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CLINICAL MANAGEMENT OF CHRONIC ORANGUTAN RESPIRATORY DISEASE SYNDROME IN THREE ADULT MALE BORNEAN ORANGUTANS (*PONGO PYGMAEUS*)

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Abstract: Orangutan respiratory disease syndrome (ORDS) is a disease unique to orangutans (*Pongo sp*), characterized by chronic bacterial infection and inflammation of any region or combination of regions of the respiratory tract, including the sinuses, air sacs, cranial bones, airways, and lung parenchyma. Aggressive early intervention during a first episode may prevent progression to chronic disease. However, in the setting of an established chronic disease, intermittent acute exacerbations are associated with worsening symptoms and increased infection and inflammation. ORDS is ultimately fatal due to loss of respiratory function resulting from chronic structural damage. Utilizing potentially lifelong medications to slow the progression of chronic, destructive inflammation in the respiratory tract, chronic treatment is aimed at stabilizing the animals' respiratory function, decreasing the frequency of recurrent exacerbations, and improving their general well-being. Three adult male Bornean orangutans (*Pongo pygmaeus*) housed at an orangutan rehabilitation and reintroduction center in Indonesia have long histories of recurrent respiratory disease. Each underwent CT scans confirming ORDS with chronic airway disease prior to initiation of a long-term treatment protocol. Based on data-driven medical management of bronchiectasis in humans, the three orangutans have been treated with long-term combination regimens of oral azithromycin, nebulized salbutamol, and nebulized hypertonic saline. Follow-up CT scans in all three animals at least 1 yr following treatment initiation showed improvements throughout their respiratory tracts. The duration of each exacerbation period decreased, and the orangutans have longer symptom-free periods compared to before the start of treatment. At an average of 5 yr into the long-term treatment protocol, all three orangutans are thriving. Chronic medical management of ORDS modeled after human treatment of bronchiectasis has been efficacious in these three orangutans and encourages further study of this approach.

INTRODUCTION

Orangutan respiratory disease syndrome (ORDS), first described in the literature in 2021, is defined as a chronic, progressive, self-perpetuating cycle of respiratory infection and inflammation in orangutans (*Pongo sp*).[24,35] Death ultimately occurs due to loss of respiratory function resulting from chronic structural change. ORDS is a leading cause of death and impacts approximately 20% of the captive orangutan population in North American and European zoos, as well as in multiple orangutan rescue and rehabilitation centers in range countries.[11,20,22,34,41] The precise pathogenesis is still unknown and the contribution of genetic and/or environmental factors responsible for the susceptibility and chronicity of this disease unique to orangutans have yet to be firmly established.[5,17,20,37,41]

Historical doctrine suggested that ORDS was initiated from infection in the upper airway which then progressed to the air sac, and finally caused fatal pathology in the lungs and airways.[20] However, our previous work demonstrated that while such a progression may occur, disease may begin anywhere in the respiratory tract and progress to affect any combination of regions of the tract.[24,35] Furthermore, previous approaches treated acute respiratory disease, even when recurrent, as isolated cases of airsacculitis, pneumonia or sinusitis.[6,20,25,39,41] We argue that the acute cases are 'episodes', exacerbations of an ongoing, chronic respiratory disease.[23,24,35] Therefore, the treatment needs to address this condition. We defined the start of an exacerbation episode of ORDS as a new appearance of clinical signs that was not observed for at least 2 mon prior to the episode, which persisted and progressed for more than 3 d, and thus warranted the administration of an antibiotic with or without surgical treatment to clear

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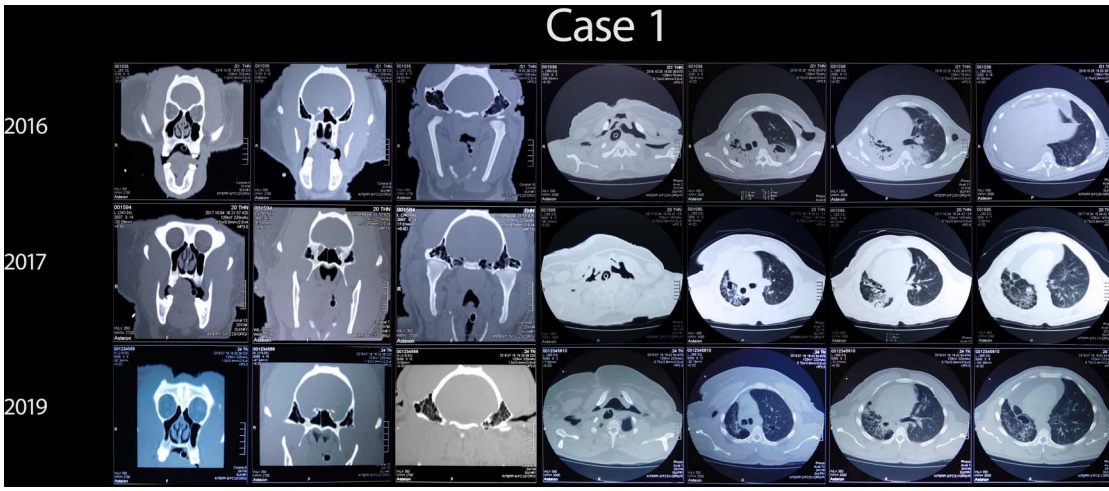

Figure 1. Serial CT Scan images of head, neck, and thorax of Case 1 from 2016 to 2019. The first CT scan in 2016 (top row) showed the baseline condition before the start of ORDS long-term treatment. The right lung was so severely consolidated that it was not visible. The second CT scan in 2017 (middle row), taken after 3 months of long-term treatment, showed a dramatic improvement of the right lung. Bronchiectasis was well observed in both lungs. The third CT scan in 2019 (bottom row), taken after 24 months of long-term treatment, showed that the right lung was relatively unchanged since the previous scan, while there were some improvements on the consolidated area in the left lung.

the air sac accumulation of purulent material. An exacerbation was considered resolved when there was no record of the clinical symptom(s) for at least 2 mon. Past work has described the similarities between ORDS and the respiratory aspects of a genetic disorder disease in humans called cystic fibrosis (CF).[35–37] We previously showed the positive efficacy of human bronchiectasis-based treatment protocols in early, acute ORDS cases.[35] In this case series, we present the positive efficacy of the long-term treatment protocols for ORDS in three chronically affected orangutans with various degrees of lung damage. Our protocol for long-term ORDS treatment consists of chronic combination therapy with low-dose azithromycin, nebulized salbutamol, and nebulized hypertonic saline, as well as an addition of 4 wk oral levofloxacin during an acute exacerbation.

