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Zoonotic *Chlamydophila psittaci* infections from a clinical perspective

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Abstract

Human psittacosis is a zoonotic infectious disease which is caused by the obligate intracellular bacterium *Chlamydophila psittaci*. Transmission of the disease usually originates from close contact with infected birds, most frequently in the context of the poultry industry, and from contact with *Psittaciformes* (cockatoos, parrots, parakeets and lories). Due to a low awareness of the disease and a variable clinical presentation psittacosis is often not recognised as such by general practitioners. This review therefore gives an overview of the epidemiology, symptoms, diagnosis and possible treatments for psittacosis in humans. The current case definition for epidemiological surveillance, as issued by the CDC, is discussed, as well as the possible emergence of *Cp. psittaci* antibiotic-resistant strains. There is an urgent need for information and for awareness campaigns directed at professional health care workers and the general public. In addition, a broader use of new diagnostic methods in medical laboratories and the development of prophylactics are called for.

Keywords: *Chlamydia*, *Chlamydophila psittaci*, diagnosis, epidemiology, review, treatment, zoonosis

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Chlamydophila psittaci strain classification

Micro-organisms in the family of the Chlamydiaceae are obligate intracellular pathogens of both mammals and birds. The different species in this family infect many hosts, with variable tissue tropism causing a multiplicity of acute and chronic diseases, from sexually transmitted infertility, to trachoma and respiratory and cardiovascular diseases. Before the reclassification in 1999, the genus *Chlamydia* (*C.*) was divided into only four species: *C. trachomatis*, *C. pecorum*, *C. pneumoniae* and *C. psittaci*. In 1999, Everett *et al.* [1,2] proposed a new classification after analysis of 16S and 23S rRNA genes, and phenotypical, morphological and genetic information (DNA–DNA hybridization). The *Chlamydiaceae* are currently divided into two genera, *Chlamydia* and *Chlamydophila* (*Cp.*), comprising nine species. All known avian strains belong to the species *Cp. psittaci* which includes six avian serovars, designated A–F, and two mammalian isolates (WC and M56) [3–5]. As the monoclonal antibodies used to distinguish avian serovars [3,6] are commercially unavailable, analysis of the MOMP encoding outer membrane protein A gene (*ompA*) is today more often used to characterize avian *Cp. psittaci* strains into different genotypes. The currently accepted *ompA* genotypes (A–F, E/B, M56 and WC) are largely congruent with the serovars and can be distinguished by sequencing [2], genotype-specific real-time PCR [7] or micro-arrays [8]. One of the advantages of these molecular techniques is that they can distinguish among the *ompA* genotypes E/B, E and B, which is impossible using serovar-specific monoclonal antibodies, as genotype E/B reacts with serovar B and serovar E specific monoclonals. Moreover, genotype E/B generates the *ompA* restriction (*AluI*) fragment length polymorphism (RFLP) pattern E [9]. Molecular characterization enables us to determine phylogenetic relationships among different *Cp. psittaci* isolates and even among *Cp. psittaci* and *Cp. abortus* strains, as was previously shown for the abortus-like *Cp. psittaci* strain 84/2334, formerly serotyped as serovar A and generating an *ompA* genotype F RFLP restriction pattern [5].

The currently known genotypes are relatively host-specific. Genotype A and B strains are usually associated with psittacine birds and pigeons, respectively. Genotype C has been isolated primarily from ducks and geese, whereas genotype D was mainly found in turkeys. Genotype F was isolated from both a psittacine bird and turkeys. The host range of

genotype E is the most diverse; *c.* 20% of genotype E strains were isolated from pigeons. In addition, genotype E was isolated in many fatal cases of chlamydiosis in ratites, during respiratory outbreaks in ducks and turkeys, and occasionally from humans. So far, genotype E/B has been isolated mainly from ducks. WC and M56 are isolates from epizootics in Wolfsen cattle and muskrats, respectively. All genotypes should be considered to be readily transmissible to humans and potentially can cause severe disease and even death.

