CHAPTER 77

Idiopathic Pulmonary Fibrosis

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Definition and Etiology

Pulmonary fibrosis is a pathological end-result of lung parenchymal inflammation. In humans, pulmonary fibrosis is a potential consequence of a wide range of clinical conditions including primary lung disorders (e.g., bronchopneumonia, eosinophilic pneumonia, or acute respiratory distress syndrome); connective tissue diseases (e.g., rheumatoid arthritis); inorganic and organic environmental or occupational pollutants (e.g., silicosis or farmer's lung); drug toxicity (e.g., bleomycin or amiodarone); and idiopathic fibrotic disorders (e.g., idiopathic pulmonary fibrosis or autoimmune pulmonary fibrosis).[1] The extent to which conditions such as the connective tissue disorders and autoimmune diseases result in lung fibrosis in the dog and cat is unknown.

There are specific conditions in both humans and animals in which lung fibrosis is an inevitable pathological consequence of the disease. In humans, this group of diseases is dominated by the occupational/environmental lung diseases and the poorly classified conditions that are grouped under the term idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis).[2,3] Information on IPF in the dog and cat is sparse. Recently, lung fibrosis conditions (e.g., chronic pulmonary disease in West Highland white terriers) that are believed to be analogous to idiopathic pulmonary fibrosis in humans have been recognized and partially reported in both the dog[4,5] and cat.[6] In addition, lung fibrosis has been recognized for many years in association with paraquat poisoning in dogs[7,8] and as a complication of Cushing's syndrome[9]; more recently, it was recognized in a case of naturally-occurring bronchiolitis obliterans with organizing pneumonia (BOOP) in a dog.[10] Previously, anecdotal references to a chronic fibrosing condition have appeared periodically in the veterinary literature,[11,12] and two older papers probably described the same clinical entity as IPF.[13,14]

Idiopathic pulmonary fibrosis (IPF) (known as cryptogenic fibrosing alveolitis [CFA] in the United Kingdom and Europe) is a diagnosis of pathological exclusion, where there is no alternative explanation for the cause of lung fibrosis and the lung pathology has clearly identifiable pathological changes. In humans, IPF is a disease of middle to old age, but there is a familial form, believed to involve an autosomal recessive trait with variable penetrance, seen predominantly in the 20- to 40-year age group.

Although there is extensive understanding of the etiology of the diseases that secondarily cause lung fibrosis, little is known of the possible causes of IPF. However, the potential involvement of environmental pollutants cannot be discounted.[15] In humans, the disorder appears to occur in susceptible individuals, and there is evidence that viral, immunologic, and genetic factors play a role in the etiopathogenesis of the disease.[3] IPF in the dog appears to be breed-prevalent, occurs most commonly in the West Highland white terrier (which is prone to allergic skin disease), and Giant cells (epithelial syncytia) reminiscent of viral infection have been noted in lung histopathological sections from affected dogs.[4,13] Anecdotal reports of human patients dating the onset of their symptoms from a flu-like illness have increased speculation that a viral etiology might be implicated.[3] There is an increasing body of evidence associating Epstein-Barr virus (EBV) infection and, to a lesser extent, adenovirus infection with IPF in some human patients.[16-18] Whereas EBV replication is known to occur in the type II alveolar epithelial cells, the exact role of EBV in the pathogenesis of IPF is unknown. It has been suggested EBV acts as an immune trigger or contributes directly to lung injury.[16] Following infection the virus becomes latent, but can continue to promote chronic inflammation and repair, leading to fibrosis.[17] It is recognized that latent viruses can maintain the inflammation and tissue damage caused by other types of injury such as environmental pollutants,[17] and it is possible that a complex interaction between genes, viruses, and environment might be the trigger for IPF. Intriguing preliminary findings from the North West Lung Centre, Wythenshawe Hospital, Manchester, UK, have tentatively identified a clinical improvement in IPF patients treated with antigammaherpes drugs, but the completed data from these studies are not yet available.

Pathophysiology and Pathogenesis

The underlying pathological mechanisms of fibrosis, either in the lung or in any other organ system, are complex

and incompletely understood.[18] End-stage lung fibrosis represents an aberrant remodelling process in response to injury.[3,19] The reason for scar formation rather than return to normal structure and function is unknown, but the key to the fibrotic response appears to be the up-regulation of gene expression for a range of cytokines. In particular there is mounting evidence that the transforming growth factor β family (TGF-β) is one of the most important groups of cytokines affecting the function and response of fibroblasts and Type II pneumocytes in the lung fibrosis response.[20] The identification of specific intracellular signals and associated gene expression offers new potential drug therapies for the fibrotic lung diseases.

Further upstream in the pathogenesis of lung fibrosis, a number of other mechanisms have the potential for drug targeting. Both acute and chronic inflammatory mechanisms are implicated in the induction and maintenance of fibrosis. A wide range of inflammatory mediators (e.g., eicosanoids, destructive tissue enzymes, and cytokines such as interleukin-1 [IL-1] and tumor necrosis factor-α [TNF-α]) prime resident tissue cells to increase production of both matrix proteins and additional cytokines such as IL-6, IL-8, and TGF-β.[19-21] Tissue fibroblasts are stimulated to differentiate and proliferate, and to increase production of collagen and other extracellular matrix proteins. The overall process is dynamic with multiple interactions between inflammatory cells and the fibroblast/fibrocyte system; thus the end result of the response to injury cannot be predicted. In lung fibrosis the capacity to arrest aberrant scar formation appears to be overwhelmed, resulting in loss of functional lung, altered lung physiology, and severe clinical signs.