CASE SERIES

Case 1

Case 1 is an adult male Bornean orangutan who was rescued from the wild at 3–4 yr old and has been cared for at the Borneo Orangutan Survival Foundation, Samboja Lestari campus (BOSF-SL) in East Kalimantan, Indonesia, for 24 yr. Case 1 was the most severe in this case series, with chronic disease leading to near end-stage lung pathology prior to the initiation of chronic therapy (Figure 1, top row). The animal had been observed with respiratory symptoms since 2013 at the age of 19 yr old (Table 1), with deep coughing and activity limitation as the most persistent symptoms. This animal had been seen expressing hiding behavior while holding his head with both hands, believed to indicate headache.

Before the initiation of a long-term drug regimen, Case 1 had experienced multiple exacerbations with prolonged respiratory symptoms between 2013 and 2016. Supplemental Table 1 provides a detailed timeline of symptoms and treatments. In addition to coughing, mucopurulent nasal discharge and air sac purulent material accumulation/drainage were also noted. This animal had five air sac marsupialization surgeries in 4 yr (Supplemental Table 1). Following each procedure, the veterinarians conducted additional air sac flushing procedures under general anesthesia every 3–28 d to aid in the clearance of purulent debris.

The first CT scan was conducted in the fourth year of disease progression (October, 2016). The animal was anesthetized using a combination of zoletil (Virbac, Carros 06516, France; 3mg/kg IM), ketamine (Troy Laboratories Pty Ltd, New South Wales 2761, Australia; 4mg/kg IM), and xylazine (Troy Laboratories Pty Ltd, New South Wales 2761, Australia; 0.75mg/kg IM). The animal was intubated and maintained with isoflurane (Piramal Pharma Limited, Telangana State 502321, India) to

Table 1. Demographic and clinical summaries for Cases 1, 2, 3. All are adult male Bornean orangutans housed at the Borneo Orangutan Survival Foundation at Samboja Lestari (BOSF-SL).

Case #	Sex	Estimated Y.O.B. (age in 2022)	Length of stay at BOSF	Area of origin within East Kalimantan, Indonesia	Date of 1st respiratory symptom (age)	Key Findings on Initial CT	Mon with ORDS symptom/mon of observation pretreatment (%)	Mon with ORDS symptom/mon of observation posttreatment (%)
1	M	1994 (28 years old)	24 years	Bengalon	May 2013 (19 years old)	• Maxillary and sphenoid sinusitis • Diffuse bilateral bronchiectasis with extensive mucus plugging • Right lung >> left lung consolidation Left lung abscess	56.4	13.8
2	M	1997 (25 years old)	24 years	Muara Wahau	July 2010 (13 years old)	• Left maxillary sinusitis • Left mastoiditis • Right lung lobe pneumonia • Bilateral bronchiectasis and mucus plugging	29.9	1.9
3	M	1998 (24 years old)	23 years	Samarinda	May 2014 (16 years old)	• Airsacculitis • mild bilateral lower lobe pneumonia • Bilateral bronchiectasis and extensive mucus plugging	49.0	10.2

Y.O.B., year of birth; ORDS, orangutan respiratory disease syndrome Mon, months.

effect. Intermittent positive pressure ventilation (IPPV) was used as needed to maintain end-tidal CO_2 levels within physiologic range. CT imaging was conducted with the animal in dorsal recumbency. Head, neck, and chest were scanned using a Toshiba Asteion 4 CT scanner, 2009 model CXXG-010A, minimum capacity 135kV, 260mAS (Canon Medical Systems Corporation, Tustin, CA 92780, United States), without contrast. The results showed maxillary and sphenoid sinusitis, bronchiectasis and extensive consolidation in the right lung, and bronchiectasis, consolidation, and abscess in the left lung. Mastoiditis and airsacculitis were not observed. Following short-term treatment with azithromycin 400mg (PT Kimia Farma, Jakarta Pusat 10110, Indonesia) for 3 wk and nebulized salbutamol 2.5mg (GlaxoSmithKline Australia Pty Ltd, Victoria 8003, Australia) q12h using a PARI e-flow nebulizer (PARI Pharma GmbH, Starnberg 82319, Germany) for 8 wk, some improvements of the clinical symptoms were recorded, but the animal still showed heavy breathing and occasional coughing. In August 2017 azithromycin was reinitiated long-term. Evaluation CT scan at month 3 of long-term treatment showed improvement of the right maxillary sinusitis, resolution of sphenoid sinusitis, and improvement of airway disease, pneumonia, and lung consolidation bilaterally. Overall, the visibility of both lungs' structure, especially the right lung, increased dramatically. Following two more exacerbations (at months 7 and 10), nebulized salbutamol and nebulized hypertonic saline 4ml (3% PT. Otsuka Indonesia, Malang 65216, Indonesia, or 7% PARI Respiratory Equipment, Inc., Virginia 23112, USA, depending on availability) q12h were added to the long-term treatment regimen.

Based on the presence of marked right lung bronchiectasis, Case 1 is expected to have lifelong recurrent exacerbations. Consequently, it has experienced a total of five exacerbation episodes during the first five years of chronic therapy. Nevertheless, clear improvement has been noted not only in CT scan assessment, but also in clinical observations (Figures 1 and 2). The last checkup CT scan was conducted 2 yr after the start of chronic treatment and showed unchanged mild maxillary sinusitis and airway disease in both lungs, but improvement in the consolidation of the left lung (Figure 1, bottom row). The exacerbations were significantly milder and shorter compared to the ones before chronic treatment was initiated. Additionally, after chronic therapy began, Case 1 had the longest symptom-free period (17 mon) since the onset of ORDS. The last exacerbation to date was recorded