Epidemiology and transmission

The first description of a psittacosis outbreak dates from 1879 and was described by Jacob Ritter, linking the disease to pet parrots and finches. Pandemic outbreaks of human psittacosis in 1929 and 1930 were linked to the import of infected psittacine birds from South America to Europe and North America. In the 1930s, isolates from South African and Californian racing pigeons were also obtained. In the years that followed, several cases of psittacosis in humans in New York and California could be attributed to contact with feral pigeons, ducks and turkeys. Although severe respiratory outbreaks in the US turkey industry lead to the isolation of *Cp. psittaci* from both turkeys and humans in the early 1950s [10], the incidence of severe *Cp. psittaci* epidemics in US poultry declined during the 1960s. Nevertheless, both birds and humans continued to be exposed to avian chlamydiosis. During the 1980s and 1990s, psittacosis outbreaks were reported in the USA [11,12] and European poultry industries, respectively [13–15]. In the last decade, considerable evidence indicating that *Cp. psittaci* is nearly endemic in the turkey industry in Belgium [16], as well as in other European countries [16,17], has been obtained. Today, infections in turkeys seem to induce mild respiratory signs and are not necessarily fatal. Evidence of human infections associated with outbreaks in poultry exists [18–26].

Recently, the number of chlamydiosis outbreaks in ducks and in people in contact with infected ducks has increased [27] (Laroucau *et al.*, 2009, Veterinary Microbiology, in press).

Chlamydophila psittaci infections occur in at least 465 bird species, spanning 30 different bird orders [28]. Especially *Psittacidae* (cockatoos, parrots, parakeets and lories) and *Columbiformes* (pigeons) seem to be affected. Therefore, psittacine pet birds, racing pigeons and free-living pigeons in urban and rural areas throughout the world should be regarded as the predominant reservoirs of zoonotic psittacosis. Transmission of *Cp. psittaci* predominantly occurs through inhalation of contaminated aerosols from urine, respiratory and eye secretions, or dried faeces from a diseased animal or asymptomatic carrier. Handling the plumage and tissues of infected birds and, in rare cases, mouth-to-beak contact or biting, represent a zoonotic risk. In addition, activities such as gardening and mowing or trimming lawns without a grass catcher have been associated with human psittacosis, suggesting that these activities may expose individuals to the infectious agent [29,30]. Person-to-person transmission of psittacosis is possible, but it is believed to be rare [31,32].

Public health significance

The impact of these *Cp. psittaci* infections on human health is difficult to determine. In most countries, psittacosis is a notifiable disease and must be reported within 48 h. An overview of reported cases of psittacosis in several countries is presented in Table 1. However, these figures most definitely represent a gross underestimation of the current number of infections, as not all infections cause pneumonia and therefore often remain unnoticed. Moreover, psittacosis is difficult to diagnose in the wake of empirical therapy for community-acquired pneumonia [33,34].

Diagnosis of psittacosis

Anamnesis: contact with birds?

A possible explanation for the current underestimation of the number of cases of psittacosis in humans is that general practitioners are not necessarily aware of the widespread occurrence and the zoonotic nature of avian chlamydiosis. Campaigns to raise awareness, organized by national or local governments, could increase the general degree of attentiveness to human psittacosis. More specifically, a more thorough enquiry with regards to the patient's medical history and professional and leisure occupations could bring contact with birds to light, thus possibly linking persistent flu-like symptoms, respiratory distress, fever, chills, headache, weakness or fatigue to human psittacosis.

