Psittacosis

Subjects: Infectious Diseases

Contributor: Zygmunt F. Dembek , Jerry L. Mothershead , Akeisha N. Owens , Tesema Chekol , Aiguo Wu

The bacterial agent *Chlamydia psittaci*, and the resulting disease of psittacosis, is a little-known and underappreciated infectious disease by healthcare practitioners and in public health in general. *C. psittaci* infections can cause significant psittacosis outbreaks with pandemic potential, with person-to-person transmission being documented in the last decade.

psittacosis Chlamydia psittaci chlamydia

1. Introduction

Exposure to the bacteria *Chlamydia psittaci* may result in the disease psittacosis (also characterized as “parrot fever”). The disease is usually contracted through zoonotic transmission, and human disease often presents as atypical pneumonia in the lower respiratory tract [1]. *C. psittaci* is a US Centers for Disease Control and Prevention (CDC) Category B biological agent. As a group, Category B agents are considered to be moderately easy to disseminate, to result in moderate morbidity rates and low mortality rates, and to require specific enhancements of CDC’s diagnostic capacity and enhanced disease surveillance [2]. It is notable that psittacosis mortality was as high as 50% during the 20th century [3]. In 1929–1930, a global pandemic of psittacosis occurred, known to have affected about 800 individuals [4]. This led to a quarantine of imported parrots into the US as a preventive measure that remained in place for over 40 years [5]. In the absence of an available effective antimicrobial treatment, this disease’s impact potential could reoccur.

2. The Pathogen

C. psittaci belongs to the family Chlamydiaceae, and the order Chlamydiales. The Chlamydiaceae family is comprised of two genera: Chlamydophila and Chlamydia. The Chlamydia genus consists of 11 species, most notably *C. trachomatis*, the cause of the most common sexually transmitted infection. Recently, two novel species were discovered, *C. avium* and *C. gallinacean* [6]. *C. psittaci* is a Gram-negative, obligate intracellular bacteria containing several genotypes that can cause infection in both birds and mammals. All genotypes have host-specific preferences, yet it can be transmitted to humans, in which they cause infections primarily by colonizing human and animal mucosal surfaces [7]. The sequencing of these genotypes by genotype-specific real-time PCR supports pathogen detection [8].

All Chlamydia (including *C. psittaci*) have a biphasic developmental cycle composed of two alternating forms: a metabolically inactive elementary body (EB) and the reticulate body (RB) [9]. An important characteristic of the EB

is that it is resistant to the environment and can survive outside of a host. Cell infection is mediated by the EB (0.2–0.3 μM diameter), and within-cell bacterial multiplication is mediated by the RB (0.5–1.3 μM diameter) [10]. Bacterial infection occurs when the EB attaches itself to the cytoplasmic membrane of a susceptible host cell, stimulating inclusion within a vacuole, thereby avoiding phagocytosis. The RBs cannibalize host cell ATP synthesis for cell division while inducing a host immune response. Within 48–72 h, RBs reorganize and condense to form new EBs that then depart the host cell to become available for a new infectious cycle. This unusual growth cycle helps to explain why *C. psittaci* cells will not grow in traditional bacterial culture media [11]. Furthermore, cell culture methods can take several weeks [12].

3. *C. psittaci* Reservoirs

C. psittaci is a globally distributed zoonotic bacterium, and the true range of reservoirs is unknown. Most cases are identified in domesticated avian species, or domesticated or farm animals, but rare cases have been identified in a variety of zoo animals, be they birds, mammals, or reptiles. The organism has also been identified in wild birds, such as eagles and doves [13][14], and feral pigeons in urban areas are a natural reservoir of *C. psittaci* [15]. Parrots are a major host, yet prevalence and risk factors for infection in wild parrots are largely unknown. Recent research suggests there is a diverse range of novel *Chlamydiales* circulating in wildlife. Novel *C. psittaci* strains have been identified in birds that are highly virulent in humans. One study found the average wild parrot seroprevalence at 37%. Host species (including crimson rosellas (*Platycercus elegans*), galahs (*Eolophus roseicapilla*), sulfur-crested cockatoos (*Cacatua galerita*) and blue-winged parrots (*Neophema chrysostoma*)) differed in seroprevalence and *Chlamydiales* prevalence. Galahs had both highest *Chlamydiales* prevalence (55%) and seroprevalence (74%). Seroprevalence differed between sites, with a larger difference in males (range of 20–63%) than females (29–44%). This higher chlamydial prevalence than previously reported in wild parrots suggests potential reservoirs and transmission risks to humans and other avian hosts [16].