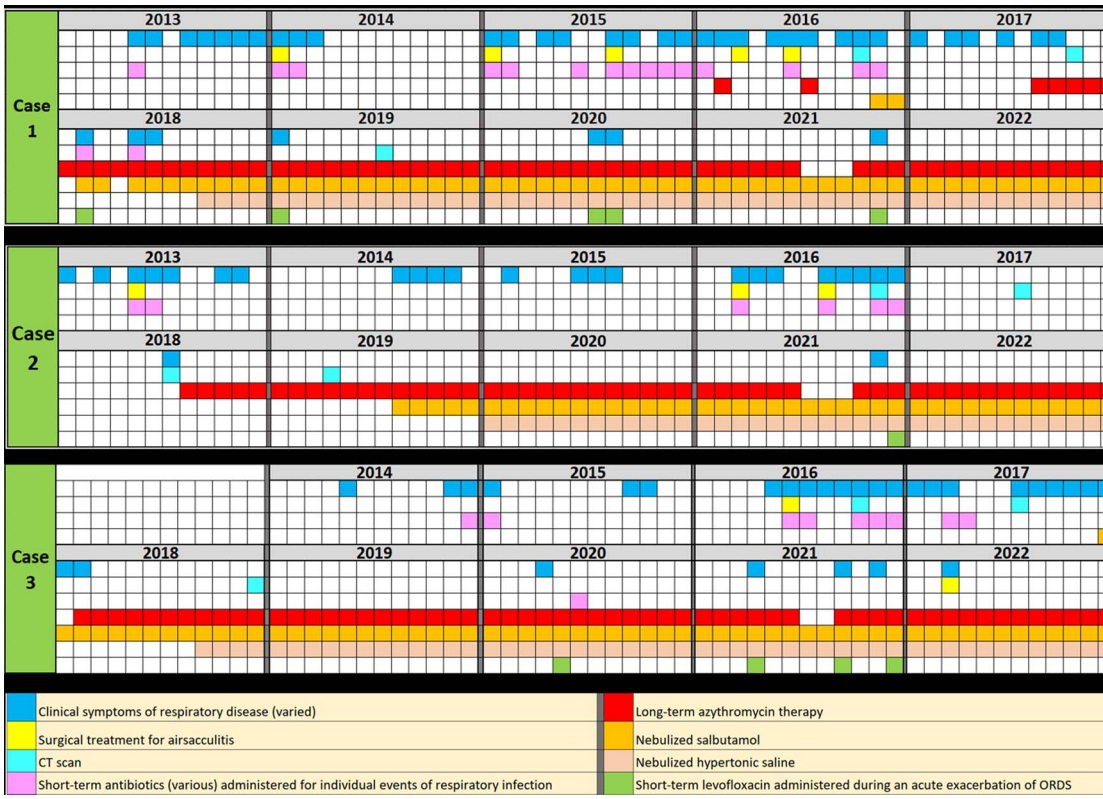

Figure 2. Color coded timeline of ORDS in Case 1 (top box), Case 2 (middle box), Case 3 (bottom box). Each cell represents one month. As explained in the legend at the bottom of the figure, each color represents either an observed clinical condition, treatment, surgery, or CT scan that occurred/was conducted in that month. This figure shows the period of 2013-2022, however Case 2 had the history of ORDS since 2010, which details can be referred to in the Supplemental Table 2. The chronic ORDS treatment period is marked by the long continuous rows of red (Azithromycin), orange (nebulized Salbutamol), and beige (nebulized hypertonic saline) cells. Corresponding to the long-term treatment period, it can be observed that there were much fewer blue cells that represented appearance of clinical signs.

after a temporary supply-related halt of azithromycin during the peak of the COVID-19 pandemic in Indonesia in 2021. As of December, 2022 Case 1 has been on azithromycin, nebulized salbutamol, and nebulized hypertonic saline for 65, 52, and 52 mon, respectively (excluding a 12-wk gap of azithromycin in 2021) and has been symptom-free for 13 mon (Supplemental Table 1).

Case 2

Case 2 is an adult male Bornean orangutan who was rescued from the wild as an infant and has been cared for at BOSF-SL for 24 yr (Table 1). This animal was first diagnosed with an episode of an acute respiratory infection in 2010 at the age of 13 yr. The animal experienced 4 more episodes of respiratory infection (Supplemental Table 2) before the ORDS diagnosis was established in August 2018 (month 1). From 2010 to July 2018, the animal also had two air sac marsupialization surgeries, followed by the repeated drainage procedures. In contrast with Case 1, Case 2 did not experience prolonged respiratory symptoms; however, the medical history clearly showed that observations of respiratory symptoms increased in frequency over the 2010–2018 period (Figure 2 and Supplemental Table 2).

Case 2 had 4 CT scans during the course of his illness. The animal was anesthetized as described for Case 1 and CT imaging was conducted with the animal in dorsal recumbency. The first CT scan, conducted in year 7 after the first respiratory episode, revealed left maxillary sinusitis, left mastoiditis, right lung pneumonia, and bilateral airway disease with bronchial wall thickening and mild bronchiectasis (Figure 3, top row). The