Clinical presentation

Chlamydophila psittaci mainly causes a respiratory infection in humans and clinical symptoms are highly variable. After initial replication in epithelial cells and macrophages from the respiratory system, bacteria might spread throughout the body, affecting different organs (heart, liver, gastro-intestinal tract). The incubation period is usually 5–14 days, although periods up to 1 month have been reported and the disease can vary

TABLE 1. Human cases of psittacosis (available data)

Country/territory	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	Notifiable
Austria	1			1	2	3	0	3	6				
Argentina					38	1							
Australia	86	35	55	81	99	137	213	200	239	164	171	62	Yes
Belgium	9	7	8	12	13	10	23	39	12	7	2	3	Yes
Bosnia and Herzegovina	162						0	0	0				
Chile					2								
Croatia	7	4	0	5	8	3		5	4				
Czech Republic	3	5	6			0	3	0	0				
Denmark		57*		30	31	8	13	14	8	22	7	11	Yes
Finland	2	1	2	0	0	0			0				
F.Y.R. of Macedonia	0			14	0	0	5	0	0				
Germany	134	124	155	109	86	56	41	41	15	33	26	12	Yes
Hungary	4	3	4	1	5	1	6 (1†)	85	7	140 (2†)	29	28 (1†)	Yes
Japan				23	18	35	54	44	40	34			Yes
New Caledonia						3	3						
Poland	2	2	0	2	0	5		2	2				
Slovakia	2	0	1	3	10	0	0	1	0		1		
Spain						5	4	0	1				
Sweden	25	66	30	29	24	12	13	12	7	5	2	9	
The Netherlands	56	28	26	25	36	23	17	27	33	49	59	27	Yes
UK/Great Britain	353	322	293	207	204	106	68	100	62	59			
UK/N. Ireland	52	37	0	0		44	16	15	13				
Ukraine	161	2	3	2	0	0	0	0	0				
USA	45	38	54	15	13		19	13	11				Yes

*Number of reported cases from 1996 to 1998.
†Number of reported casualties.

from unapparent, as also recognised by the Centers for Disease Control (CDC) [35], to fatal in untreated patients [36]. An overview of selected recent case reports is given in Table 2.

Symptoms frequently include high fever (up to 40.5°C) accompanied by a relatively low pulse, chills, headache, myalgia, non-productive coughing and difficult breathing. Occasionally, slimy sputum can be contaminated with traces of blood. Other symptoms described are non-specific rash or gastro-intestinal problems such as vomiting, abdominal pain and diarrhoea [37]. In rare cases, complications such as myocarditis, endocarditis [38], encephalitis [39], icterus [40], adult respiratory distress syndrome (ARDS) [41] and multi-organ failure [42] have been described. Among pregnant women, atypical pneumonia, hepatitis, renal insufficiency, sepsis, premature birth or foetal death have been observed (overview in Refs [43,44]). Furthermore, *Cp. psittaci* has also been linked to ocular lymphoma, although this is still a matter of debate [45–48].

Haematology

White cell count is usually normal to slightly lowered during the acute phase of the disease, developing into leucopoenia in on average 25% of cases [43]. Anaemia has been observed secondary to haemolysis, and in patients with overwhelming infections, disseminated intravascular coagulation may rarely occur.

Augmented C-reactive protein (CRP), aspartate and alanine aminotransferase or γ-glutyl transpeptidase blood parameters in psittacosis patients and liver enzyme levels seem to be related to the severity of the infection.

Radiographic findings

For patients with psittacosis, chest X-rays are abnormal in up to 90% of hospitalized cases. Most commonly, unilateral, lower lobe dense consolidation is observed [49], but also bilateral, nodular, miliary or interstitial infiltrates can be present [43].

Case definition

To date, a patient is considered to suffer from human psittacosis if the clinical representation is in concordance with psittacosis and the case is laboratory confirmed by at least one of the following methods: (i) isolation of the causative agent from respiratory secretions, (ii) four-fold or more increase of antibody titre between paired sera as determined by a complement fixation test (CFT) or the more sensitive micro-immunofluorescence (MIF) test or (iii) IgM antibodies against *Cp. psittaci* detected by MIF to a reciprocal titre of 16 or more [44]. These case definitions have been issued by the CDC for the purpose of epidemiological surveillance, but are frequently used to diagnose single human cases.

