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Bordetella pertussis as a Cause of Chronic Respiratory Infection in an AIDS Patient

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A 60-year-old heterosexual man with AIDS was admitted to hospital with dyspnea, a severe paroxysmal non-productive cough of two months' duration, low-grade fever and exhaustion. *Bordetella pertussis* was cultured from a bronchoalveolar lavage specimen. After erythromycin therapy (500 mg q.i.d. for two weeks) all respiratory symptoms resolved progressively over a four-week period. *Bordetella pertussis* should be added to the long list of pathogens that may cause respiratory disease in persons with HIV infection.

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Bordetella pertussis infection has been described in both adults (1, 2) and children infected with the human immunodeficiency virus (HIV) (3, 4). However, in only three patients was sufficient clinical information available to prove a causal relationship between *Bordetella pertussis* infection and respiratory symptoms (1–3). In two other patients a causal relationship was strongly suggested because no other etiologic agent was identified and patients responded clinically to erythromycin therapy (1, 2). In three children with HIV infection and pulmonary infiltrates, *Bordetella pertussis* was detected intracellularly in macrophages in broncho-alveolar lavage fluid (4). All children had received at least one injection of diphtheria-tetanus-pertussis-vaccine. However, none of the cultures of specimens from these children grew *Bordetella pertussis*.

We describe another case of *Bordetella pertussis* infection in an adult AIDS patient. This case report suggests that *Bordetella pertussis* may cause chronic respiratory illness in HIV infected adults.

Case Report. In April 1991, a 60-year-old heterosexual man with AIDS was admitted to the University Hospital of Antwerp with dyspnea, severe paroxysmal non-productive cough of two months' duration, low-grade fever and exhaustion (due to the cough). His medical history included diagnosis of HIV infection in 1988, candida oesophagitis and cytomegalovirus ulceration of the oesophagus in 1989. At the time of admission he was receiving zidovudine and *Pneumocystis carinii* prophylaxis with aerosolized pentamidine. Clinical examination on admission revealed extensive psoriasis lesions which appeared after he acquired the HIV infection. Chest X-ray and CT scan of the chest were normal.

Laboratory tests on admission showed anaemia (haemoglobin 10.6 g/dl), leucopenia (2100/mm^3) with a low CD4 lymphocyte count (17/mm^3) and thrombopenia (76,000/mm^3). Abnormal results of liver tests included LDH 410 U/I (normal range 120–240 U/I), ASAT 46 U/I (normal range 2–18 U/I), ALAT 38 U/I (normal range 5–22 U/I), alkaline phosphatase 219 U/I (normal range 61–157 U/I) and GT 114 U/I (normal range 4–25 U/I).

Arterial pO_2 was 72.5 mmHg, with normal pCO_2 and an O_2 saturation of 93.7 %.

Lung function tests revealed a mild degree of bronchospasm (vital capacity 80 % of the expected value and forced expiratory volume 78 % of the expected value). Bronchoscopy showed no macroscopic abnormalities, but microscopic examination of broncho-alveolar lavage (BAL) fluid showed numerous small intracellular and extracellular gram-negative rods. After four days of incubation at 37 °C in air, non-motile, oxidase-positive urease-negative rods were cultured on BCYE medium (a non-selective legionella agar). There was no growth on the following culture media: blood agar (with horse blood), a selective haemophilus medium (lysed horse blood with bacitracin and cloxacillin) and a selective legionella medium (BCYE with cefamandole, polymyxin and anisomycin). The organism was identified as *Bordetella pertussis* and was urease-negative and oxidase-positive. In addition the organism reacted with a *Bordetella pertussis* antiserum (Difco, USA) in a direct immunofluorescent test. PCR to detect any *Mycoplasma pneumoniae* and cultures to detect any other bacteria (including mycobacteria and chlamydia), viruses or fungi were negative.

Three days after bronchoscopy, the patient developed hoarseness. Erythromycin was given (500 mg q.i.d. for two weeks). Cough and hoarseness progressively regressed over a four-week period. Lung function tests performed two months after starting therapy showed a slight improvement (vital capacity 83 % of the expected value, forced expiratory volume 91 % of the expected value).

The patient, as well as his 45-year-old wife who was also HIV seropositive but asymptomatic, had never been vaccinated against *Bordetella pertussis*. Their 16-year-old HIV seronegative daughter had been vaccinated as a child. Although both the patient's wife and daughter reported a one-week coughing episode before the onset of the patient's symptoms, throat swabs, obtained six weeks after their coughing episode, failed to grow *Bordetella pertussis*. None of the hospital personnel developed clinical signs of pertussis during the patient's hospital stay.