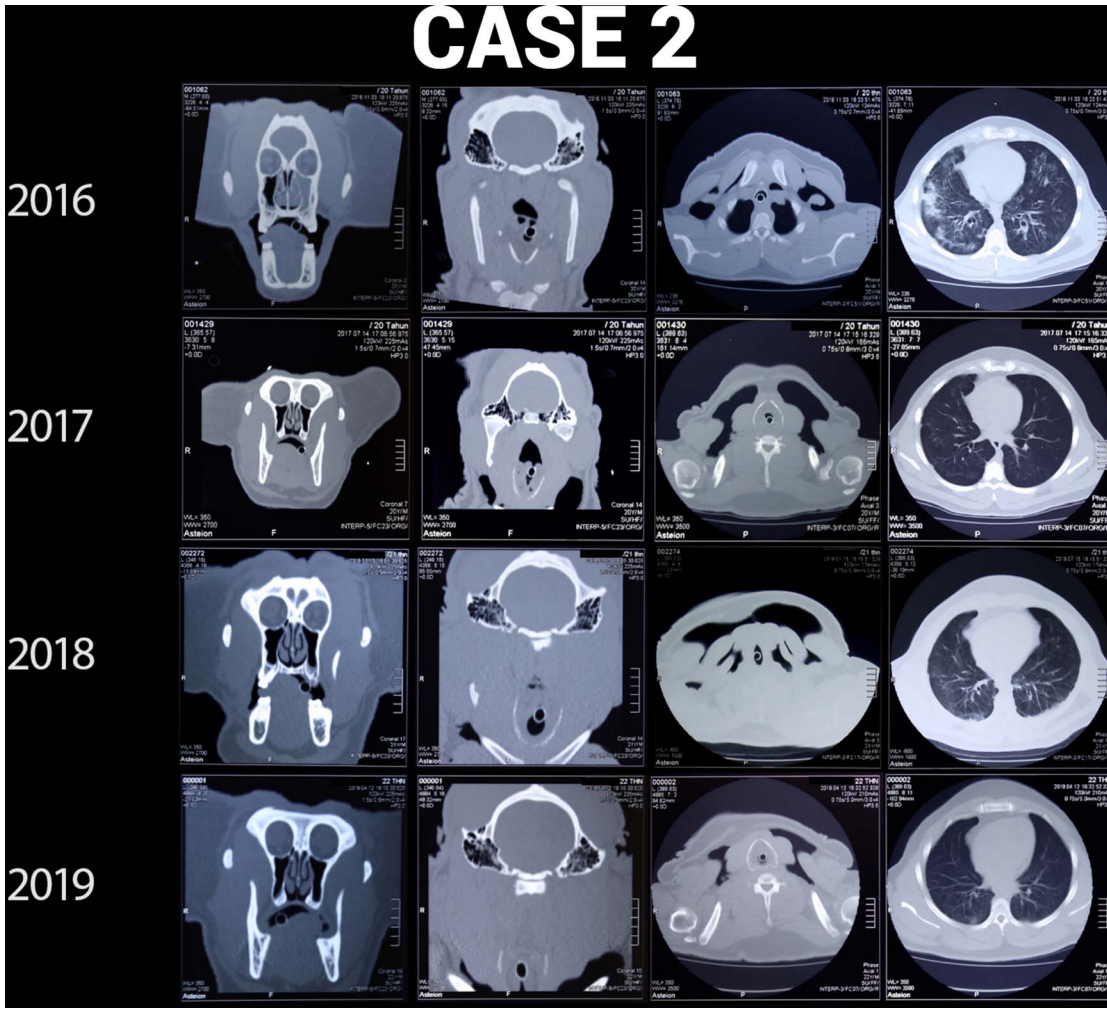

Figure 3. Serial CT Scan images of head, neck, and thorax of Case 2 from 2016 to 2019 (top to bottom row). The 2016 and 2017 CT scan results had been published in Sriningsih & Lung et al, 2021[35] as a representation of a baseline condition (pre-treatment) and after an acute treatment, respectively. In this manuscript we followed up the case to 2018 scan where it showed re-appearance of bilateral pneumonia (third row), 18 months after completion of the acute treatment. Responding to this, a long-term treatment of azithromycin was initiated. A follow up CT scan in 2019 in month 18 of the treatment again showed improvement in the airway wall thickening and mucus plugging (bottom row).

regimen for an acute ORDS episode as described in previous work[35] was given for 8 wk (Supplemental Table 2). An evaluation CT scan conducted eight months later showed resolution of the sinusitis, as well as improvement of the mastoiditis, airway wall thickening, mucus plugging, and pneumonia (Figure 3, row two.)

However, a follow up CT scan conducted a year after the end of treatment revealed persistent airway wall thickening and mild pneumonia (Figure 3, third row), although it was not apparent on clinical observation. In response to another exacerbation, a chronic treatment regimen of azithromycin 400 mg (PT Kimia Farma, Jakarta Pusat 10110, Indonesia) 3x per week was initiated. The added combination of nebulized salbutamol 2.5 mg (GlaxoSmithKline Australia Pty Ltd, Victoria 8003, Australia) q12h and nebulized hypertonic saline 4ml (3% PT, Otsuka Indonesia, Malang 65216, Indonesia, or 7% PARI Respiratory Equipment, Inc., Virginia 23112, USA) q12h was introduced gradually through positive reinforcement training. Following the initiation of chronic therapy, Case 2 was clear from respiratory symptoms for 39 consecutive months. As

shown in Table 1 and Figure 2, this prolonged symptom-free period contrasts with the pre-chronic therapy clinical status when the animal experienced an average of four mon per year with visible respiratory symptoms (ranging from 1–8 mon per year).

At the end of December 2022, Case 2 has been on azithromycin, nebulized salbutamol, and nebulized hypertonic saline for 53, 41, and 36 mon respectively (excluding a 12-wk gap of azithromycin in 2021). A final CT scan performed in 2019 showed that the air sacs were clear, with persistence of minimal sinus and airway disease and mild residual infiltrate in the right lower lobe and the mastoid air cells (Figure 3, bottom row). Unfortunately, CT availability ended for all cases in 2019, so no additional CT data is available. Since the initiation of chronic therapy, Case 2 has had only one exacerbation (November 2021), following a temporary 12-week hiatus in azithromycin administration due to the scarcity of the drug during the peak of COVID-19 pandemic in Indonesia in mid-2021.

Case 3

Case 3 is an adult male Bornean orangutan who was rescued from the wild as an infant and has been cared for at BOSF-SL for 23 years. Respiratory symptoms had been observed in Case 3 since 2014 at the age of 16 yr old (Table 1). Before the initiation of the chronic ORDS treatment, Case 3 had experienced three exacerbations and one air sac marsupialization surgery (Supplemental Table 3 and Figure 2). Similar to Case 2, Case 3's medical history clearly showed progression of frequency of observed respiratory symptoms over the years, and similar to Case 1, Case 3 also had a prolonged episode of respiratory infection lasting 11 mon. The most prominent symptoms were nasal discharge, accumulation of purulent material with drainage from the air sac, and audible breathing.

Case 3 had three CT scans during the course of his illness. For each scan the animal was anesthetized as described for Case 1 and CT imaging was conducted with the animal in dorsal recumbency. The first CT scan was performed at 2.5 yr after onset of respiratory signs (2016) and revealed mild airsacculitis, mild bilateral lower lobe pneumonia, and bilateral mild bronchiectasis with extensive mucus plugging (Figure 4, top row). Images of the mastoid air cells were not available from this scan, so the status of the mastoids is unknown. The antibiotic combination regimen for acute ORDS,[35] was given for a total of 12 wk (see Supplemental Table 3 for detailed timeline and drugs). The animal continued to display clinical symptoms of mucopurulent nasal discharge and heavy breathing, although the follow up CT scan showed resolution of the pneumonia, and improvement in the airway disease. Mild airsacculitis persisted and mastoiditis was noted (Figure 4, middle row).

