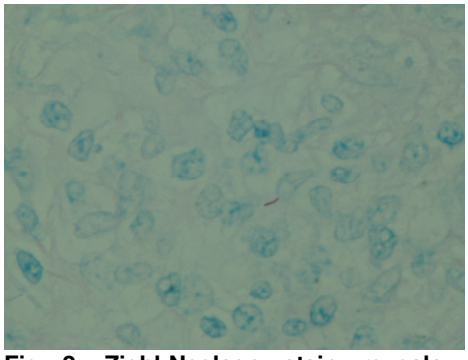

Fig 2. Ziehl-Neelsen stain reveals acid-fast bacillus.

Discussion

In Hong Kong, the overall incidence of tuberculosis was 84 cases per 100,000 inhabitants in the year 2006. Tuberculosis of gastrointestinal tract accounted for 74 (1.28%) of the 5,766 new tuberculosis cases attending Tuberculosis and Chest Clinic in 2006 and accounted for 1.7% of the 294 tuberculosis-related deaths in the same year [1].

The pathogenesis of intestinal tuberculosis has been attributed to four mechanisms: swallowing of infected sputum in patients with active pulmonary tuberculosis; haematogenous spread from active pulmonary or military tuberculosis; ingestion of contaminated milk or food; and contiguous spread from adjacent organs [2]. Within the gastrointestinal tract, the ileocaecal area is the most common site of involvement [2-4]. The affinity of Mycobacterium tuberculosis for this site may be due to the abundance of lymphoid tissue in this region, the increased physiological stasis and minimal digestive activity causing increased contact time between the bacteria and the intestinal mucosa, as well as the high rate of fluid and electrolyte absorption in this region [2-4]. Other commonly involved sites are the colon and the jejunum, whereas the esophagus, stomach, duodenum and anus are rarely involved [2-4].

The diagnosis of intestinal tuberculosis is difficult and requires a high index of suspicion, as its presenting signs and symptoms and laboratory abnormalities are non-specific. Only 15% to 25% of patients had concomitant active pulmonary tuberculosis [2,3]. Chronic abdominal pain is the most common complaint, occurring in 80 to 90 percent of patients. Anorexia, fatigue, fever, night sweats, weight loss, diarrhea, constipation or per rectal bleeding may be present. 25 to 50 percent of patients may have a palpable right lower quadrant abdominal mass [2]. Intestinal obstruction is the most common complication and occurs in about 20% to 30% of patients [3-5]. Free intestinal perforations have been reported in 1% to 15% of cases [6-8], even after the commencement of anti-tuberculous

treatment. In one report, a patient paradoxically developed intestinal perforation 3.5 months after the initiation of anti-tuberculous treatment [9].

Concerning the clinical manifestations, our case had a history of vitamin B12 deficiency anaemia who finally diagnosed to have ileocaecal tuberculosis. Generally, a middle aged patient with a history of vitamin B12 deficiency without pernicious anaemia may give a hint to the ileal pathology affecting the absorption of vitamin B12. However, this assumption probably cannot apply to our patient as the anaemia was quite long standing. Besides, serum vitamin B12 level was normalized after oral replacement therapy and this favors the cause of nutritional insufficiency rather than malabsorption.

Suspected diagnosis of intestinal tuberculosis can be confirmed with histology, smear and culture, although each of these tests has low sensitivity (table1)[10].

Diagnostic Tests (alone or in combination)	Sensitivity (%)
Positive histology	41
Positive histology and negative cultures	16
Positive histology and negative smear	70
Positive culture and negative histology	13
Positive culture and negative smear	40

Table 1. Reported sensitivities of positive histology, culture and/or smear results in patients with known intestinal tuberculosis.

Colonoscopy is considered to be the most valuable diagnostic tool [11-16]. Mucosal ulcers and nodules are the most commonly found endoscopic lesions, being present over 80% to 90% of cases [13-16] and in about half of the cases the ileocaecal valve is deformed [14-15]. The main differential diagnosis at endoscopy is Crohn's disease. The endoscopic finding of aphthous ulcers with normal surrounding mucosa or the presence of cobblestoning favors the diagnosis of Crohn's disease as these lesions are rarely seen with tuberculosis. In contrast to Crohn's disease, the tuberculous ulcers tend to be circumferential and are usually surrounded by inflamed mucosa. A patulous valve with surrounding heaped up folds or a destroyed valve with a fish mouth opening is more likely to be caused by tuberculosis than Crohn's disease. Endoscopic biopsy specimens should always be examined histologically for granulomas and acid-fast bacilli, and cultured for mycobacteria.