Incidence, Prevalence, and Epidemiology

The incidence of IPF in the dog and cat is unknown, but the condition appears to be prevalent in the terrier breeds and in the West Highland white terrier in particular.[4,5,13] Reports of the incidence of IPF in humans vary greatly and in part reflect the difficulty in diagnosis. The prevalence in the United Kingdom is approximately 6 per 100,000, but closer to 30 per 100,000 in the United States.[22] The overall incidence of human IPF is rising, which probably reflects improvement in diagnosis, and a similar trend may be expected in veterinary medicine as we become more aware of the disease. A gender bias towards males has also been reported for IPF in humans, with males twice as likely to be affected.[22] In one study of West Highland white terriers, 17 were male and 12 were female, giving an approximate ratio of 60% to 40%.[4] The identification of a true male gender bias for IPF in the dog will rely on identification of a much larger number of cases. IPF has a median age of onset of approximately 9 years in the West Highland white terrier.[4]

The incidence of paraquat poisoning is low and sporadic and has become less common over the years because of its reduced use as a herbicide and because of safer handling and storage. Paraquat intoxication does not appear to have an age prevalence, although in one report the majority of dogs were under 5 years of age.[7] Recently a single case of lung fibrosis, similar to interstitial pneumonia in humans, has been reported in a cat, but the condition appears to be rare in this species.[6]

Risk Factors and Environmental Influences

The question of whether or not environmental industrial airborne pollutants are implicated in canine lung fibrosis is problematic. Obviously, occupational hazard is very important in the genesis of human lung fibrosis.[2] It has been speculated that a single case of BOOP in a dog with attendant lung fibrosis could have been caused by exposure to airborne toxins in the owner's workshop.[10] The author has seen one case of suspected lung fibrosis in a springer spaniel that had ready access to a pottery workshop where the workers used protective face masks, and speculated that the lung disease might have been caused by inhaled particulate material present in the workshop environment. However, beyond such occasional anecdotal reports there is no direct evidence that environmental pollutants are implicated in canine lung fibrosis.

Historical Findings, Clinical Signs, and Progression

Apart from breed predisposition, the only other specific historical features of IPF in the dog are the slow onset and progression of the disease. In the author's experience, coughing occurs late in the disease process and may be the prime reason the owner seeks veterinary advice. The owner may have noted exercise intolerance, dyspnea, and tachypnea, but attributed these signs to advancing age rather than primary respiratory disease.[4] Approximately 30% of cases are presented because of dyspnea. Additional clinical features include intermittent cyanosis and presyncope or syncope. Because the majority of affected dogs are over 9 years of age, concurrent medical problems (e.g., musculoskeletal disorders, endocrinopathies such as hypothyroidism[5] and hyperadrenocorticism, and obesity) may complicate the clinical picture. Additional respiratory conditions can also be present, particularly tracheal collapse and chronic bronchitis, further complicating the clinical presentation. Apart from these presenting signs the dogs are often bright, alert and responsive, and have normal appetite. Despite the respiratory impairment the owners are usually content with the dogs' overall quality of life.

Humans with IPF have a similar clinical presentation, with coughing and breathlessness occurring in equal numbers of patients, and bilateral basilar crackles audible on auscultation in most cases. Finger clubbing is seen in approximately half of the patients.[22] In one report, 30% of human patients had evidence of a concurrent immunological disorder (e.g., polyarthritis, chronic active hepatitis, and Sjögren's syndrome) with the remainder having "lone" CFA.[23] Although there is a single

case report of a dog with lung fibrosis and polyarthritis that might have been an early report of IPF,[14] the incidence of concurrent immunological disorders with IPF in the dog is unknown. In the author's experience, concurrent immunological disease appears to be unusual.

The main finding on physical examination in dogs is diffuse pulmonary crackles on thoracic auscultation. Wheezes and rhonchi can also be auscultated in many cases. The intensity of the crackles can be sufficient to make auscultation of the heart difficult.[4,5] Varying degrees of dyspnea, tachypnea, and cyanosis can also be noted.

Specific information on disease progression of canine IPF is not readily available, but it appears to be a slowly progressive disease, and deterioration is inevitable irrespective of treatment. Eventually respiratory failure develops and euthanasia is performed. The expected survival time from the onset of clinical signs varies widely. A range of 3 to 41 months has been reported in the West Highland white terrier, with a median survival of 15.5 months.[4] In human IPF, the median survival can be up to 12 years for desquamative interstitial pneumonitis (DIP), but is only 5 years for the more common usual interstitial pneumonitis (UIP) form. End-stage pulmonary fibrosis in humans results in extreme respiratory distress and total incapacity, followed by death caused by intractable hypoxemia and respiratory failure.[2]

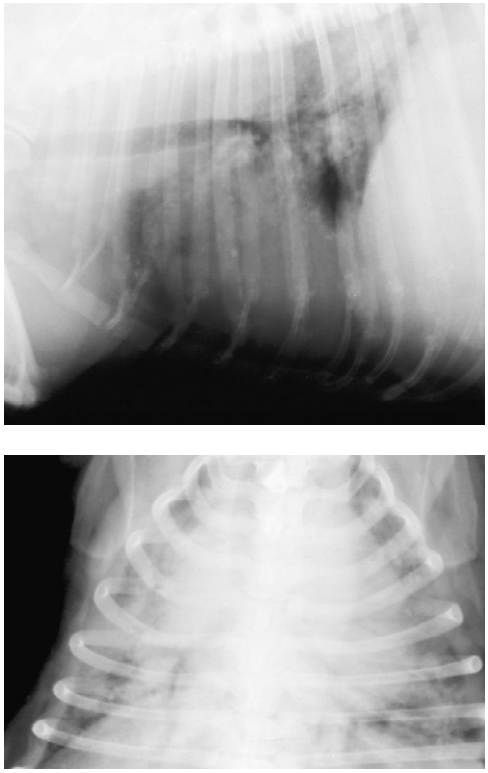

Figure 77-1. A, *Lateral and* ***B,*** *ventro-dorsal radiographs of the thorax of a dog with histopathologically confirmed idiopathic pulmonary fibrosis, showing a marked diffusely increased interstitial pattern.*