In late 2017, the long-term drug combination regimen was initiated gradually because it was also necessary to simultaneously begin positive reinforcement training for the animal to comply with the nebulization. First, nebulized salbutamol 2.5mg (GlaxoSmithKline Australia Pty Ltd, Victoria 8003, Australia) q12h began (month 1), followed with oral azithromycin 400 mg (PT Kimia Farma, Jakarta Pusat 10110, Indonesia) q24h 3x/week (Monday, Wednesday, Friday) in month 3, and lastly nebulized hypertonic saline, which has a "salty" taste that may initially impede acceptance (3% PT. Otsuka Indonesia, Malang 65216, Indonesia, or 7% PARI Respiratory Equipment, Inc., Virginia 23112, USA), q12h was added in month 10. Clinical symptoms resolved on month 4, and the animal was symptom-free for the next 25 months, the longest symptom-free period observed since onset of disease (Figure 2). A third CT scan performed in month 13 showed resolution of rhinitis, unchanged bilateral mastoiditis, improved airsacculitis, and marked improvement in airway wall thickening and mucus plugging (Figure 4 bottom row).

During chronic therapy, Case 3 had five more exacerbations in the span of 5 yr, although each episode was significantly shorter than those pre-chronic treatment initiation (Supplemental Table 3 and Figure 2). Like Cases 1 and 2, Case 3 experienced an exacerbation in month 46 after a temporary halt of azithromycin availability during the COVID-19 peak pandemic in Indonesia in 2021. Further, there was one more mild exacerbation at month 52. As of the end of 2022, Case 3 had been on azithromycin, nebulized salbutamol, and nebulized hypertonic saline for 57, 61, and 52 months respectively and has been symptom free for 9 mon (Supplemental Table 3).

DISCUSSION

This case series describes the recurrent and chronic respiratory episodes associated with ORDS in three adult Bornean orangutans (Supplemental Tables 1, 2, and 3). These animals are wild-caught orangutans that were confiscated by or dispatched to the BOSF-SL rehabilitation center in East Kalimantan, Indonesia during the 1990s when they were aged between ten months to five years. During their residence at the BOSF center, they have

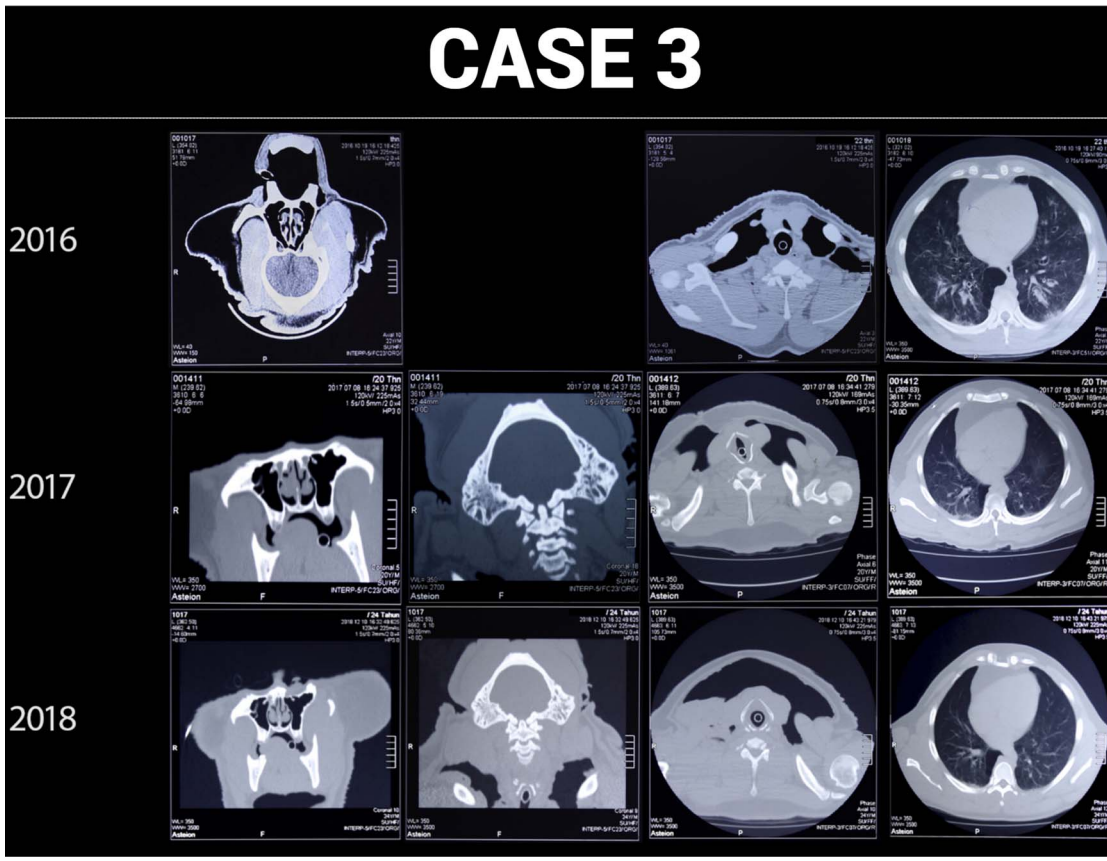

Figure 4. Serial CT Scan images of head, neck, and thorax of Case 3 in 2016 (top row), 2017 (middle row), and 2018 (bottom row). The first scan, which was the baseline condition of the animal before treatment, showed bilateral bronchiectasis and mucus plugging. The second scan in 2017 showed resolution of the pneumonia, however the bronchiectasis persisted. Bilateral mastoiditis was also observed. The last scan in 2018, month 13 of the long-term treatment, showed clear lungs with permanent bronchiectasis and persisted mastoiditis.

been housed in a variety of enclosures, ranging from group cages with daily access to outdoor forests (forest school), to permanent individual outdoor cages where they are currently housed (Supplemental Figure 1). All orangutans at BOSF-SL are screened for tuberculosis every 1–2 years using a combination of thoracic radiography and submission of bronchoalveolar samples for acid fast staining, mycobacteria culture, and polymerase chain reaction (PCR). All three animals included in this case series have been tuberculosis-free throughout their time at BOSF.

CT scans were conducted on all animals prior to initiation of long-term treatment to confirm both the diagnosis of ORDS and the degree of baseline structural lung damage.[14] Pneumonia and bronchiectasis were confirmed in all three cases. All of them also had airsacculitis, which the authors observed can be missed on CT scan when the flushing procedure has been done shortly before the scan.