The pathognomonic histological lesion of epitheloid granulomas with Langhans' gaint cells and central caseation necrosis is not completely reliable. Their presence in colonoscopic biopsy specimens is highly variable from 0% to 44% [1,11-16]. One of the reason is that caseation may be seen only in the lymph nodes and would therefore not be included in a biopsy specimen. Furthermore, caseation may be totally absent in patients who have received ant-tuberculous medications in the past [11,17]. In view of the high variability in tests of histology, smear and culture, the diagnostic yield is increased by routinely performing each of these tests on all specimens [10.18]. Polymerase chain reaction assay of biopsy specimen may facilitate diagnosis since it has higher sensitivity and specificity than routine culture, and results can be obtained in 48 hours instead of weeks [19].

The management of intestinal tuberculosis is primarily medical, with surgery reserved for complications or an unclear diagnosis. A 6 to 9-month course of anti-tuberculous chemotherapy is effective for immunocompetent patients treated with a standard regimen consisting of four first-line drugs. Consensus recommends Isoniazid, rifampicin, pyrazinamide and streptomycin or ethambutol for the initial 2 months followed by isoniazid and rifampicin for another 4 to 7 months [20,21]. A prolonged therapy is necessary if one or more of these four first-line drugs cannot be used because of intolerance or drug resistance [20]. A trial

of anti-tuberculous therapy may be indicated when clinical suspicion of the infection is high and when there is no typical granulomas and acid-fast bacilli detected in the affected tissues. Surgery is usually reserved for intestinal tuberculosis complicated by perforation, obstruction or uncontrollable haemorrhage [2,3,5]. If surgery is to be performed, the most conservative approach should be used [2,3,5]. Conservative management has been advocated for tuberculous intestinal obstruction in stable patients, as most patients will improve with anti-tuberculous chemotherapy.

Acknowledgement:
Special thanks to Dr Mak Kwok Shing from Department of Microbiology, Tuen Mun Hospital, for the provision of slides.

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Disseminated *Mycobacterium avium complex* infection in a lady with anti-interferon-gamma autoantibody

Ada W. C. LIN, Department of Medicine, Pamela Youde Nethersole Eastern Hospital

A 67-year-old Chinese lady presented with intermittent fever, generalized malaise and weight loss. She enjoyed good past health until 6 months ago when she had an episode of pneumonia with parapneumonic effusion. Computer tomography (CT) scan of thorax with contrast at that time showed consolidative change over right upper and middle lobe with right-sided pleural effusion. Shotty enlarged lymph nodes were noticed at pre-tracheal, para-tracheal and bilateral axillary areas. Culture for bacteria and mycobacteria from bronchoalveloar lavage and right pleural fluid yielded no growth. She was empirically treated with amoxicillin-clavulanate and clarithromycin. Fever subsided after antibiotic treatment, and follow-up chest X-ray showed resolution of consolidation and effusion.

However, fever recurred soon after completion of antibiotic treatment. There was associated constitutional symptoms including malaise, poor appetite and weight loss, but otherwise no localizing symptom was reported. Blood tests showed a white cell count of 25.9 x 10^9/L, normochromic normocystic anemia of 8g/dL, platelet count of 626 x 10^9/L, and elevated erythrocyte sedimentation rate greater than 100. Serum albumin was 32g/dL, and globulin level was 37g/dL. Serum alkaline phosphatase was mildly elevated to 146 IU/L with normal bilirubin and alanine transaminase levels. Renal function test and serum calcium level were unremarkable. Serum protein electrophoresis showed positive result of IgG/Kappa band of 11.9g/L. A contrast CT scan of abdomen showed multiple lymphadenopathies involving para-aortic, mesenteric and left iliac nodes. Positron Emission Tomography (PET) also disclosed multiple 'hypermetabolic' signals over the left supraclavicular, periportal, mesenteric, aortocaval and para-aortic lymph nodes. In addtion, multiple active metabolic lesions were noted over both lung fields, suggestive of infective foci over those areas.