4. Diagnostics

The differential diagnosis of psittacosis is usually that of atypical pneumonia, and includes the following: bacterial pneumonia; brucellosis; Chlamydia pneumonias; fungal pneumonias; infective endocarditis; Legionnaires Disease; *Mycoplasma pneumonia*; Q Fever; tuberculosis; tularemia; typhoid fever; and viral pneumonias [17].

Since most cases of psittacosis are mild, a definitive diagnosis is often not made. Some laboratory tests are difficult, and are often only available at specialized laboratories. Therefore, patients are often treated presumptively based on exposure history and clinical signs and symptoms. Nonetheless, the importance of *C. psittaci* infection as a cause of CAP is likely underestimated. A review of the literature from 1986 to 2015 using only studies of ≥100 patients revealed that *C. psittaci* was the causative pathogen in 1.03% of all CAP cases from the combined studies. For burden of disease estimates, it is a reasonable assumption that 1% of incident cases of CAP are caused by psittacosis [18].

Confirmation should certainly be made if the patient is at high risk of severe disease, fails to respond to appropriate treatment, or complications develop. The following diagnostic tests may be helpful or definitive in determining the etiology of the disease presentation, coupled with a history of zoonotic contact: [19]

- Chest radiograph may demonstrate lobar or lobular pneumonia;
- Liver function tests may be slightly elevated;
- The erythrocyte sedimentation rate (ESR) may be elevated;
- Urinalysis may show mild proteinuria (<3500 mg/d).

Due to non-specific signs during psittacosis, the early detection of psittacosis infection and differentiation from hypersensitivity pneumonitis may be difficult. Cell culture and ELISA were once the 'gold standard' for *C. psittaci* detection, with poor results received from real-time polymerase chain reaction (PCR) analysis [20]. PCR has been used experimentally, and metagenomic sequencing data is being used more frequently for definitive diagnosis [21]. Today, commonly used laboratory techniques for positive pathogen identification include considerably improved PCR and serology [22]. While serologic testing is most often used, PCR has since evolved such that PCR testing is recommended for detecting the presence of *C. psittaci* in the lower respiratory tract and from other clinical specimens [23].

Serological tests used for *C. psittaci* detection include complement binding reactions, ELISA, immunofluorescence tests, and immuno-peroxidase tests. Serological testing, whether via the complement fixation or anti-Chlamydia microimmunofluorescence (MIF) assay, is known to evince cross-reactivity between the different species [24]. Both acute and convalescent samples are required for serological confirmation. There is a need for serologic *C. psittaci*-specific testing methods with good specificity and sensitivity that does not require convalescent serum sampling [25].

Human psittacosis (presenting as pneumonia) with a diagnosis based on clinical findings may be confirmed by PCR despite negative serological testing. The increased use of PCR for the early diagnosis of human psittacosis and the early initiation of correct antibiotic treatment has been recommended to reduce psittacosis morbidity and mortality [26]. Similar to PCR, metagenomic data from next generation sequencing (mNGS) has higher sensitivity and is faster than culture [27]. Metagenomics data has successfully been used to identify *C. psittaci* cases within 24 h [28]. Given the potential ability to find evidence of *C. psittaci* infection from NGS versus a negative serological test, NGS use has been referred to as 'hypothesis-free pathogen detection' [29].

To date, 15 genotypes of *C. psittaci* have been identified [30]. Infection with different *C. psittaci* strains can present with different clinical features. A case study of patients infected with *C. psittaci* strains SZ18-2 and SZ15 claimed that each patient demonstrated different clinical manifestations [31]. Such bacterial strain differences may also be rapidly detected with mNGS.