ORDS was not recognized as a clinical entity until 2016. Prior to that time, respiratory disease in orangutans was diagnosed and treated as isolated episodes of disease,[6,20,28,35] which was the situation for Cases 1, 2 and 3. Clinical signs recorded in the animals' medical records include coughing, prolonged rhinorrhea with clear to thick nasal discharge, accumulation of purulent material in the air sac, and behavioral signs of headache. These symptoms were often accompanied by systemic signs such as fever, lethargy, and weight loss. Airsacculitis, arguably the most prominent sign of a respiratory infection, was managed with short term (7–21 days) courses of antibiotics and marsupialization surgery to clear

the accumulation of purulent material from the sac. Following each marsupialization surgery, periodic air sac flushing was conducted for up to six procedures. These treatments provided only temporary relief and posed significant risk to already compromised animals. Signs predictably reappeared,[20,28] supporting our contention that airsacculitis can present as a sign of the more diffuse and chronic disease process.[24]

Once bronchiectasis is established in the lungs, human patients experience alternating episodes of stable symptoms and acute exacerbations over their lifetime, with frequency and intensity dependent on baseline severity of disease.[2] As airway destruction progresses, exacerbations become more frequent and/or severe, ultimately resulting in respiratory failure. The three orangutans in this case series were confirmed to have bronchiectasis and demonstrated comparable symptoms to humans, therefore their therapeutic management was tailored to follow well-established human bronchiectasis protocols.[26,29] The goals of chronic therapy are to reduce the progression of airway destruction by controlling the chronic infection and inflammation.

The combination treatment used in the orangutans of this case series was based on the medical treatment for pancreatic-sufficient CF in humans.[31] The first component of chronic ORDS treatment[24,29] includes lifelong use of oral azithromycin as an anti-inflammatory[1,2,7,9,32,33] combined with nebulized salbutamol followed by nebulized hypertonic saline administered twice daily.[12,15,30,42] Per standard CF protocols, long-term azithromycin is effective in humans with bronchiectasis when administered as 250mg PO q24h or 500mg PO 3x/wk. Nebulization of salbutamol is performed to dilate the muscles in the airways in order to prevent bronchospasm during administration of the second nebulized drug,[42] hypertonic saline, which is used to hydrate the airway mucociliary surface and therefore increase mucus clearance.[15] In this case series, nebulization treatment (Supplemental Figure 2) demonstrated great improvement in relieving the animals' respiratory signs and symptoms. Copious drainage of nasal secretions and productive coughing and sneezing often occur during the nebulization. This drainage presumably relieves sinus pressure and assists with airway clearance. In the authors' experience, the orangutans demonstrate visibly relaxed breathing patterns and improved drainage immediately following nebulization.

The second component of chronic ORDS treatment is the addition of a 4–8 wk course of a broad-spectrum antibiotic administered during an acute exacerbation of clinical disease. Levofloxacin 500 mg PO q24h is a preferred antibiotic to cover for common gram positive and gram negative bacteria associated with these episodes in orangutans.[24,35] Other commonly used antibiotics include doxycycline 100 mg PO q12h, nebulized colistin 77 mg q12h, nebulized tobramycin 160 mg q12h, or meropenem 500 mg IM q12h.

On average, the three animals in this series have been on oral azithromycin for 56.3 mon (50–62 mon), on salbutamol/albuterol nebulization for 51.3 mon (41–61 mon), and on hypertonic saline nebulization for 46.7 mon (36–52 mon). Prior to the chronic ORDS treatment, the orangutans in this case series experienced years in which they were more often sick than not (Figure 2 and Table 1). For example, in the years 2013, 2015, and 2017, Case 1 had 7-9 mon each year when he suffered from respiratory infection symptoms (Figure 2). This exacerbation frequency and duration is in contrast with the animal's disease state after chronic ORDS treatment in which he was observed to manifest symptoms for 0–3 mon per year from 2018 to 2022. In fact, following the initiation of chronic ORDS treatment, the three animals experienced an average of 1.1 mon per year of exacerbation periods compared to an average of 5.4 mon prior to initiation of chronic therapy.

Based on numerous positive clinical trials and meta-analyses demonstrating efficacy, the use of azithromycin in chronic treatment to decrease the frequency of exacerbation in human cystic fibrosis and non-CF bronchiectasis is now considered standard of care.[3,9,19,21,32,33,38,40] The anti-inflammatory effect of azithromycin is far more important that its antibiotic modality.[9] Although some clinicians have expressed concern about its chronic use promoting the development of antibiotic resistance, multiple studies on the use of chronic azithromycin have not demonstrated clinically important resistance.[8,16,27,40]

CT scan following long-term treatment showed improvement throughout the respiratory tract in all three orangutans as expected. Given the animals' severe baseline disease, chronic structural pulmonary changes remain notable despite ongoing therapy. Once structural damage to the airway walls is at an advanced stage, such as was seen in Case 1, the damage is likely irreversible (Figure 1). Recent studies in human patients have shown, however, that when airway disease is identified in the early stages, the damage is potentially reversible.[10,13,18] This possibility highlights the importance of early detection and effective treatment of ORDS, in hopes of altering the course of

disease and halting the progression of structural change. Case 1 demonstrates that airways with severe permanent damage can still receive great benefit of chronic therapy and that the patient can experience greatly improved quality and length of life.

Previous literature and historical doctrine hypothesize that chronic respiratory disease in orangutans is initiated from an airborne upper respiratory tract infection which then seeds the air sac and finally the lungs.[20] However, Case 3 in this series had normal sinus imaging on initial CT scan, but nonetheless had airsacculitis and lower airway disease including chronic pneumonia and bronchiectasis (Figure 4). This case and several others in the authors' experience demonstrate that the ORDS initial symptoms and infection can begin in and migrate to any area of the respiratory tract in any order.[24,35]

Previous study suggests that Bornean orangutans are more likely to be affected by ORDS than Sumatran orangutans.[41] Anecdotally, it seems true in the population of orangutans in rescue centers in Indonesia where there are more ORDS cases reported in centers in Borneo than in Sumatra. However, this interpretation could be biased by the fact that there are less orangutan centers in Sumatra than in Borneo. Investigations into specific genetic mutations is ongoing.[37]

This case series provides the strongest evidence that when left untreated, respiratory infection in orangutans may progress from mild symptoms (chronic nasal discharge or occasional cough) to a severe, life-threatening condition (bronchiectasis and pneumonia). Often runny noses are managed as chronic allergies when they actually represent a visible sign of underlying disease. Because disease progression is quite slow, affected animals could be in a negative welfare state for extended periods, from years to decades. Thus, consistent with our previous observations, CT scan is critical in diagnosing ORDS as well as for monitoring the progress of the disease.[4,24] Even with unrecognized or minimal clinical symptoms, all three animals in this case series were shown to have clinically important abnormalities in their mid and lower respiratory tract ranging from airway wall thickening and mucus plugging to bronchiectasis, pneumonia, and airsacculitis. Critically, if CT scan had not been available, the severity of each animal's disease would have been under-recognized. These "silent cases" likely demonstrate the animals' chronic adaptation to their slowly progressive respiratory deterioration over years.