Discussion. Since in the present case cultures of BAL fluid revealed *Bordetella pertussis* to be the only pathogen and since the respiratory symptoms disappeared following erythromycin therapy, we think that *Bordetella pertussis* may be a potential cause of respiratory disease in persons with HIV infection.

The origin of the infection in this patient remains unclear. *Bordetella pertussis* is highly contagious. Several outbreaks of *Bordetella pertussis* infection among adults have been described recently (5, 6). Therefore there is a risk of *Bordetella pertussis* epidemics among immunocompromised patients such as HIV infected patients treated at AIDS treatment centres. There may also be a risk of transmission of *Bordetella pertussis* to health care workers. In epidemics it has been shown that less than 5 % of those vaccinated more than 12 years earlier were protected (7).

Bordetella pertussis in non-immunocompromised adults may cause a mild transient respiratory illness or prolonged paroxysmal cough (8). The clinical manifestations of *Bordetella pertussis* infection in patients with HIV infection seem to be even less specific and very different from those of classic whooping cough observed in children. Therefore, diagnosis of *Bordetella pertussis* infection may be delayed as was the case in our patient as well as in those cases reported in the literature. *Bordetella pertussis* infection may even remain undiagnosed, thus increasing the risk of transmission.

Prevalence studies of *Bordetella pertussis* infection in patients with HIV infection are urgently needed. In a small cross-sectional evaluation of 60 HIV-infected adults no case of *Bordetella pertussis* infection was found although 72 % of the patients had a cough (9). This case report suggests that *Bordetella pertussis* infection should be considered in the differential diagnosis of all HIV infected patients with unexplained chronic cough.

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Imipenem and Meropenem Induced Resistance to Beta-Lactam Antibiotics in *Pseudomonas aeruginosa*

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The ability of imipenem and meropenem in subinhibitory concentrations to influence the results of disk diffusion susceptibility tests was assessed. Selection of stably derepressed mutants resistant to beta-lactam antibiotics other than carbapenems was also investigated. Beta-lactams were shown to be subject to carbapenem-mediated antagonism in the disk diffusion test. On the other hand in vitro selection of stably derepressed mutants resistant to other beta-lactams could not be demonstrated.

Chromosomal Class I β-lactamases are produced by many species of gram-negative organisms. Their expression may be inducible or constitutive. The production of inducible β-lactamases can be substantially increased if the bacteria are exposed to an inducing agent (1–3). Some antimicrobial agents, such as cefoxitin and imipenem, have been shown to be potent inducers of β-lactamase production (4–6). Strains classified as susceptible to β-lactam agents in routine laboratories may show a marked decrease in susceptibility if the culture medium is supplemented with an inducing agent. Moreover, emergence of resistance may occur as a result of mutations which involve stable derepression of genes coding for chromosomal β-lactamases. Imipenem and meropenem are two carbapenem β-lactams that possess a wider spectrum of antibacterial activity than other β-lactam antibiotics. The basis for this expanded spectrum includes resistance to a variety of β-lactamases and greater intrinsic activity (7, 8). However, it has been shown that for many gram-negative species imipenem has an antagonistic effect on the activity of other β-lactams in vitro, this antagonism being the result of the above-mentioned induction of chromosomal β-lactamase production (5, 6, 9, 10). On the other hand carbapenems are only slightly affected by these chromosomal β-lactamases, their hydrolysis being extremely slow and the drugs remaining active against inducible strains (11). Attempts to select spontaneously resistant mutants have not been successful: although they induced β-lactamase activity, the strains remained susceptible to the two carbapenems (7, 8, 11).

Since the increased production of chromosomal β-lactamases occurs either as a result of induction by an inducing agent or selection of stably derepressed mutants, we investigated the ability of imipenem and meropenem in subinhibitory concentrations to influence the results of disk diffusion susceptibility tests and their ability in concentrations equal to half the MIC to select stably derepressed mutants resistant to β-lactams other than carbapenems.

Materials and Methods. The antibiotic susceptibility of 30 strains of *Pseudomonas aeruginosa* randomly selected from our collection of clinical isolates and the reference strain *Pseudomonas aeruginosa* ATCC 27853 was tested by a disk diffusion method using Mueller-Hinton agar plates and commercially prepared disks (Becton Dickinson, USA) containing carbenicillin, piperacillin, aztreonam, cefoperazone, cefotaxime, ceftazidime and ticarcillin plus clavulanic acid (12). Antibiotic antagonism was investigated by measuring the inhibition zones in three series of Mueller-Hinton agar plates containing imipenem (0.02 μg/ml), meropenem (0.02 μg/ml) or without

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