5. Treatment Options and Outcomes

The psittacosis mortality rate today is about 20% without treatment and as low as 1% with timely intervention. It is notable that psittacosis mortality was 50% in an outbreak in London in 1930 [3]. In the absence of appropriate and effective antimicrobial treatment, this disease's considerable impact could reoccur.

Human psittacosis is effectively treated with doxycycline and tetracycline for 10–14 days, and as long as 21 days. For those whom tetracycline is contraindicated (pregnant woman and children <8 years) azithromycin and erythromycin are often used [32]. Fluoroquinolones are also active against *C. psittaci* infections but less than tetracyclines and macrolides [33]. With treatment, symptoms begin to regress after 24 to 48 h. Relapses have been known to occur. Severely ill patients require intravenous treatment with doxycycline hyclate [34]. Effective antimicrobial therapies have significantly contributed to the decreasing numbers of psittacosis cases. However, quinolones used to treat chlamydia infections have resulted in treatment failure [35]. Notably, *Chlamydia* can be induced through antimicrobial stimuli to undergo a temporary interruption in their replication cycle, entering into persistence, i.e., a viable but non-cultivable state. The regulatory mechanisms of *Chlamydia* persistence are unknown [36].

References

1. Al-Abbad, E.A.; Albarra, Y.A.I.; Al Shuqayfah, N.I.; Nahhas, A.A.; Alnemari, A.F.; Alqurashi, R.K.; Abu Thiyab, S.H.M.; Alqubali, M.K.; Alhawiti, M.A.; Almutairi, S.M. An overview of atypical pneumonia clinical features and management approach. Arch. Pharm. Pract. 2022, 13, 24–30.
2. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention Bioterrorism Preparedness and Response. Available online: https://emergency.cdc.gov/agent/agentlist-category.asp (accessed on 19 July 2023).
3. Weston, K.M.; Polkinghorne, A.; Branley, J.M. Psittacosis contagion in 1930: An old story in a new era of zoonotic disease. Microbes Infect. 2022, 25, 105076.
4. Psittacosis. Fast Facts You Need to Know about Psittacosis. US Centers for Disease Control and Prevention. 2022. Available online: https://www.cdc.gov/pneumonia/atypical/psittacosis/about/fast-facts.html (accessed on 1 September 2023).
5. Hasseltine, H.E. Some epidemiological aspects of psittacosis. Am. J. Public Health Nations Health 1932, 22, 795–803.
6. Sachse, K.; Laroucau, K.; Riege, K.; Wehner, S.; Dilcher, M.; Creasy, H.H.; Weidmann, M.; Myers, G.; Vorimore, F.; Vicari, N.; et al. Evidence for the existence of two new members of the family Chlamydiaceae and proposal of Chlamydia avium ap. nov. and Chlamydia gallinacean sp. nov. Syst. Appl. Microbiol. 2014, 37, 79–88.