In conclusion, acute episodes of respiratory illness in orangutans that have previously been treated as isolated incidents should be approached differently. More recent data suggests that a notable proportion of orangutans experience acute exacerbations that represent an escalation of a chronic respiratory condition. This case series describes improvements in ORDS cases that were treated with the chronic therapies used in humans with CF. However, our understanding of ORDS is still evolving and future refinements of these recommendations for prevention and treatment are likely over time, as more animals are studied over longer time periods. To ensure the health and future existence of this critically endangered species, continued research on the etiology, predisposing factors, and management of ORDS in captive orangutans is critical.

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LITERATURE CITED

1. Aaron SD, Vandemheen KL, Ferris W, Fergusson D, Tullis E, Haase D, Berthiaume Y, Brown N, Wilcox P, Yozghatlian V, Bye P, Bell S, Chan F, Rose B, Jeanneret A, Stephenson A, Noseworthy M, Freitag A, Paterson N, Doucette S, Harbour C, Ruel M, MacDonald N. Combination antibiotic susceptibility testing to treat exacerbations of cystic fibrosis associated with multiresistant bacteria: a randomised, double-blind, controlled clinical trial. Lancet. 2005;366:463–471.

2. Altenburg J, de Graaff CS, Stienstra Y, Sloos JH, van Haren EH, Koppers RJ, van der Werf TS, Boersma WG. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non–cystic fibrosis bronchiectasis: the BAT randomized controlled trial. J Amer Med Assoc. 2013;309(12):1251–1259.

3. Anwar GA, Bourke SC, Afolabi G, Middleton P, Ward C, Rutherford RM. Effects of long-term low-dose azithromycin in patients with non-CF bronchiectasis. Resp Med. 2008;102(10):1494–1496.

4. Aronson RK, Sriningsih AP, Sulistyo F, Taylor-Cousar JL, Aronson SA, South A, Nutter F, Lung NP. Use of computed tomography (CT) to determine the sensitivity of clinical signs as a diagnostic tool for respiratory disease in bornean orangutans *(Pongo pygmaeus)*. J Zoo Wildl Med. 2021;52(2):470–478.

5. Banes GL, Fountain ED, Karklus A, Huang HM, Jang-Liaw NH, Burgess DL, Wendt J, Moehlenkamp C, Mayhew GF. Genomic targets for high-resolution inference of kinship, ancestry and disease susceptibility in orang-utans (genus: *Pongo*). BMC Genomics. 2020;21(1): 873. doi:10.1186/s12864-020-07278-3. PMID: 33287706.

6. Cambre RC, Wilson HL, Spraker TR, Favara BE. Fatal airsacculitis and pneumonia, with abortion, in an orangutan. J Am Vet Med Assoc. 1980;177(9): 822–824.

7. Chang Y-T, Lin C-Y, Chen Y-H, Hsueh P-R. Update on infections caused by *Stenotrophomonas maltophilia* with particular attention to resistance mechanisms and therapeutic options. Front Microbiol. 2015. doi:10.3389/fmicb.2015.00893

8. Cogen JD, Onchiri F, Emerson J, Gibson RL, Hoffman LR, Nichols DP, Rosenfeld M. Chronic Azithromycin Use in Cystic Fibrosis and Risk of Treatment-Emergent Respiratory Pathogens. Annals Amer Thorac Soc. 2018;15(6):702–709. doi:10.1513/AnnalsATS.201801-012OC

9. Cymbala AA, Edmonds LC, Bauer MA, Jederlinic PJ, May JJ, Victory JM, Amsden GW. The disease-modifying effects of twice-weekly oral azithromycin in patients with bronchiectasis. Treat in Resp Med. 2005;4(2):117–122.

10. David M, Benlala I, Bui S, Benkert T, Berger P, Laurent F, Macey J, Dournes G. Longitudinal evaluation of bronchial changes in cystic fibrosis patients undergoing Elexacaftor/Tezacaftor/Ivacaftor therapy using lung MRI with ultrashort echo-times. J Magn Reson Imaging. 2023. doi:10.1002/jmri.29041

11. Dharmalingam S. Respiratory tract infection in infant orangutan (*Pongo pygmaeus*) at Orang Utan Island, Bukit Merah. J Med Medical Sci 2016;3(2): 5–9.

12. Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. N Engl J Med. 2006;354(3):241–250. doi: 10.1056/NEJMoa043891

13. Eastham KM, Fall AJ, Mitchell L, Spencer DA. The need to redefine non-cystic fibrosis bronchiectasis in childhood. Thorax. 2004;59(4):324–327. doi:10.1136/thx.2003.011577

14. Eichinger M, Heussel CP, Kauczor HU, Tiddens H, Puderbach M. Computed tomography (CT) is the current "gold standard" for assessment of lung morphology and is so far the most reliable imaging modality for monitoring cystic fibrosis (CF) lung disease. J Mag Res Imaging. 2010;32(6):1370–1378.

15. Elkins MR, Robinson M, Rose BR, Harbour C, Moriarty CP, Marks GB, Belousova EG, and Xuan W, Bye PT, and National Hypertonic Saline in Cystic Fibrosis (NHSCF) Study Group. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. N Engl J Med. 2006;354(3):229–40.

16. Fan LC, Lu HW, Wei P, Ji XB, Liang S, Xu JF. Effects of long-term use of macrolides in patients with non-cystic fibrosis bronchiectasis: a meta-analysis of randomized controlled trials. BMC Infec Dis. 2015; doi:10.1186/s12879-015-0872-5

17. Fox MK. Respiratory Disease in the North American Captive Orangutan Population. Master's thesis, 2017. California State University, Fullerton.

18. Gaillard EA, Carty H, Heaf D, Smyth RL. Reversible bronchial dilatation in children: comparison of serial high-resolution computer tomography scans of the lungs. J Radiol. 2003;47:215–220.

19. Kelly C, Chalmers JD, Crossingham I, Relph N, Felix LM, Evans DJ, Milan SJ, Spencer S. Macrolide antibiotics for bronchiectasis. Cochrane Database Syst. Rev. 2018; 3(3):CD012406. doi:10.1002/14651858.CD012406.pub2

20. Lawson B, Garriga R, Galdikas BM. Airsacculitis in fourteen juvenile southern Bornean orangutans (*Pongo pygmaeus wurmbii*). J Med Primatol. 2006;35: 149–154.