Culture

Isolation of the causative agent during the acute phase of the infection and before the administration of antimicrobials is the most reliable method to prove the presence of viable bacteria in a human (or avian) case of psittacosis. Samples

TABLE 2. Overview of selected recent human psittacosis case reports

Country	Year	No	Symptoms	Diagnosis	Treatment	Source	References
The Netherlands	/	1	Severe pneumonia, respiratory failure	Serology and PCR on bronchoalveolar lavage fluid	Doxycyclin 200 mg IV	Collection of exotic birds, including parrots	[65]
Belgium	2004	3	No severe clinical symptoms	PCR on pharyngeal and nasal swabs, culture Serology on two persons	None	Visit to a parrot relief centre	[33]
The Netherlands	2005	10	None Community acquired pneumonia Sepsis with multi-organ failure	PCR on sputum or throat swab Serology on convalescent sera	None or doxycycline	Parrots used in a practical class in a veterinary teaching hospital	[42]
Germany	2005	24	Flu-like symptoms (fever, headache, myalgia, cough, malaise) Diarrhoea, interstitial pneumonia, multiple lesions in several organs, coma	Serology and/or PCR on bronchoalveolar lavage fluid	Not mentioned	Contact with a mixed poultry flock (chickens, ducks and geese)	[19]
Belgium	2005	7	Shortness of breath and rhinitis or coughing	PCR on pharyngeal swab Culture	None	Breeding facilities for *Psittaciformes*	[34]
Switzerland	2007	1	Febrile illness without pneumonia, diarrhoea	Serology on convalescent sera	Ciprofloxacin	Dissection of a dead Amazon parrot	[37]
Germany	2007	1	Flu-like symptoms (fever, headache, myalgia, cough, malaise)	PCR on brochoalveolar lavage fluid	Antibiotic treatment (not specified)	Culling of H5N1-positive ducks	[66]
The Netherlands	2007	12	At least two of the following: over 39°C fever, headache, myalgia, coughing, shortness of breath, cold shivers or sweating, gastro-intestinal complaints	PCR on pharyngeal swabs and/or serology	200 mg doxycyclin for 10 days PO	Bird exposition	[67]

from sputum, pleural fluid or clotted blood can be used for this purpose. Diagnosis by culture can only be performed in a limited number of laboratories because of the requirement of a biosafety level three facility.

In the early days, mainly inoculation into mice and especially the yolk sac of 6-day-old SPF chicken embryos was performed for primary isolation of the infectious agent. Today, isolation of *Cp. psittaci* is routinely performed on cell cultures, often in the presence of cycloheximide. Numerous cell types have been described in the literature, such as Buffalo Green Monkey (BGM) (Fig. 1), McCoy, HeLa, African Green Monkey (Vero) and L-929 cells, with BGM cells shown to be the most sensitive artificial host [50]. *Chlamydophila psittaci* growth is usually confirmed by immunofluorescence techniques and negative samples are repassaged after 6 days of inoculation, to confirm negative results. Treatment of the patient with antibiotics or improper handling and storage of samples may however impair bacterial growth.

Serology

Frequently used serological tests for *Cp. psittaci* diagnosis in humans are CFT, ELISA and MIF, which is regarded as the reference standard. One has to keep in mind however that detection of anti-chlamydial antibodies, although historically regarded as highly reliable, is extremely prone to the generation

FIG. 1. Transmission electron microscopy photograph of a *Cp. psittaci* infected BGM-cell (5200×). Cells were seeded on a thermanox slide and inoculated with *Cp. psittaci* strain 92/1293 for 30 h until fixation.

of both false-negative and false-positive results. False-negative MIF results in ill psittacosis patients have already been reported [20]. On the other hand, both MIF and CFT use whole chlamydial organisms to capture antibodies. As some of the surface-located antigens, such as the chlamydial LPS or HSP, can cross-react with antibodies to other bacteria [51], caution is needed when interpreting positive results. To circumvent this problem, MIF tests and ELISAs using chlamydial organisms without the LPS were developed, the latter being more sensitive than MIF. However, another problem still remains. None of the current serological tests is *Cp. psittaci*-specific due to serological cross-reaction between different species of the Chlamydiaceae family, which makes it difficult to distinguish *Cp. psittaci*, *C. trachomatis* and *Cp. pneumoniae* antibodies in humans. The case definitions as issued by the CDC should therefore not be used as the sole criteria for reliable diagnosis of human psittacosis.