7. Cheong, H.C.; Lee, C.Y.Q.; Cheok, Y.Y.; Tan, G.M.Y.; Looi, C.Y.; Wong, W.F. Chlamydiaceae: Diseases in primary hosts and zoonoses. Microorganisms 2019, 7, 146.
8. Kalim, F. An overview of psittacosis. In One Health Triad; Aguilar Marcellino, L., Younus, M., Khan, A., Saeed, N.M., Abbas, R.Z., Eds.; Unique Scientific Publishers: Faisalabad, Pakistan, 2023; Volume 3, pp. 45–52.
9. AbdelRahman, Y.M.; Belland, R.J. The chlamydial development cycle. FEMS Microbiol. Rev. 2016, 29, 949–959.
10. Escalante-Ochoa, C.; Ducatelle, R.; Haesebrouck, F. The intracellular life of Chlamydia psittaci: How do bacteria interact with the host cell? FEMS Microbiol. Rev. 1998, 22, 65–78.
11. Psittacosis. Disease Specifics. US Centers for Disease Control and Prevention. Psittacosis: Clinical Disease Specifics|CDC. 2022. Available online: https://www.cdc.gov/pneumonia/atypical/psittacosis/hcp/disease-specifics.html (accessed on 1 September 2023).
12. Psittacosis. Diagnosis, Treatment and Prevention. US Centers for Disease Control and Prevention. Psittacosis: Clinical Diagnosis, Treatment, and Prevention|CDC. 2022. Available online: https://www.cdc.gov/pneumonia/atypical/psittacosis/hcp/diagnosis-treatment-prevention.html (accessed on 1 September 2023).
13. Seibert, B.A.; Keel, M.K.; Kelly, T.R.; Nilsen, R.A.; Ciembor, P.; Pesti, D.; Gregory, C.R.; Ritchie, B.W.; Hawkins, M.G. Chlamydia buteonis in birds of prey presented to California wildlife rehabilitation facilities. PLoS ONE 2021, 16, e0258500.
14. Kasimov, V.; Dong, Y.; Shao, R.; Brunton, A.; Anstey, S.I.; Hall, C.; Chalmers, G.; Conroy, G.; Booth, R.; Timms, P.; et al. Emerging and well-characterized chlamydial infections detected in a wide range of wild Australian birds. Transbound. Emerg. Dis. 2022, 69, e3154–e3170.
15. Kowalczyk, K.; Wojcik-Fatla, A. Chlamydia psittaci in faecal samples of feral pigeons (Columba livia forma urbana) in urban areas of Lublin city, Poland. Curr. Microbiol. 2022, 79, 367.
16. Stokes, H.S.; Martens, J.M.; Walder, K.; Segal, Y.; Berg, M.L.; Bennett, A.T.D. Species, sex and geographic variation in chlamydial presence in abundant wild parrots. Sci. Rep. 2020, 10, 20478. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7686501/ (accessed on 1 September 2023).
17. Lessnau, K.D. Psittacosis. Medscape Drugs and Diseases On-Line. 24 July 2019. Available online: https://emedicine.medscape.com/article/227025-overview (accessed on 1 September 2023).
18. Hogerwerf, L.; Gier, B.D.; Baan, B.; Van Der Hoek, W. Chlamydia psittaci (psittacosis) as a cause of community-acquired pneumonia: A systematic review and meta-analysis. Epidemiol. Infect. 2017, 145, 3096–3105.