21. Li W, Qin Z, Gao J, Jiang Z, Chai Y, Guan L, Chen Y. Azithromycin or erythromycin? Macrolides for non-cystic fibrosis bronchiectasis in adults: a systematic review and adjusted indirect treatment comparison. Chron Respir Dis. 2019. doi:10.1177/1479972318790269

22. Lowenstein LJ, McManamon R, Bonar C, Perkins L. Preliminary results of a survey of United States and Canadian Orangutan Mortality in the North American SSP Population from 1980 to March, 2008. In: Proc Am Assoc of Zoo Vet, 2008:40.

23. Lung NP, Pratamiutami AS, Steinmetz H, Taylor-Cousar JL. Collaboration across institutions and across continents facilitates advancements in the diagnosis and management of chronic respiratory disease of orangutans (*Pongo spp*.). In: Proc Am Assoc Zoo Vet. 2018:100–102.

24. Lung NP, Taylor-Cousar JL. Chapter 99. Orangutan Respiratory Disease Syndrome. In: Miller RE, Calle PP, and Lamberski N (eds); Zoo and Wild Animal Medicine, Volume 10. St. Louis (MO): Elsevier, 2022. p. 685–694.

25. McManamon R, Swenson RB, Orkin JL, Lowenstine LJ. Update on diagnostic and therapeutic approaches to airsacculitis in orangutans. In: Proc. Am. Assoc. Zoo Vet. 1994. p. 219–220.

26. Mogayzel Jr PJ, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, Lubsch L, Hazle L, Sabadosa K, Marshall B, and Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013 Apr 1;187(7):680–689.

27. Parnham MJ, Haber VE, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin:

mechanisms of action and their relevance for clinical applications, Pharmacol Ther. 2014;143(2):225–245.

28. Phillipa J, and Dench R. Infectious diseases of orangutans in their home ranges and in zoos. In: Miller RE ed, Fowler's Zoo and Wild Animal Medicine, Volume 9, Current Therapy. St. Louis (MO): Elsevier; 2019. p. 565–573.

29. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, Murris M, Cantón R, Torres A, Dimakou K, De Soyza A, Hill AT, Haworth CS, Vendrell M, Ringshausen FC, Subotic D, Wilson R, Vilaró J, Stallberg B, Welte T, Rohde G, Blasi F, Elborn S, Almagro M, Timothy A, Ruddy T, Tonia T, Rigau D, Chalmers JD. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017. doi:10.1183/13993003.00629-2017

30. Ratjen F, Davis SD, Stanojevic S, Kronmal RA, Stukovsky KD, Jorgensen N, Rosenfeld M, Kerby G, Kopecky C, Anthony M, Mogayzel P. Inhaled hypertonic saline in preschool children with cystic fibrosis (SHIP): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2019;7(9):802–809.

31. Rodman DM, Polis JM, Heltshe SL, Sontag MK, Chacon C, Rodman RV, Brayshaw SJ, Huitt GA, Iseman MD, Saavedra MT, Taussig LM, Wagener JS, Accurso FJ, Nick JA. Late diagnosis defines a unique population of long-term survivors of cystic fibrosis. Am J Crit Care Med. 2005;171(6):621–626.

32. Saiman L, Anstead M, Mayer-Hamblett N, Lands LC, Kloster M, Hocevar-Trnka J, Goss, CH, Rose, LM, Burns JL, Marshall BC, Ratjen F, Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa: a randomized controlled trial. JAMA. 2010;303(17):1707–1715.

33. Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, Coquillette S, Fieberg AY, Accurso FJ, Campbell PW III, and Macrolide Study Group. Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial. J Amer Med Assoc. 2003;290(13):1749–1756.

34. Smith J, Lung N, and Perkins L. The current state of orangutan health in North America and the orangutan SSP's plans for moving forward. In: Proc Am Assoc Zoo Vet. 2012. p. 171.

35. Sriningsih AP, Lung NP, Sulistyo F, Aronson SA, Aronson RK, Taylor-Cousar JL. Evaluating the efficacy of human bronchiectasis-based antibiotic therapy in the treatment of orangutan respiratory disease. J Zoo Wildl Med. 2021;52(4):1205–1216.

36. Stringer E, Cossaboon C, Han S, Taylor-Cousar JL. Sinusitis, bronchiectasis, and flatus in a Sumatran Orangutan (*Pongo Abelii*): could this be Cystic Fibrosis? J Zoo Wildl Med. 2016;47(1):347–350.

37. Taylor-Cousar JL, Evans TA, Cutting GR, Sharma N. Potentially lethal cystic fibrosis gene variant in the orangutan. Am J Primatol. 2021;83(12):e23097.

38. Wang D, Fu W, and Dai J. Meta-analysis of macrolide maintenance therapy for prevention of disease exacerbations in patients with noncystic fibrosis bronchiectasis. Medicine. 2019;98(17):e15285.

39. Weinreich UM, Alstrup AK, Frost M, Iyer VV, Bertelsen HC, Clausen P, Jensen TH. [Recurrent periods of respiratory tract infections in a 22-year-old]. Ugeskr Laeger. 2014 Dec 8;176(50):V65601. Danish.

40. Wu Q, Shen W, Cheng H, Zhou X. Long-term macrolides for non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis. Respirol. 2014;19(3):321–329.

42. Ziebach R, Pietsch-Breitfeld B, Bichler M, Busch A, Riethmüller J, Stern M. Bronchodilatory effects of salbutamol, ipratropium bromide, and their combination: Double-blind, placebo-controlled crossover study in cystic fibrosis. Pediatr Pulmonol. 2001;31(6):431–435.

41. Zimmermann N, Pirovino M, Zingg R, Clauss M, Kaup FJ, Heistermann M, Hatt JM. Upper respiratory tract disease in captive orangutans (*Pongo sp.*): prevalence in 20 European zoos and predisposing factors. J Med Primatol. 2011;40(6):365–375. [PubMed: 221770970].

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Supplemental Figure 1. Individual cages at Borneo Orangutan Survival Foundation Samboja Lestari, where most of Orangutan Respiratory Disease Syndrome (ORDS) cases are housed. Photo Credit by BOSF.

Supplemental Figure 2. Nebulization process of orangutan case 1 using PARI nebulizer, which is held by the operator outside of the cage mesh as close to the orangutans' nose as possible. All three orangutans in this series have been trained to receive treatments using snacks or sweetened drinks for positive reinforcement during the nebulization session.