Differential Diagnosis

The major differential consideration in dogs with IPF is chronic bronchitis.[4] Chronic bronchitis is also a disease of small terrier breeds, has a similar clinical presentation and course to IPF, and diffuse pulmonary crackles can be heard on chest auscultation.[24-26] In contrast to IPF, dogs with chronic bronchitis often have minimal radiographic changes and have bronchoscopic evidence of the disease.[25,27] Diffuse pulmonary crackles are also a cardinal sign of pulmonary edema, and conditions causing congestive heart failure and noncardiogenic pulmonary edema must be considered. As IPF results in nonspecific diffuse interstitial radiographic changes, a wide range of interstitial lung diseases (e.g., respiratory infections, pulmonary infiltration with eosinophils, and infiltrative neoplasms) should be considered differential diagnoses for IPF.[4]

In humans, the main differential considerations are the occupational/environmental lung disorders and the connective tissue disorders. An exhaustive list of unclassified (primary) disorders resulting in interstitial disease must also be considered, including sarcoidosis, eosinophilic pneumonia, and acute respiratory distress syndrome.[1]

Diagnostic Tests

Thoracic radiography is important in the diagnosis of IPF in the dog because collection of diagnostic biopsy material is unlikely. The radiographic changes can vary but tend to reflect the severity of the clinical presentation with varying degrees of a diffuse interstitial pattern and right-sided cardiomegaly (Figures 77-1, *A* and *B*)[4,5,13] The sensitivity and specificity of radiography in the diagnosis of IPF in the dog is unknown. In human IPF the sensitivity and specificity of radiography is very poor, and there is a very poor correlation with severity of disease, unless honeycombing (advanced disease) is present.[3] The radiographic changes in humans can have a more patchy distribution compared with the dog, with an interstitial pattern usually described as reticular or reticulonodular.

Open lung biopsy is the main method for definitive diagnosis of lung fibrosis and the other interstitial lung diseases in humans,[28] but has not been widely adopted in veterinary patients. Although biopsy is necessary for confirmation of lung fibrosis, in a British Thoracic Society study, diagnosis of CFA in humans was still made on the basis of clinical findings in 60% of cases.[29] These clinical findings included breathlessness, finger clubbing and bilateral basilar crackles, typical chest radiographic features, and evidence of impaired gas transfer on lung function tests. Similarly, in dogs with IPF a strong tentative diagnosis can be made on the basis of the clinical presentation of chronic-onset coughing and dyspnea, diffuse pulmonary crackles, and radiographic changes, without necessarily undertaking invasive diagnostic procedures.[4,5] The utility of blood gas analysis in the diagnosis of IPF in dogs is not known, but severely affected individuals have hypoxia with normo- or hypocapnia and alveolar-arterial oxygen gradients typical of ventilation-perfusion mismatch.[4] In human IPF,

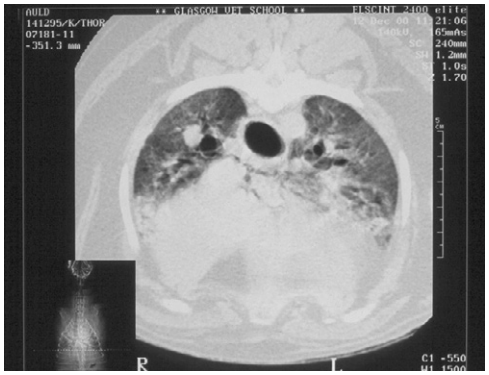

Figure 77-2. *High-resolution computed tomography image of a dog with suspected idiopathic pulmonary fibrosis at a level slightly caudal to the tracheal bifurcation. Notice the generalized ground-glass lung opacity and additional areas of consolidation in the lung periphery.* (Courtesy Dr. T. Schwarz, University of Glasgow.)

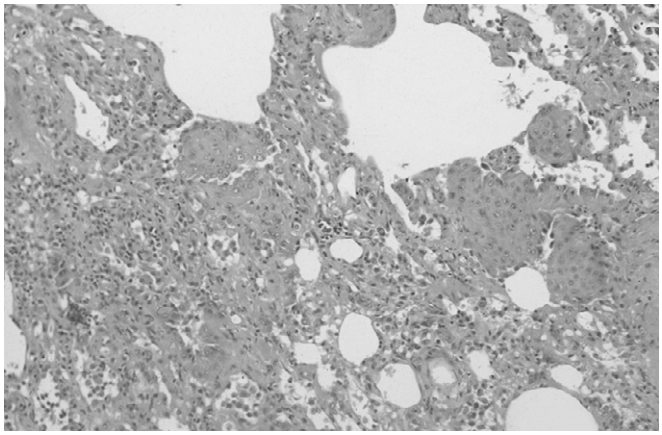

Figure 77-3. *H & E stained section of lung from a dog with idiopathic pulmonary fibrosis. The section illustrates the marked destruction of normal lung architecture, with squamous metaplasia, alveolar fibrosis, and diffuse inflammation.*

pulmonary function tests (e.g., measurement of total lung capacity, single breath carbon monoxide diffusing capacity, and oxygen desaturation on exercise) are also used for the initial diagnosis and assessment, and for monitoring progression and response to therapy.[1,30,31]

In humans, imaging modalities such as high resolution computed tomography (HRCT) can improve diagnostic accuracy by identifying active inflammation, thereby improving the diagnosis, treatment, and management of patients with IPF.[22] Some limited information on HRCT for IPF in the dog is available (Figure 77-2). Video-assisted thoracoscopic lung biopsy has been found to be comparable to open-chest lung biopsy in terms of morbidity and mortality in humans, but has distinct advantages in terms of postoperative care and complications.[32] This technique may prove to be useful for diagnosis of IPF in dogs in the future.

Bronchoscopy and bronchoalveolar lavage (BAL) may be useful tests in canine IPF because they may allow exclusion of chronic bronchitis, which is the major differential diagnosis.[4,5] The limited data on BAL fluid cytology in affected dogs makes assessment of the utility of this diagnostic test difficult. In the majority of cases of canine IPF the BAL samples are normal or have low to moderate mixed populations of inflammatory cells.[4] In human IPF, BAL lymphocytosis is documented in a proportion of patients, and there have been reports that such individuals respond better to therapy.[22,28,33,34] The prognosis further improves if the patient has HRCT results suggestive of an active inflammatory process.