19. Lessnau, K.-D.; Arjomand, F.; Anariba, D.E.I.; Lanza, J. Psittacosis (Parrot Fever) Workup. Medscape. Psittacosis (Parrot Fever) Workup: Laboratory Studies, Imaging Studies, Other Tests. 2019. Available online: Medscape.com (accessed on 1 September 2023).
20. Trevejo, R.T.; Chomel, B.B.; Kass, P.H. Evaluation of the polymerase chain reaction in comparison with other diagnostic methods for the detection of Chlamydia psittaci. J. Vet. Diagn. Investig. 1999, 11, 491–496.
21. Shi, Y.; Chen, J.; Shi, X.; Hu, J.; Li, H.; Li, X.; Wang, Y.; Wu, B. A case of Chlamydia psittaci caused severe pneumonia and meningitis diagnosed by metagenome next-generation sequencing and clinical analysis: A case report and literature review. BMC Infect. Dis. 2021, 21, 621.
22. Missault, S.; De Meyst, A.; Van Elslande, J.; Van den Abeele, A.M.; Steen, E.; Van Acker, J.; Vanrompay, D. Three cases of atypical pneumonia with Chlamydia psittaci: The role of laboratory vigilance in the diagnosis of psittacosis. Pathogens 2023, 12, 65.
23. McGovern, O.L.; Kobayashi, M.; Shaw, K.A.; Szablewski, C.; Gabel, J.; Holsinger, C.; Drenzek, C.; Brennan, S.; Milucky, J.; Farrar, J.L. Use of real-time PCR for Chlamydia psittaci detection in human specimens during an outbreak of psittacosis—Georgia and Virginia, 2018. Morb. Mortal. Wkly. Rep. 2021, 70, 505–509.
24. Burgener, A.V.; Seth-Smith, H.M.B.; Kern-Baumann, S.; Durovic, A.; Blaich, A.; Menter, T.; Bruder, E.; Roloff, T.; Martinez, A.; Borel, N. A case study of zoonotic Chlamydia abortus infection: Diagnostic challenges from clinical and microbiological perspectives. Open Forum Infect. Dis. 2022, 9, ofac924. Available online: https://academic.oup.com/ofid/article/9/10/ofac524/6758542?login=true (accessed on 1 July 2023).
25. Nieuwenhuizen, A.A.; Dijkstra, F.; Notermans, D.W.; van der Hoek, W. Laboratory methods for case finding in human psittacosis outbreaks: A systematic review. BMC Infect. Dis. 2018, 18, 442.
26. Vande Weygaerde, V.; Versteele, C.; Thijs, E.; De Spiegeleer, A.; Boelens, J.; Vanrompay, D.; Van Braeckel, E.; Vermaelen, K. An unusual presentation of human psittacosis. Respir. Med. Case Rep. 2018, 23, 138–142.
27. Ni, Y.; Zhong, H.; Gu, Y.; Liu, L.; Zhang, Q.; Wang, L.; Wan, B.; Chen, S.; Cao, M.; Xu, J.; et al. Clinical features, treatment and outcomes of psittacosis pneumonia: A multicenter study. Open Forum Infect. Dis. 2023, 10, ofac518.
28. Zhu, Z.; Wang, X.; Zhao, J.; Xie, Z.; Yang, C.; Li, L.; Liu, Y. Clinical characteristics of six patients with Chlamydia psittaci infection diagnosed by metagenomic next-generation sequencing: A case series. Infect. Drug Resist. 2023, 16, 869–878.
29. Paul, L.; Comstock, J.; Edes, K.; Schlaberg, R. Gestational psittacosis resulting in neonatal death identified by next-generation RNA sequencing of postmortem, formalin-fixed lung tissue. Open

Forum Infect. Dis. 2018, 5, ofy172.

30. Wang, K.; Liu, X.; Liu, H.; Li, P.; Lin, Y.; Yin, D.; Yang, L.; Li, J.; Li, S.; Jia, L.; et al. Metagenomic diagnosis of severe psittacosis using multiple sequencing platforms. BMC Genom. 2021, 22, 406.
31. Wang, Z.; Chen, C.; Lu, H.; Wang, L.; Gao, L.; Zhang, J.; Zhu, C.; Du, F.; Cui, L.; Tan, Y. Case report: Clinical characteristics of two cases of pneumonia caused with different strains of Chlamydia psittaci. Front. Cell. Infect. Microbiol. 2023, 13, 1086454.
32. Tantengco, A.O.G. Gestational psittacosis: An emerging infection. Lancet Microbe 2022, 3, e728.
33. Chu, J.; Yarrapu, S.N.S.; Vaqar, S.; Durrani, M. Psittacosis. StatPearls. 8 May 2023. Available online: www.ncbi.nlm.nih.gov/books/NBK538305/ (accessed on 1 September 2023).
34. Balsamo, G.; Maxted, A.M.; Midla, J.W.; Murphy, J.M.; Wohrle, R.; Edling, T.M.; Fish, P.H.; Flammer, K.; Hyde, D.; Kutty, P.K.; et al. Compendium of measures to control Chlamydia psittaci infections among humans (Psittacosis) and pet birds (Avian Chlamydiosis). J. Avian Med. Surg. 2017, 31, 262–282.
35. Beeckman, D.S.A.; Vanrompay, D.C.G. Zoonotic Chlamydophila psittaci infections from a clinical perspective. Clin. Microbiol. Infect. 2009, 15, 11–17.
36. Panzetta, M.E.; Valdivia, R.H.; Saka, H.A. Chlamydia persistence: A survival strategy to evade antimicrobial effects in-vitro and in-vivo. Front. Microbiol. 2018, 9, 3101.