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Mémoire de Maîtrise en médecine

PERTUSSIS IN ADULTS IMMUNOCOMPROMISED PATIENTS

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Table des matières

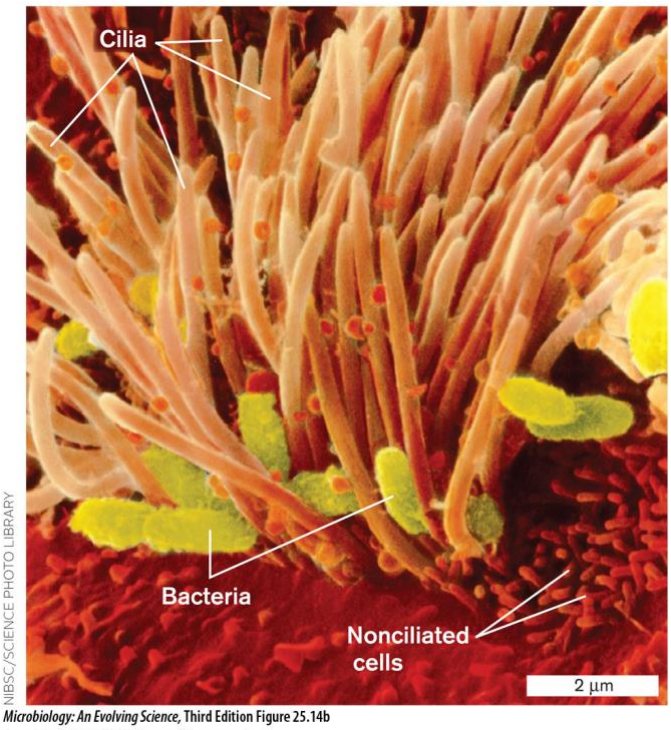
INTRODUCTION:

1. Pertussis

Pertussis (whooping cough) is a highly contagious upper respiratory tract infection, caused by *Bordetella pertussis*. This disease is particularly serious in infants, mostly in those younger than 6 months that have not, or only partially, been vaccinated. Since the introduction of a global anti- *B. pertussis* vaccination program, the incidence of pertussis has considerably decreased in the past few decades.

In Switzerland, global letality rate is 0.05 deaths/1000 cases. This rate is four time higher in children from 0-5 years old (0.2 deaths/1000 cases), and even greater in infants under 3 months (10 deaths/1000 cases). (1)

Causative agent of pertussis, *Bordetella pertussis,* is a gram-negative coccobacillus, whose humans are the only known reservoir. *B. pertussis* is spread by airborne droplets and binds to the epithelial cells of the trachea, bronchi and bronchioles thanks to its virulence factors. These include *filamentous hemaglutinin*, an adhesin that promotes adhesion to ciliated respiratory epithelial cells and phagocytosis by macrophages in view to upgrade bacterial survival, *Pertussis toxin*, a factor promoting systemic effects, such as lymphocytosis and *adenylate cyclase toxin*, inhibing anti-bacterial functions of innate cells. (2)



Microbiology: An Evolving Science, Third Edition Figure 25.14b
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« *B. pertussis colonizing the trachea* » (3)

B. pertussis organisms are inhalated by patients and then expand on the mucosal surface without invading underlying tissue. Clinical manifestations of the infection develop in three phases. After an incubation period of 7 to 10 days following exposure comes the catharral phase, characterized by nonspecific symptoms such as generalized malaise, rhinorrea and mild cough. This phase lasts one to two weeks and is followed by the paroxysmal phase. This second phase is characterized by the hallmarks symptoms: paroxysmal cough, defined by a violent cough occuring during a single expiration, inspiratory whoops, posttussive vomiting and generally no fever. Last phase is named convalescent phase, with a progressive reduction of severity and frequency of the symptoms. Generally, adults and adolescents, presents mild disease or can even be asymptomatic. (4)

Culture of a posterior nasopharynx swab was the gold standard method for diagnosis of pertussis, but nowadays, PCR method is more often used: results are obtained faster and sensitivity is higher compared to culture. PCR is usually positive during the first three weeks of symptoms and thereafter serology starts being positive. Thus, one or the other test needs to be performed depending on the duration of symptoms.