Pathological and Histopathological Findings

The pathological characteristics of paraquat poisoning in dogs are well described but there is little information on the pathology of IPF. Paraquat poisoning results in progressive and irreversible lung fibrosis, which appears to be preceded by alveolar epithelial detachment and alveolar macrophage activation and recruitment, followed by extensive fibroblast proliferation and laying down of excess collagen.[7,35]

Information on the pathology of canine and feline IPF is sparse. The changes are nonspecific and therefore easily ascribed to a number of etiological factors, particularly viral infections and toxicoses.[13] On gross pathology, the lungs tend to be firm, heavy, and noncollapsable.[5,6,13] Associated right ventricular changes have also been noted (e.g., right ventricular hypertrophy and dilatation). In the limited histopathology reports of IPF in the dog and cat to date, the major finding has been extensive but patchy alveolar fibrosis (Figure 77-3).[4-6,13,14] Additional findings include epithelial cell hyperplasia, localized areas of squamous metaplasia, variable degrees of chronic interstitial inflammation predominantly involving lymphocytes and macrophages, and localized areas of emphysema and peri-arterial fibrosis.[4-6,14] Giant cells, similar to epithelial syncytia, have been reported in three cases, but no viral inclusion bodies have yet been identified.[5,13]

IPF/CFA in humans is divided into two broad histopathological categories.[22] The less common form is known as desquamative interstitial pneumonitis (DIP), and has close similarities to the recent report of feline CFA.[6] DIP mainly involves a lymphocytic cellular reaction with minimal fibrosis and is believed to be either an early form of IPF or a distinct and separate clinical entity. It is also the most amenable to therapy with glucocorticosteroids. Usual interstitial pneumonitis (UIP) is the most common form of IPF/CFA in humans and consists of a mixed inflammatory and fibrosis pattern with a distinctive peripheral distribution.[22] UIP is comparable to the form of IPF reported in the dog.[4,5] The locally extensive nature of the lung pathology, as opposed to widespread diffuse disease, is also comparable between human and canine patients.[4,36]

Management and Monitoring

Often decisions are made not to treat humans with IPF because of the unpredictability of progression of the disease and the poor response to current therapeutic regimes.[37,38] However, some authors question this approach, suggesting that it impedes progress in the diagnosis, management, and treatment of IPF.[28]

The medical treatment of IPF in the dog relies on glucocorticoids (prednisolone) and bronchodilators.[4] There is anecdotal clinical evidence that this drug combination may be beneficial in some cases, but exact figures or data from controlled studies are not available.[4] In human IPF prednisolone is widely used and appears to be beneficial in a number of cases. DIP patients are more responsive to glucocorticoids, reflecting the active inflammatory nature of the condition.[28] Up to 60% of DIP patients respond favorably to such treatment.[39] In the more common UIP where there is extensive fibrosis, glucocorticoids are less effective, which is not surprising because these drugs do not have any effects on the mechanisms of fibrosis.[28] Additional approaches to drug therapy in human patients include immunosuppressive and cytotoxic drugs (e.g., azathioprine and cyclophosphamide). However, convincing data that their use in combination with prednisolone results in a better outcome compared to prednisolone alone are lacking.[28,40,41] Of the two (azathioprine or cyclophosphamide), adjunctive therapy with azathioprine appears to give a marginal improvement over prednisolone therapy alone.[41]

Theoretically, drugs such as colchicine that have antifibrotic activity should be of benefit in IPF. Some studies in human IPF suggested that colchicine was at least as beneficial as prednisolone therapy in terms of clinical improvement and survival, but is a much more benign drug with minimal side effects.[38,42] A more recent study, however, suggests colchicine has no appreciable effect on survival compared to no therapy, and low dose prednisolone therapy gives the best survival outcome.[43] Colchicine inhibits fibroblast proliferation and thereby decreases the rate of collagen synthesis rather than affecting collagen gene transcription.[44] It also has weak inhibitory effects on the release of profibrotic cytokines (e.g., IL-6, TNF-α, IL-1, PDGF, and TGF-β) from inflammatory cells and suppresses production of macrophage-derived growth factor and fibronectin.[44] Through these various mechanisms colchicine should theoretically slow the rate of progression of fibrosis but will not reverse it. The author has no experience in the use of colchicine in IPF dogs, but it may have future applications in this condition.

There is also increasing interest in the development of antifibrotic drugs that either directly affect fibroblast proliferation and function or interfere with the production or activity of profibrotic cytokines. These drugs include cytokine-specific antibodies (e.g., anti-TNF-α), interferon-γ, niacin, taurine, pirfenidone, platelet activating factor antagonists, hydroxyproline analogs, and relaxin,[21,38,45] but clinical trial data on their efficacy in the treatment of IPF are not yet available. Lastly, single lung transplantation is an option in human patients with life-threatening illness.[46,47]

Outcome and Prognosis

With the limited data available it is difficult to provide accurate outcome information and prognosis guidelines for IPF in the dog. In one study of IPF in 29 West Highland white terriers, the median age of onset of clinical signs was 9 years, with a median survival of 15.5 months and a range of 3 to 41 months.[4] The effect of therapy could not be evaluated. Because some dogs survived up to or greater than 3 years, considering the late age of onset (diagnosis), some dogs might live close to their expected life-span. This compares with IPF in humans where the mean age of presentation in one study was 54 years, with a median survival of approximately 5 years.[23] Survival times in humans are best in young patients, especially if they are female,[23] whereas the presence of right-sided cardiomegaly and right axis deviation, suggestive of cor pulmonale, are poor prognostic indicators.[23] Fourteen of 29 cases of IPF in the dog had radiographic evidence of cor pulmonale, but its relationship to survival was not reported.[4]

Human patients with DIP have a much better outcome, with median survival up to 12 years.[28,39] In 20% of DIP patients spontaneous resolution can occur, and this again raises the possibility that DIP may be a separate clinical entity. Outcome in human patients might also be a function of level of care in that IPF patients referred to a specialist interstitial lung clinic have a median survival time significantly greater than those referred to a general respiratory clinic.[47] However, this difference is not seen with patients over 60 years of age. Whether or not specialist intervention in canine IPF would improve survival is not known. Because of the late age onset of clinical signs and the slow progression of the disease, many owners delay presenting their dogs until the disease is well advanced. It is conceivable that more rapid intervention and diagnosis might improve outcome and survival in dogs with IPF.