On the other hand, treatment with antibiotics 2–3 weeks before testing may inhibit the development of antibodies, thus generating false-negative results, as is also the case when patients are sampled before seroconversion.

Molecular detection and characterization

Given the high prevalence of *Cp. pneumoniae* in man, ranging from 44% to 66% [52], and the limited discriminatory properties of serology testing, nucleic-acid based *Cp. psittaci*-specific diagnostic assays targeting highly divergent antigenic determinants were developed. Multiple nested PCRs based on *ompA* detection have been described and are now routinely being used [53,54]. Moreover, the emergence of quantitative real-time PCR, sequencing and micro-arrays has now provided the opportunity to not only confidently determine the species [7,55], but also the genotype of the causative agent [7,8,56]. Both the intrinsic sensitivity and the efficiency of the DNA extraction from the clinical sample are of crucial importance for the sensitivity of the assay. Particularly, inhibitors of DNA polymerase have to be removed. However, none of the described nucleic-acid amplification techniques (NAATs) are currently commercially available.

Treatment of Psittacosis Patients

Human cases of psittacosis are preferably treated with tetracyclines, such as doxycycline (100 mg peroral-PO, every 12h-q12h) or tetracycline hydrochloride (500 mg PO, q6h). In order to be effective and to prevent relapse, treatment must continue for at least 10–14 days. In patients for whom tetracycline is contra-indicated (pregnant women) and in children under 8 years, treatment with macrolides is probably the best alternative (azithromycin and erythromycin, 250–500 mg PO qd $\times$ 7 days) [44,57]. Tetracyclines and macrolides bind to 16S or 23S rRNA, respectively, and consequently affect bacterial translation [58]. Quinolones have been used to treat chlamydial infections but there have been reports of treatment failure. To our knowledge, clinical studies on the effectiveness of quinolones against agents of the *Cp. psittaci* group are not yet available. Butaye *et al.* did however test the *in vitro* susceptibilities of 14 avian strains to doxycycline and enrofloxacin. The minimal inhibitory concentration (MIC) of doxycycline ranged from 0.05 to 0.2 μg/L, while the MIC of the fluoroquinolone antibiotic was 0.25 μg/L [59], justifying the choice of tetracyclines rather than quinolones.

Although chlamydial infections can easily be resolved by treatment with antibiotics and the acquisition of antibiotic resistance genes from other organisms is limited due to their obligate intracellular life style, stable tetracycline resistance through horizontal gene transfer has already been reported for *Chlamydia suis* [60,61]. In addition to the insertion of resistance genes into the bacterial genome, drug resistance can also arise through point mutations, altering the expression or the functionality of the antibiotic target [62,63]. As the use of antibiotics, and especially tetracyclines, is widespread in the poultry and pet bird industry, resistance to tetracyclines could emerge among *Cp. psittaci* strains as well.

Furthermore, treatment with antibiotics might lead to subclinical persistent infections, possibly evolving to chronic disease and relapse when antibiotics are no longer administered (for a review, see Ref. [64]).

Conclusion

At present, the presence and zoonotic aspects of *Cp. psittaci* are seriously underestimated by the authorities, professional health care workers and the general public. This is partly attributable to the rather archaic definition of human cases of psittacosis based on serological MIF (cross-reactive, insensitive as compared to ELISA) or CFT (cross-reactive, even less sensitive than MIF) results. Therefore, criteria defining human cases of psittacosis should be adapted to include nucleic-acid amplification tests (NAATs), which are *Cp. psittaci*-specific and extremely sensitive. Psittacosis, whether human or avian, is currently manageable through administration of tetracyclines or macrolides. However, as the use of antibiotics is widespread in the poultry and pet bird industry, the possible emergence of antibiotic resistant zoonotic field strains should be taken into consideration.

Transparency Declaration

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