B. pertussis is susceptible to macrolides: treatment of infection usually consists in azithromycin or clarithromycin for five days. Complications of pertussis include general complications of respiratory infections, such as pneumonia or media otitis.

Vaccination is the major strategy to prevent the spread of *B. pertussis*. Whole cell pertussis vaccine was replaced in the nineties with an acellular preparation, which had fewer side effects than the whole-cell vaccine. There are two types of acellular vaccine, one for children and the other one for adults. In North America and Europe, children receive a 5-dose DTaP vaccine series. Although immunization program is actually widespread, incidence in adults and adolescents is rising. Several reasons are accountable for that, including aging of undervaccinated cohorts and more sensitive diagnostic methods. Another major reason is waning of immunity of vaccinated individuals. According to a recent meta-analysis (5), risks of developing pertussis increase by 1.33 times for every additional year after the last dose of DTaP. Accordingly, after a certain period, a vaccinated individual is once again at risk of developing whooping cough or of being asymptomatic reservoirs.

2. Pertussis in immunocompromised patients

Immunosuppressive drugs are increasingly used in modern medicine for a growing number of medical conditions. These include organ and stem cell transplantation, cancer patients, and the use of biological agents for treating inflammatory disorders such as inflammatory bowel diseases or rheumatological diseases. Infection by the Human Immunodeficiency Virus (HIV) is also a frequent cause of adquired immunodeficiency.

Solid-organ transplantation (SOT) is nowadays the main therapeutic choice for a large number of end-stage organ diseases and is a routinely performed procedure. Kidney is the most frequently transplanted organ, followed by liver, lung and heart [Swisstransplant 2017 report]. Organ transplantation is possible because alloreactions can now be controlled by giving them immunosuppressive drugs. A combination of three type of drugs is used in clinical routine to induce immunosuppression: calcineurin inhibitors, antimetabolites and corticosteroids. These are anti-inflammatory and immunosuppressive drugs, which basically inhibit cell activation and cytokine production and alter homing of lymphocytes, which prevents effector T cells from attacking the allograft. At the Transplantation Center of the CHUV, standard therapy includes tacrolimus, mycophenolate mofetil, and prednisone. Immunosuppression is more intensive in the early period after transplantation. This is the most important and effective method to prevent organ rejection, but it also implies an increased susceptibility of the patient to infection. This is the reason why the drug dose is then progressively reduced to a "maintenance level" which prevents graft rejection in one hand and in the other, assures a minimum immune protection against infections.

Hematopoietic stem cell transplantation (HSCT) is indicated for children with genetic immunodeficiencies and for patients with cancers of the blood cells, such as leukemias. The immune system of the host is destroyed with cytotoxic drugs and irradiation in order to avoid graft rejection and to kill all the remaining tumor cells. The bone marrow of the patient is then replaced with the immune system of the donor. The alloreaction in HSCT is called graft-versus-host disease and occurs when mature T cells of the donor attack tissues of the host because of HLA incompatibility. The most vulnerable tissues are skin, intestines and liver. The periods at higher risk for infection include the pre-engraftment period (at high risk for bacterial and fungal infections) and in case of GVHD, where opportunistic infections including viral (CMV) and fungal infections are more common.

Another cause of immunodeficiency is infection with HIV. HIV is a retrovirus infecting persons through transfer of bodily fluids, such as sexual intercourse or intravenous drug use. HIV enters mostly in macrophages, dendritic cells and CD4 T cells. When not treated, HIV infection induces a progressive decline of CD4 T cells that causes syndrome of acquired immunodeficiency (AIDS). This condition makes the patients particularly vulnerable to infections, mostly those caused by opportunistic pathogens.