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CHAPTER 51

Bronchiectasis

Carol R. Norris

Bronchiectasis is defined as a pathological destruction of the elastic and muscular components of the bronchial wall leading to chronic abnormal dilation and distortion of the bronchi.[1] A variety of congenital and acquired conditions have been described in humans, dogs, and cats that lead to a cycle of chronic airway infection and inflammation and resulting bronchiectatic changes.[2-6] Damage to the epithelial cells lining the airways induces squamous metaplasia and ciliary loss, which leads to impairment of the mucociliary apparatus.[2] Clearance of both normal and abnormal pulmonary secretions is dependent on transport of mucus and associated particulate materials by the ciliated epithelial cells of the mucociliary apparatus. Dysfunction of the mucociliary apparatus allows pooling of mucus, exudate, and microbes in the distal airways. Obstruction of the airways can occur due to accumulation of mucus, hemorrhage, inflammatory cells, and necrotic tissue; or due to a mass effect from neoplasia or enlarged lymph nodes.[2] Secondary infection stimulates a host inflammatory response, creating a vicious cycle of further damage to the airway walls.[7-9] Neutrophil lysosomal enzymes (e.g., elastase, collagenase, and cathepsin G) and oxygen radicals play a role in this damage,[1,4] as does the recruitment and activity of other inflammatory cells such as macrophages, T cells, and eosinophils.[10]

Reversible dilation of the bronchi has been described in acute pulmonary diseases in humans (e.g., pneumonia, tracheobronchitis, and atelectasis) and must be differentiated from true bronchiectasis.[1] True bronchiectasis is permanent; this fact has important implications in the management of the condition. Reversible or pseudobronchiectasis has also been described in the dog.[11]

Etiology

Bronchiectasis may be congenital or may develop secondary to acquired disease, with the latter etiology being much more common. In humans, congenital causes of bronchiectasis include congenital anatomical defects (e.g., developmental arrest of the tracheobronchial tree or cartilage deficiency), immunodeficiency states (e.g., panhypogammaglobulinemia; antibody subclass deficiency; and defects of neutrophil adhesion, respiratory burst and chemotaxis), cystic fibrosis, α_1-antitrypsin deficiency, and primary ciliary dyskinesia.[1,6,12-14] In dogs, bronchiectasis is a common sequela of primary ciliary dyskinesia,[15] and markedly dilated bronchi have been seen in dogs with bronchial cartilage aplasia[16] and bronchial hypoplasia.[17] Bronchiectasis was detected by thoracic radiography in a 10-month-old miniature dachshund with *Pneumocystis carinii* pneumonia,[18] an infection affecting dogs of this breed less than 1 year of age. Recently, these dogs were found to have a primary immunodeficiency called common variable immunodeficiency (CVID).[19] Despite the young age of the dogs affected, CVID is considered an acquired or adult onset deficiency of B and T cells.[19] Congenital bronchiectasis was reported in a cat with bronchial dysgenesis,[20] and computed tomographic evidence of bronchiectasis was found in a cat with presumptive primary ciliary dyskinesia.[21]

Acquired causes of bronchiectasis in humans include diseases that cause bronchial obstruction (e.g., asthma, chronic bronchitis, panbronchiolitis, neoplasia, foreign body, hilar lymphadenopathy, recurrent aspiration pneumonia, and broncholiths) and necrotizing or suppurative

pneumonia.* In dogs, acquired bronchiectasis usually develops as a result of eosinophilic bronchitis, chronic bronchitis, bronchiolitis, or bronchopneumonia.[2,3,24-30] Interestingly, although allergic bronchitis (feline asthma) and chronic bronchitis are common clinical disorders in the cat, bronchiectasis is rarely found in association with these diseases. In studies evaluating cats with bronchial disease, thoracic radiographic evidence of bronchiectasis was not reported in any cat.[31,32] Histologic evidence of bronchiectasis was not detected in an experimental model of feline asthma.[33] In a recent retrospective study evaluating cats with a histological diagnosis of bronchiectasis, only 12 cases were found over a 12-year period.[5] Although bronchiectasis in the cat is a rare sequela to bronchopulmonary disease, the most commonly identified underlying diseases included chronic bronchitis and bronchiolitis, neoplasia, and bronchopneumonia.[5] Bronchiectasis was also reported in a cat with miliary broncholithiasis.[34]

Clinical Presentation

Most dogs and cats with bronchiectasis are middle age or older, consistent with the higher incidence of acquired versus congenital bronchiectasis. In one study, 92% of dogs were age 7 years or older,[3] and in another, the mean age was 7 years (range 2 to 17 years).[25] A study of cats with bronchiectasis reported a mean age of 12 years (range 7 to 16 years).[5] There appear to be breed predispositions for American cocker spaniel dogs and Siamese cats.[3,5,25] No sex predisposition has been reported in dogs, but a trend for male overrepresentation was noted in cats.[5]

Clinical signs associated with bronchiectasis likely reflect the underlying disease process. In humans these signs include chronic cough; purulent or mucopurulent sputum production; wheezing; dyspnea; recurrent fever; hemoptysis; and, in advanced stages, anorexia and weight loss.[1,14,23] Clinical signs in dogs include cough; gag; tachypnea; dyspnea; and, occasionally, fever.[2,35,36] In the retrospective study of bronchiectasis in cats, only 5 of 12 cats had clinical signs referable to the respiratory system (i.e., cough, tachypnea, and dyspnea).[5] Four of the cats had chronic respiratory symptoms (range 1 to 8 years duration).