Subsequently, *Mycobacterium avium complex* (MAC) was isolated from the peripheral blood samples and bone marrow aspirate of the patient. Bone marrow examination showed mild plasmacytosis, which was commented to be reactive in nature. Antibody to human immunodeficiency virus (HIV) was negative. Serum autoantibodies including antinuclear antibody, rheumatoid factor, anti-neutrophil cytoplasmic antibody and complement level were all unremarkable. Immunology tests revealed normal lymphocyte subset profile and lymphocyte proliferation assay. Serum antibody against the cytokine interferon-gamma was found to be positive by Enzyme-Linked Immunosorbent Assay (ELISA).

This patient was diagnosed as having disseminated MAC infection, possibly related to the presence of autoantibody against interferon-gamma. She was treated with a combination of rifampicin, ethambutol, clarithromycin and amikacin. Fever subsided gradually after treatment, and she is still maintained on such therapy after six months. In addition, she fulfilled the criteria as having monoclonal gammopathy, of which the clinical significance was uncertain at this stage. The plan of management would be monitoring of clinical response to the treatment of disseminated MAC infection with follow-up CT scan and serum paraprotein level.

Discussion

Nontuberculous mycobacteria (NTM) are ubiquitous in the environment. They have been recovered from water, soil, domestic and wild animals, milk and food products. NTM could occasionally cause pulmonary

disease in healthy individuals. However, disseminated disease due to NTM infection can reflect underlying immune defect of the affected host. Most disseminated NTM infection occurs in patients with advanced AIDS. Other immunosuppressive conditions reported to be associated with disseminated NTM infection include chronic steroid use, haematological malignancy, post renal and cardiac transplantation, as well as advanced stage of solid tumor [1]. Organisms reported to cause disseminated disease in non-HIV-infected patients include *Mycobacterium avium complex* (MAC), *Mycobacterium kansasii*, *Mycobacterium chelonae*, *Mycobacterium abscessus*, *Mycobacterium haemophilum*, M*ycobacterium scrofulaceum* and *Mycobacterium gordonae*. A recent study from Taiwan has shown that MAC was the most commonly found isolate from non-HIV-infected patients with disseminated NTM infection, followed by *M. abscessus* and *M. kansaii* [1]. Disseminated infection caused by MAC usually manifested as pyrexia of unknown origin as in the patient reported in this case, whereas those caused by *M. kanasaii, M. chelonae and M. abscessus* ususally manifested as multiple subcutaneous abscesses.

Recently, there have been reports of disseminated NTM infection in individuals with anti-interferon-gamma IgG neutralizing autoantibodies [2,3,4,5]. T-helper 1 cytokines, namely interleukin (IL) 2, interleukin 12 and interferon-gamma, are important in the defense pathway for infection caused by intracellular microorganisms including mycobacteria. Among those, interferon-gamma is perhaps the key cytokine involved in the defense mechanism. Interferon-gamma, produced by activated lymphocytes, acts on monocyte-macrophage to enhance killing of intracellular microorganisms. IL-2 and IL-12 promotes proliferation of the activated lymphocyte and production of interferon-gamma respectively. Individuals with defective IL-12 pathway would still have residual interferon-gamma production, thus these individuals are in general less severely affected.
Interestingly, all the reported cases of disseminated NTM infection with neutralizing anti-interferon-gamma autoantibodies in the literature were of Asian ethnicity. Majority of them were female, and the age of affected individuals ranged from 25 to 66 years old [2,3,4,5]. Co-infection with multiple NTM organisms other than MAC was commonly seen, and affected organs included lymph node, bone marrow, skin, bone, pericardium, liver and lungs. Apart from disseminated NTM infection, serious bacterial infection with other environmental pathogens has been reported [3]. Furthermore, these patients were also susceptible to infections by other intracellular pathogens including *Salmonella* species and fungi. There has been another local case of disseminated NTM infection in a lady with anti-interferon-gamma autoantibody who was also infected with *Penicillium marneffei*.. In another case report, a 45-year-old Filipino male, who suffered from disseminated *M. chelonae* disease, was also found to have other organ-specific autoimmunity, namely primary hypothyroidism and autoimmune type I diabetes mellitus [4].