Finally, an increased number of patients are treated with biological agents for a large number of medical conditions. Biological agents have the main characteristic of altering a specific pathway directly related to the pathogenesis of a given disease, thus being a more targeted therapy for treating oncologic, autoimmune and inflammatory disorders. In parallel, biological agents may increase the risk of specific pathogens for which the immune control is altered with the drug. For example, the C5 inhibitor eculizumab inhibits the complement cascade thus increasing the risk of meningococcal disease.

There are very few data on the clinical manifestations and outcomes of pertussis in immunocompromised patients. In this study, we present two cases of pertussis: a patient who has undergone both cardiac and renal transplantation and a patient infected with HIV. These two conditions involve a same particulary state: immunosuppression and thus vulnerability to infections. We will also review all published cases of pertussis in immnocompromised patients to increase our knowledge of the clinical manifestations and outcomes of this infection in this at risk population.

METHODS:

For the present study, we included two cases of pertussis in immunocompromised patients that were followed by the infectious diseases consultation over the last years. We additionally performed a search of electronic database (Pubmed) with the following keywords: pertussis, solid organ transplant, HIV, AIDS, stem cell transplant, biological therapy, immunodeficiency, pertussis vaccine. We included articles presenting cases of pertussis in SOT or HSCT recipients, patients with HIV and patients undergoing biological therapies. Articles in French and in English with these criteria were included. We also included adolescents, but children were excluded from our study.

We retained six articles fulfilling the criteria. Data that were systematically collected included the underlying disease and immunosuppressive condition, the clinical presentation, the diagnostic methods used (serology, culture, PCR), period between symptoms and diagnosis, outcomes, as well as severity criteria such as need to hospitalization, complications and mortality rate among patients with pertussis.

CASE REPORTS:

1. Case report 1

A 70-year-old Swiss patient known for a heart transplantation in 2004 for dilated cardiomyopathy and a kidney transplantation in 2014 for a nephroangiosclerosis and calcineurin-inhibitor toxicity, presented with a one-month history of progressive cough and dyspnea. He also reported a nasal discharge and occasional headache but denied sputum, fever, or chills. Patient was receiving a standard immunosuppressive regimen (tacrolimus, mycophenolate mofetil and prednisone) and had no longer co-trimoxazole prophylaxis. Additional personal medical history included a metabolic syndrome.

His vital signs were within normal limits and physical examination revealed diffuse expiratory wheezing but was otherwise unremarkable. The chest X-ray did not show any infiltrate. Laboratory results showed an elevated leucocyte count (13G/l) and a normal CRP. The patient was admitted at the hospital with the diagnosis of bacterial respiratory tract infection and antibiotic therapy with amoxicilline/clavulanate was started.

Urine antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae* were negative. A nasopharyngeal swab performed for respiratory viral panel (influenza, parainfluenza, coronarovirus, human metapneumovius, and rhinovirus) was negative. A polymerase chain reaction (PCR) for *Bordetalla pertussis* was positive with 1'900'000'000 copies/ml.

The patient was discharged home with a 5-day course of oral azithromycine. Clinical evolution was confirmed to be favorable at the outpatient clinics a few days later. There was no information in the chart of the patient regarding the date of the last vaccination for Bordetella.

2. Case report 2

A 57-year-old Swiss patient presented in the emergency department with a 10-day history of persistant cough with yellow sputum and anterior nasal discharge. He reported an episode of syncope during a paroxystic cough spasm, but no dyspnea or any other symptoms.

Medical history revealed an HIV infection diagnosed in 1987, treated with emitricitabine, tenofovir and efavirenz. Viremia was undetectable and the CD4+ level was at 144 cell/mm3 one month prior to the current visit. The patient told to have had a contact with another HIV-positive patient presenting similar symptoms two weeks before the onset of disease.

On physical examination the patient was in good general condition and his vitals signs within normal limit and he had no fever. Clinical status was unremarkable and chest X-Ray did not show any infiltrate.