Diagnostic Tests

There are two key components in the diagnostic evaluation of patients with bronchiectasis. First, the dilated airways must be recognized and localized because this pathologic process by itself is responsible for ongoing bronchopulmonary inflammation. Second, the underlying disease process that led to the development of bronchiectasis must be identified. Bronchiectasis can be detected by survey thoracic radiography, bronchography, high resolution computed tomography (HRCT), bronchoscopy, and histology. In humans, HRCT is considered the gold standard because it is highly sensitive and noninvasive.[1,6] The utility of HRCT to specifically demonstrate bronchiectatic airway changes in dogs and cats has not been evaluated to date, aside from a single case report in a cat with presumptive primary ciliary dyskinesia.[21]

Different radiographic patterns can be seen in patients with bronchiectasis. The major forms include cylindrical, saccular, cystic, and varicose bronchiectasis.[2,11] Cylindrical bronchiectasis appears as dilated bronchi with nontapering ends of approximately the same diameter that terminate in consolidated or atelectatic lung tissue.[2,11] This form tends to affect the larger, thick-walled bronchi. Saccular bronchiectasis has the appearance of a cluster of grapes and results from circumscribed sacculations of bronchial walls at their terminal end, separated by inflamed or indurated lung tissue.[2,25] In contrast to saccular bronchiectasis, which affects the intermediated-sized bronchi, cystic bronchiectasis is believed to be a severe form of saccular bronchiectasis that involves terminal bronchi.[2] The varicose form of bronchiectasis consists of beaded, widened bronchi with irregular contours.[11] Most cases of bronchiectasis in dogs and cats are of the cylindrical form, with saccular bronchiectasis being the next most common form.[5,25] Cystic bronchiectasis has been described in the dog but not in the cat.[2,5] Varicose bronchiectasis has not been reported in either dogs or cats.

Thoracic radiography is also useful in determining whether bronchiectasis is focal or diffuse. In the retrospective study of cats with bronchiectasis,[5] thoracic radiography demonstrated a nearly equal distribution of focal and diffuse lesions; this was similar to one report in dogs[3] but contradictory to another study that found the diffuse form of bronchiectasis to be more common.[25] Focal lesions tend to correspond to the presence of solitary masses (e.g., neoplasms) or regional infection (e.g., aspiration pneumonia) causing localized obstruction. Diffuse lesions are usually seen with generalized inflammatory processes such as chronic bronchitis, bronchiolitis or bronchopneumonia. Thoracic radiographs should be thoroughly examined for the presence of other underlying disease processes.

Survey thoracic radiography may not be a sensitive test for bronchiectatic changes because imaging of the bronchial walls is dependent on inflammation and fibrosis of the airways, conditions typical of advanced disease.[25] In humans, thoracic radiography has been shown at times to be unremarkable in the early stages of disease. In both dogs and cats, bronchiectasis has been documented by other diagnostic modalities (e.g., histology) in patients with normal thoracic radiography.[24,37]

The technique for bronchography has been previously described in small animals,[36,38] and this tool has been used successfully to document and localize bronchiectasis in the dog.[36] Visual examination of the airways using bronchoscopy can also help in the recognition of bronchiectatic lesions. Bronchoscopy has the advantages of being able to grossly visualize the airways for evidence of an obstructive lesion and enabling collection of samples for cytological examination and culture.

*References 1, 6, 9, 12, 14, 22, and 23.

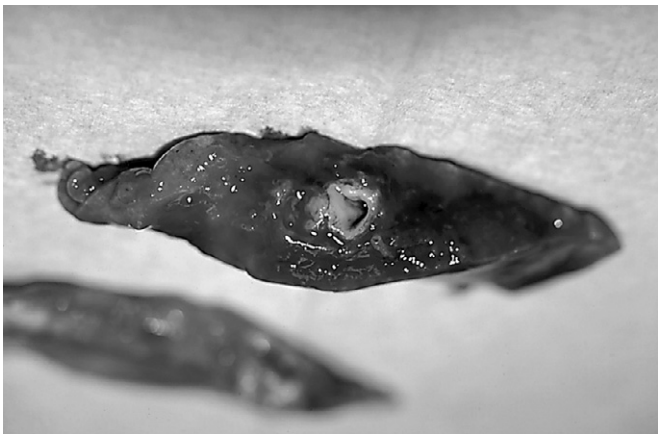

Figure 51-1. *A lung biopsy from a dog demonstrating a grossly dilated airway (bronchiectasis) with intraluminal mucopurulent exudate. This dog had severe diffuse bronchiectasis secondary to chronic eosinophilic bronchitis.*

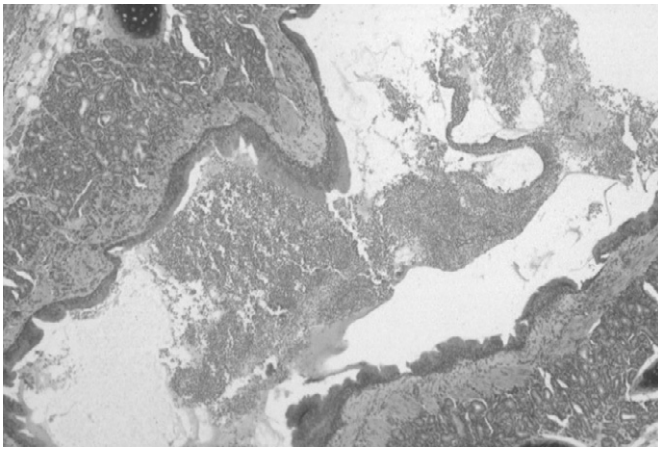

Figure 51-2. *A histologic specimen of the lung from a cat with bronchiectasis secondary to bronchopulmonary dysplasia. Note the widely dilated airway with accumulation of intraluminal cells (neutrophils). Hematoxylin and eosin stain; 40×.* (Courtesy of Stephen M. Griffey, University of California, Davis).