It has been shown that low titre of antibody against interferon-gamma also existed in normal healthy individuals. However, these antibodies, in contrast with those found in individuals with disseminated NTM infection, did not lead to inhibition of interferon-gamma signal transduction pathway[5]. This presence of low-titer low avidity anti-interferon-gamma autoantibodies in normal individuals may act as a part of normal immune regulation network. In response to unknown environmental or genetic triggers, B-cell response become auto-active and produce excessive amount of high avidity autoantibodies, which result in clinical disease. Together with the possible association with other autoimmunity, this

disease entity may represent a disease spectrum similar to other autoimmune conditions. However, details of the underlying mechanism, as well as the triggers involved in the regulation, remain unclear.

There has been no standard recommendation for treatment of disseminated NTM infection in non-HIV-infected patients. Treatment of choice for disseminated MAC has been based on internationally recognized recommendation in HIV-infected patients, which consists of a combination of ethambutol, clarithromycin, and rifabutin. Other drugs of choice include aminoglycoside and quinolone [6]. Duration of therapy is unknown. Despite prolonged therapy lasting up to 5 years in certain cases, treatment outcome has been unsatisfactory with persistent infection in majority of patients [5].

In summary, disseminated NTM infection occurs in non-HIV-infected individuals with underlying immunosuppressive conditions. Patients with anti-interferon-gamma autoantibodies, mostly found in Asian females, have been increasing recognized as a cause for this condition. Treatment outcome in these patients has been disappointing so far. Other treatment modalities such as plasmapheresis, intravenous immunoglobulin and rituximab, as used in other autoimmune diseases might be explored in the future for effective treatment. Although there has not been any guideline for prophylactic therapy for patients with anti-interferon-gamma autoantibodies as in HIV-infected patients, long-term prophylaxis for NTM and dimorphic fungi may be warranted in affected patients before more definite treatment for the underlying condition is available.

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Journal Review

Alan K. L. Wu, Department of Pathology, Pamela Youde Nethersole Eastern Hospital

Andrews JR, Gandhi NR, Moodley P, et al. Exogenous Reinfection as a Cause of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis in Rural South Africa. J Infect Dis. 2008 Oct 10. [Epub ahead of print]

In November 2006, a serious outbreak of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) was reported in a rural district of South Africa where there was a high prevalence of HIV infection. Although most cases of drug-resistant TB occurring worldwide are believed to be secondary to treatment failure, many patients in this particular outbreak had not received prior therapy. It was hypothesized that many of the cases occurred due to exogenous re-infection with a resistant TB strain.

Investigators reviewed data from a number of patients with MDR- or XDR-TB who had previously received treatment for culture-positive, drug-susceptible TB. Among the 17 patients who were included in the analysis, fifteen were HIV positive, whereas the remaining 2 had unknown HIV status. Primary drug resistance (due to exogenous re-infection) was distinguished from acquired resistance by comparing genotypes of the isolates from the first and second TB episodes using spoligotyping. In all 17 patients, the initial and follow-up isolates were found to be different, indicating that exogenous re-infection with drug resistant organisms had occurred.

Points to note: Current efforts to prevent emergence of drug-resistant TB are mainly based on the assumption that in most cases, resistance occurs as a result of poor compliance to treatment; hence, much attention is focused on the administration of directly observed, short course therapy (DOTS). However, as this study has clearly shown, such efforts alone may not adequately address the problem in areas with high prevalence of both HIV and TB infection. Rather, public health efforts should be expanded to prevent the transmission of drug-resistant TB strains, particularly in AIDS treatment programs; such programs often create multiple opportunities for person-to-person spread of TB by bringing together large numbers of susceptible patients in relatively enclosed areas (e.g. waiting rooms, patient queues, and public transport to hospitals). As a minimum, AIDS treatment clinics must improve infection-control measures to prevent interpersonal spread of TB (by means of patient segregation, proper use of personal protective equipments, and engineering measures to improve air changes and air filtration etc), and should consider implementing protocols for treatment of latent infection in selected populations in order to prevent subsequent risk of reactivation and transmission of TB.