Laboratory results showed a normal leucocyte count and an elevated CRP at 48 mg/l.

PCR posterior nasopharyngal swab returned positive for *B. Pertussis* with 11'000'000'000 copies/ml. Infection was treated with azithromycin and clinical evolution was favorable.

LITERATURE REVIEW:

There are seven additional reported cases in the literature. A summary of the clinical characteristics and outcomes of patients with pertussis is summarized in **Table 1**. With the two patients from our center, we collected a total of nine immunocompromised patients with pertussis. Two of them were SOT recipients, one patient had a metastatic cancer under chemotherapy, three patients underwent HSCT, and three patients were HIV-infected individuals.

Regarding the two SOT recipients, both underwent kidney transplantation and one also had a cardiac transplantation. Both were on standard immunosuppressive therapy. One of them, a 70-year-old man presented with upper and lower respiratory symptoms and clinical evolution was favorable after antibiotic administration (Patient #1). The other one, a 62-year-old female was admitted to the emergency department with an acute respiratory distress syndrom and paroxystic cough spasms

followed by apnea that required urgent treatment. (6) This clinical episode was preceded by a one-month history of non-productive cough and dysphonia. The patient showed clinical improvement under antibiotic therapy. In both cases, time between onset of symptoms and diagnosis was about four weeks.

The patient with the cancer was a 72-year-old female with a metastatic ovarian cancer and under chemotherapy with intrathecal methotrexate, gemcitabine and carboplatine. (7) She presented with productive cough with yellow sputum and shortness of breath. Diagnosis was made by PCR twelve days after onset of the clinical manifestations. Evolution was favorable under azithromycine.

Three of the patients underwent HSCT for different forms of leukemia. (7–9) They presented with lower respiratory symptoms as well as general manifestations, such as fatigue or malaise. Diagnosis was made by PCR in two of the patients in the two first weeks of the infection. In the left one, diagnosis was made by culture and no information was found about the time to diagnosis. Only one of them required hospitalization. Clinical evolution was good for all of them.

The last three cases were diagnosed in HIV-infected patients. One of them was patient #2 and is described above. The other two case reports were cases published in the nineties.(10,11) They had a low CD4+ cell count. One of the patients had clinical criteria for AIDS. Both of them presented with severe respiratory and systemic clinical manifestations, which lasted for respectively two and four months before diagnosis was established by culture. Clinical evolution of pertussis was favorable for both of them. One of the patients developed HIV encephalopathy a few months after contracting pertussis and was thereby diagnosed with AIDS.

DISCUSSION:

In our hospital, only two immunocompromised patients have contracted pertussis over the last years. We found seven additional cases reported in the literature. Thus, we decided to gather all these cases together to describe susceptibily to pertussis, clinical manifestations, diagnosis and outcomes of pertussis in this type of patients. We also wanted to know if there are differences in these parameters between immunocompetent and immunocompromised patients. In particular, we wanted to assess if pertussis was associated with a greater risk of complications in immunocompromised patients.

We found that very few cases of pertussis in immunocompromised patients have been published. Although this can be partially explained by a publication bias, the low number of cases reported in the literature suggests that the incidence of pertussis is not higher in immunocompromised patients than in immunocompetent individuals. Several hypotheses can explain this. First, it has been established that pertussis is underdiagnosed in adult population because practicians do not consider *Bordetella pertussis* as a possible ethiologic agent for respiratory illness. The same diagnosis bias may occur in immunocompromised patients and it could explain this low number of cases reported. Also, it can be that immunocompromised patients are vaccinated on a regular basis before establishment of their

immunosuppressed state and that are therefore better protected against pertussis. An additional reason is that transplant recipients and other immunocompromised patients receive universal prophylaxis with cotrimoxazole, which is active against *Bordetella pertussis.*

The second question that we wanted to answer was whether pertussis is a more severe disease in immunocompromised patients. We assessed in our study some variables to estimate the severity of the published cases with pertussis.