Gross examination of bronchiectatic airways reveals prominent dilation and luminal filling with purulent secretions (Figure 51-1). Histological examination of the lungs reveals dilation of the affected airways and various degrees of airway wall remodeling with granulation tissue and fibrosis. Microscopically, the lumen of the airways is usually filled with mucus, proteinaceous material, and inflammatory cells (Figure 51-2).[1,2,4] The types and quantity of cellular infiltrates in the lung parenchyma are dependent on the underlying cause of disease. Inflammation in the peribronchial tissues is common.[1,2,4]

Ancillary tests used in the diagnosis of bronchiectasis in humans include sputum examination and pulmonary function testing.[7,8,13] These tests are not routinely employed in the diagnosis of bronchiectasis in dogs or cats.

Treatment

Because bronchiectasis is irreversible, the goal of therapy is to control clinical signs and slow the progression of disease.[1] Patients with focal bronchiectasis are the exception; in these animals' surgical removal of the affected lung lobe may be curative.[1,2,39] Most cases of bronchiectasis in dogs and cats are acquired secondary to an underlying disease. Addressing the primary pathological process is vital to attempt to halt the progression of destruction of the bronchial walls. Treatment of recurrent bacterial infections (ideally based on culture and sensitivity) is critical in breaking the cycle of the host inflammatory response to microorganisms and further damage to the bronchial walls. Airway humidification may help loosen secretions and avoid inspissation and subsequent airway obstruction.[1,2] If the underlying disease is inflammatory (e.g., chronic bronchitis, canine idiopathic eosinophilic bronchitis, or feline asthma), antiinflammatory drugs such as corticosteroids are indicated. However, systemic corticosteroids must be administered with caution because of the risk of further infection. A beneficial role of inhaled steroids has been shown in humans with bronchiectasis[10]; similar studies using metered dose inhaled steroids delivered through a valved holding chamber* are warranted in dogs and cats with inflammatory airway disease.

Prognosis

In humans, bronchiectasis can lead to bronchopneumonia, pulmonary hemorrhage, bronchiolitis obliterans and emphysema, chronic respiratory insufficiency, and cor pulmonale.[1] Focal bronchiectasis treated with surgical lobectomy is associated with a good prognosis.[2] The prognosis for patients with diffuse bronchiectasis depends on the underlying disease process, the severity of pulmonary lesions and their resultant clinical manifestations, and the response to antimicrobial and/or antiinflammatory therapy.

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*OptiChamber,® Respironics, Cedar Grove, NJ.

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CHAPTER 52

Chronic Bronchitis in Dogs

Ned F. Kuehn

Definition and Etiology

Chronic bronchitis is essentially an incurable disease of insidious onset usually seen in middle age or older dogs of the small breeds. It is characterized clinically by a chronic, persistent cough and characterized pathologically by chronic inflammation of the airways, as well as mucus hypersecretion.[1] The cough is usually productive with gagging, but because dogs do not expectorate, the production of excess mucus may be difficult to recognize. Chronic bronchitis in humans is defined as chronic or recurrent excessive mucus secretion in the bronchial tree, occurring on most days for at least 3 months of the year during at least 2 years. The diagnosis is made in ab-

sence of other specific pulmonary diseases such as cancer, pneumonia, and tuberculosis.

Because of their shorter lifespans, the definition is modified somewhat for dogs.[2] Chronic bronchitis in dogs is defined as a condition of chronic or recurrent excessive mucus production in the bronchial tree for at least 2 consecutive months in the preceding year, and manifested clinically by chronic coughing. As in man, the chronic hypersecretion of bronchial mucus is not attributable to other lung disease. Therefore, the diagnosis of chronic bronchitis requires fulfillment of three major criteria:

1. Chronic cough
2. Evidence of excessive mucus or of mucus hypersecretion
3. Exclusion of other chronic cardiorespiratory diseases (e.g., congestive heart failure, chronic bacterial pneumonia, pulmonary neoplasia, parasitism, and fungal pneumonia). In dogs, coexisting diseases (e.g., congestive heart failure and airway collapse) may be present and may complicate the diagnosis and treatment of chronic bronchitis.

The most common functional sequela of chronic bronchitis is chronic airflow obstruction, which is generally referred to as chronic obstructive pulmonary disease (COPD).[3]

Pathophysiology and Pathogenesis

Chronic bronchitis is characterized pathologically by excessive viscid mucus or mucopus (mucopurulent matter) in the tracheobronchial tree.[3] The viscid mucus contains a large number of neutrophils and macrophages admixed with varying amounts of cellular debris and edema fluid. Smaller bronchi are often occluded by thick mucus plugs. The bronchial mucosa is usually hyperemic, thickened, and edematous. Polypoid proliferations often project from the mucosa into the bronchial lumen. Patchy pneumonia is a complicating factor in about one quarter of the dogs. Emphysema is a much less important lesion in the dog than in humans, and is primarily confined to the edges of the lung lobes.

It is generally accepted that the development of chronic bronchitis is the result of a vicious cycle of airway damage and patient response. The airways are protected in health by a set of pulmonary defense mechanisms that includes normal ciliary action, normal quantity and quality of mucus, efficient collateral ventilation, and an efficient cough mechanism.[4] Persistent infection or chronic inhalation of airborne irritants can result in sustained injury to the bronchial epithelium, stimulating metaplastic transformation of the ciliary epithelium, hyperplasia and hypertrophy of mucus-secreting glands and cells, and hyperemia and cellular infiltration of the bronchial mucosa. Chronic saccular dilatation and destruction of the walls of bronchi and bronchioles (bronchiectasis) may result from long-standing airway inflammation.[1] Once bronchiectatic airway changes occur, they are irreversible. Furthermore, because all these changes impede normal defense mechanisms, bacterial colonization of the airways commonly results. The irreversible airway changes associated with bronchiectasis cause severe impairment of mucociliary clearance, which allows for mucus accumulation in the airways and predisposes those animals to recurrent bronchopulmonary infections.