Johnson L, Sabel A, Burman WJ, et al. Emergence of fluoroquinolone resistance in outpatient urinary Escherichia coli isolates. Am J Med. 2008; 121: 876-84.

It is well known that urinary tract infections (UTIs) are among the most common reasons for outpatient antibiotic prescriptions. Traditionally, trimethoprim-sulfamethoxazole (TMP-SMX) is the preferred agent for treatment of such infections; however, its efficacy has been hampered by increasing incidence of resistance. At the Denver Community Health Services in US, which manages >400,000 outpatient visits each year, levofloxacin was substituted as the preferred antibiotic for outpatient UTI therapy in 1999, when the resistance rate of TMP-SMX reached 24%. Unfortunately, a rise in the levofloxacin resistance rate was subsequently observed.

The investigators used databases from their pharmacy and microbiology laboratory to assess the changes in outpatient antibiotic use and resistance between 1998 and 2005. During that period, levofloxacin prescriptions per 1000 outpatient visits increased significantly from 3.1 to 12.7. At the same time, the percentage of Escherichia coli isolates resistant to levofloxacin increased from 1% to 9%. The overwhelming majority of levofloxacin-resistant isolates identified from outpatient specimens in 2005 were from urinary sources. In addition, despite a

decrease in the number of outpatient prescriptions for sulfonamides by almost 50% during the same period, resistance rate of E. coli to TMP-SMX continued to increase, from 26% in 1999 to 30% by the end of 2005. In multivariate analysis, two factors were significantly associated with levofloxacin resistance: previous hospitalization and levofloxacin use during the preceding year. Levofloxacin-resistant E. coli isolates were also significantly more likely than levofloxacin-susceptible strains to be resistant to other classes of antibiotics.

Points to note: The findings from this large study clearly demonstrate a linear relationship between increased use of levofloxacin for treating UTIs and development of resistance. Unfortunately, no concomitant decrease was seen in resistance to TMP-SMX despite reduced use. In fact, levofloxacin-resistant isolates showed an increased likelihood of resistance to other classes of antibiotics that are used to treat UTIs. These findings should call for more judicious and sensible use of antibiotics even in outpatient settings, as there could be serious and far-reaching consequences resulting from such apparently “trivial” prescriptions.

Prakash V, Lewis JS 2nd, Jorgensen JH. Vancomycin MICs with methicillin-resistant Staphylococcus aureus (MRSA) isolates differ based upon the susceptibility test method used. Antimicrob Agents Chemother. 2008 Oct 6. [Epub ahead of print].

A number of recently published reports have suggested that vancomycin treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections may fail more frequently for isolates with MICs on the high end of the currently defined susceptible category of the Clinical and Laboratory Standards Institute (CLSI) standards (i.e. 1.5 or 2 µg/mL). What is less certain is the effect of the MIC testing method on the results of vancomycin susceptibility. Using 101 MRSA bacteremia isolates from 2002 to 2006, researchers in Texas have examined whether vancomycin susceptibility results might vary depending on the test method used. Vancomycin MICs for each isolate were assessed by CLSI broth dilution, CLSI agar dilution, and the Etest using two different brands of Mueller-Hinton agar plates. All tests for each isolate were performed at the same time from the same inoculum suspension under standard conditions.
The researchers found that the modal vancomycin MIC of the isolates was 2 µg/mL when tested by Etest on both Mueller-Hinton agars, but was only 1 µg/mL when tested by CLSI broth or agar dilution methods. Overall, 89% to 98% of the MICs fall in the range of 1.5 to 2 µg/mL when tested by the Etest method, compared with only 3% to 12% of those determined by CLSI broth or agar dilution methods.

Points to note: In this study, the vancomycin MICs generated by Etest were found to be higher than those generated by CLSI broth or agar dilution by at least one 2-fold dilution. Published reports have indicated that MRSA with vancomycin MICs >1.5 µg/mL is seen relatively frequently at some institutions but infrequently at others. Such disparity might be attributable, at least in part, to use of different MIC testing methods at different laboratories. When assessing the significance of elevated vancomycin MICs in MRSA isolates, clinicians should liaise closely with clinical microbiologists who should be able to provide valuable inputs and additional insights in interpretation of such information.