In one hand, two-thirds of the patients of our series required hospitalization (66%). In confront, percentage of immunocompetent adults with pertussis necessitating hospitalization is 12 %. (4). This means that hospitalization rate in immuncompromised patients is much higher. One of the reported patients even made a severe clinical picture of pertussis, with an acute respiratory distress syndrom requiring urgent treatment of corticosteroids, bronchodilatators and adrenaline. Likewise, one of the HIV-infected patients developed AIDS six weeks after being diagnosed with pertussis for a four-month history of cough and dyspnea. The authors suggested *B. pertussis* may survive intracellularly and cell-mediated immunity is needed to eliminate it. This is the reason why pertussis lasted four months without recovering and it has weakened an already deficient immune system, precipitating it into AIDS.

Another point arguing for a more severe clinical disease in immunocompromised patients is that all the patients of our series needed to be treated. This is not the case for adults in usual good health, who naturally clear *Bordetella pertussis* of their nasopharynx in several weeks and which antibiotherapy is only given to decrease duration and severity of the symptoms.

On the other hand, we may have a publication bias, as the reported cases are probably the most severe ones. We also notice that none of the immunocompromised patients died from pertussis and that the clinical outcome under antibiotic therapy was favorable for every patient of the series. These observations, in addition to the fact that we found very few cases reported in the literature, may argue against a more severe clinical presentation of pertussis in immunocompromised patients.

One point about control of pertussis by host immune system is that innate immune mechanisms are effective to control the infection, but to clear completely *B. Pertussis* from the host, adaptative immune system is essential. Innate immune cells, such as macrophages, dendritic cells and neutrophils, are the first line of defense against *B. pertussis.* They operate by phagocytosis, secretion of pro-inflammatory cytokines and activation of adaptative immune cells. The most effective adaptative immune cells against *B. pertussis* are T-helper type 1 and T-helper type 17 CD4+ cells, in addition to IgA and IgG antibodies. The problem is that most immunosuppressive drugs act specifically by bloquing the signals that are used to activate the effector T-cells. This results in an insufficient activation of adaptative immune system to clear *B. pertussis* in patients under immunosuppressive drugs. For example, tacrolimus, the most important immunosuppressive drug, acts by inhibiting calcineurin, which is a protein of one of the three activating pathways and this results in a lowered activation of T cells.(12)

Diagnosis of pertussis can be made by culture, PCR or serology. Culture has higher diagnostic yield if the nasopharyngeal swab is sent within three weeks after onset of the cough, and it is estimated to have a 100% specificity and 60% sensibility and a turnaround time of three to seven days. PCR is a more sensible method with a sensibility of 97% and results return much faster than culture. It has become therefore the test of choice for early diagnosis of pertussis. Serology is an indirect method by detection of IgG in blood. Because IgG are produced in a late phase of the infection, it has only a good sensitivity in case of late presentation. (1,13) In our series of 9 patients, five of them (55%) were diagnosed by PCR and the four left (45%) by culture. This was mostly dependent on the year of diagnosis, with the most recent cases diagnosed only by PCR. The value of serology for the diagnosis of pertussis in immunocompromised patients at the late stage of infection is not known.

Our study has a number of limitations. First, there is certainly a diagnosis bias in our series as pertussis is not a frequent disease in immunocompromised patients and practicians forget to think about it in this population. The second bias is the publication bias, as we found very few articles about this topic, which means that cases similar to ours may have not been published. We also specificaly searched for cases in other centers in Switzelrand included in the Swiss Transplant Cohort Study (STCS), but we did not find any additional case. Therefore, the low number of cases of pertussis diagnosed in immunocompromised patients seems general to the whole country. The main strength of the study is to increase our knowledge regarding a common disease, as it is the first litterature review about this subject.

CONCLUSION:

Pertussis is a widespread infection that does not seem to be more frequent in immunocompromised patients. Reasons for that include a potential higher rate of vaccination in immunocompromised patients, antibiotic prophylaxis with active agents, and larger differential diagnosis of upper respiratory tract infections in immunocompromised patients that makes clinical suspicion of pertussis more difficult in this population.

The low number of reported cases makes difficult to extract any firm conclusion regarding the severity of pertussis in the immunocompromised host. The fact that *B. pertussis* persists longer in patients with impaired function of T-cells, put them theorethically at risk for more severe clinical manifestations, but this has not been clearly observed in our case series.

Pertussis can be effectively treated with macrolides, which is why it is important to look actively for it when patients present with respiratory symptoms. Nevertheless, there is not enough articles published on this topic and we strongly encourage centers dealing with immunocompromised patients to report additional cases of pertussis.

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Table 1. Clinical characteristics and outcomes of the nine immunocompromised patients with pertussis.

STUDY	YEAR OF PUBLICATION	AGE	GENDER	UNDERLYING DISEASE	TYPE OF IMMUNO-SUPPRESSION	IMMUNOSUPPRESSIVE THERAPY	OTHER RISK FACTORS	CLINICAL MANIFESTATIONS	DURATION OF SYMPTOMS AFTER DIAGNOSIS	DIAGNOSIS	SEVERITY CRITERIA	CLINICAL EVOLUTION
Case #1	Present report	70	M	Nephroangiosclerosis and dilated cardiomyopathy	Kidney and heart transplantation	Tacrolimus, MMF, prednisone	Metabolic syndrome	Progressive cough, dyspnea, nasal discharge	4 weeks	PCR	Hospitalization	Favorable
Case #2	Present report	57	M	HIV infection	Nadir of 144 CD4+ cell/mm3	None	Contact with symptomatic HIV+ adult	Persistant cough, yellow sputum, anterior nasal discharge	10 days	PCR	Hospitalization	Favorable
(6)	2016	62	F	Chronic kidney disease secondary to polycystic kidney disease	Kidney transplantation	Sirolimus, MMF, Prednisone	Prvious contact with children with respiratory symptoms	Productive cough,dysphonia, fever, dyspnea at rest, tachypnea	>4 weeks	Culture	Acute respiratory distress requiring urgent treatment (corticosteroids, bronchodilatators and adrenaline)	Favorable
(7)	2016	72	F	Metastatic ovarian cancer	Chemotherapy	Intrathecal methotrexate, Gemcitabine, Carboplatine	Non available	Productive cough with yellow sputum Shortness of breath	12 days	PCR	-	Favorable
(7)	2016	61	M	5-year history of chronic lymphocytic leukemia	Matched, unrelated stem cell transplantation	None at the time of onset	Non available	Productive cough Sore throat Fatigue	<7 days	PCR	Hospitalization	Favorable

(8)	2006	42	M	Chronic myeloid leukemia in accelerated phase	Matched unrelated donor PBSCT	Cyclophosphamide Total Body Radiation 14.4 Gy	Chronic cutaneous GvHD 10 year-old daughter with pertussis	Dry cough Malaise Characteristic whoop	NA	Culture	None	Symptomatic for 4 weeks on antibiotic therapy, then favorable
(9)	2006	16	M	Acute B-lymphoblastic leukemia	Matched related bone marrow transplantation	None at the time of onset	Non available	Persistant, non productive cough	>2 weeks	PCR	-	Favorable
(10)	1994	60	M	HIV infection	Nadir of 17 CD4+ cell/mm3	None	Non available	Severe paroxysmal nonproductive cough, dyspnea, low grade fever, exhaustion, hoarseness	2 months	Culture	Hospitalization	Favorable
(11)	1990	25	M	HIV infection	Nadir of 13 CD4+ cell/mm3	None	Non available	Paroxysmal nonproductive cough, dyspnea, fatigue, malaise, night sweats, fever to 38.9, chills and weight loss	4 months	Culture	Hospitalization	Favorable

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