Toy breeds of dogs often develop weakness of the cartilaginous rings of the trachea and major bronchi, resulting in tracheobronchial collapse during expiration and during coughing. Collapse of the major airways impedes expiratory airflow and efficient clearance of mucus from the bronchial tree, exacerbating the clinical condition of patients with chronic bronchitis.

Chronic insult to the bronchial epithelium not only contributes to decreased efficiency of normal pulmonary defense mechanisms but also promotes the development of functional obstruction to intrapulmonary gas flow. Airway diameter is reduced in chronic bronchitis by a combination of the following mechanisms:

- Edema and cellular infiltration of airway walls
- Copious quantities of tenacious intraluminal mucus
- Localized endobronchial narrowing associated with fibrosis of the lamina propria and polypoid proliferations of the mucosa
- Spasticity of bronchial smooth muscles causing reactive airway narrowing (may not be as significant in dogs as in humans)
- Collapse of larger bronchi associated with weakening of the bronchial walls subsequent to chronic inflammatory activity
- Plugging of smaller airways by tenacious mucus
- Obliteration of bronchioles as a result of inflammatory activity
- Emphysema develops following flooding of the alveoli with mucus

Chronic obstructive pulmonary disease is an insidious condition characterized by minimally reversible airflow obstruction that cannot be explained by any specific or infiltrative lung disease but that occurs as an end result of chronic bronchitis. The minimal reversibility of COPD differentiates it from asthma, which is a disease of significant reversibility of airflow obstruction. The small peripheral airways are the predominant sites of irreversible airflow obstruction. The persistent airway inflammation associated with chronic bronchitis is responsible for the development of refractory airflow obstruction.

The small airways normally only contribute a small percentage of total airway resistance because the tremendous number of small airways dramatically increases the total cross-sectional area for gas flow. Disease of small airways, therefore, must be diffuse and extensive before airway resistance is enhanced sufficiently to bring about clinical signs. Dogs normally have extensive interconnections between alveoli and adjacent respiratory bronchioles. Collateral ventilation through these channels allows alveoli primarily served by obstructed bronchioles to continue to be ventilated. One can therefore appreciate that small airway disease in the dog must be remarkably extensive before clinical signs of shortness of breath associated with COPD are observed. In humans, the diagnosis of COPD relies upon quantitative documentation of airflow obstruction by

pulmonary function testing. Enhanced airway resistance and a decline in maximum expiratory airflow rate are characteristic findings. Because pulmonary function testing is not widely available in veterinary medicine, the diagnosis of COPD is usually determined on the basis of clinical and radiographic findings. Extensive obstruction of small airways primarily manifests clinically as expiratory dyspnea. Gas trapping in COPD occurs with premature closure of the small airways during expiration. In advanced cases of COPD, gas trapping may occur during quiet breathing, resulting in a barrel-chested appearance of some patients. Hyperinflation of the lung fields is seen radiographically.

Patients with advanced chronic bronchitis and COPD develop maldistribution of ventilation in relation to blood flow through the lung. This ventilation-perfusion inequality occurs because ventilation is universally reduced within the lung in relationship to blood flow. Chronic hypoxemia stimulates erythropoiesis, resulting in mild to moderate erythrocytosis (secondary polycythemia). The overall increase in airway resistance associated with advanced chronic bronchitis increases the work of breathing and intensifies the hypoxemic state. Vasoconstriction of the pulmonary arteries occurs in response to hypoxemia. This pulmonary hypoxic vasoconstrictor response causes an increase in pulmonary vascular resistance and pulmonary artery pressure. Chronic pulmonary hypertension may lead to right ventricular heart failure (cor pulmonale).

BOX 52-1
Possible Causes of Chronic Bronchitis in Dogs

Atmospheric Pollution

Passive Smoking

Chronic exposure to smoke in poorly ventilated confined spaces

Respiratory Tract Infections

Chronic fungal infection
Chronic bacterial infection
- *Bordetella bronchiseptica*
- *Mycoplasma spp.*

Viral infection
- Canine distemper virus
- Adenovirus (types 1 and 2)
- Herpesvirus

Parasites
- *Filaroides milksi; Filaroides herthi*
- *Crenosoma vulpis*
- *Capillaria aerophila*
- *Dirofilaria immitis*

Genetic or Acquired Defects

α_1-antitrypsin deficiency
Mucociliary defects
Immunodeficiency

Hypersensitivity (Allergic) Lung Disease

Epidemiology, Risk Factors, and Environmental Influences

The causes of chronic bronchitis are poorly understood in the dog, and usually remain unknown in individual patients. The major difficulty in determining the cause of chronic bronchitis is because the disease is detectable only in its advanced stages. This is largely because chronic bronchitis has an insidious onset and lengthy pathogenesis, and the diagnosis is largely based on a descriptive clinical definition.

The three etiologic factors in man considered most important for the hypersecretion of mucus in the bronchial tree are smoking, atmospheric pollution, and infection. Chronic exposure to sulfur dioxide (SO_2), a common atmospheric pollutant, causes mucus hypersecretion, bronchial mucus gland hypertrophy, bronchiectasis, and emphysema in dogs.[5] Box 52-1 lists several possible causes of chronic bronchitis in dogs.

Historical Findings, Clinical Signs, and Progression

Chronic bronchitis is most commonly seen in middle age to older (age greater than 5 years) smaller breeds of dogs (e.g., terriers, poodles, and cocker spaniels); however, the diagnosis should not be overlooked in large breed dogs.[6] Clinical signs usually seen in patients with chronic bronchitis include:

- Persistent, intractable, productive cough with gagging and production of sputum, which is typically swallowed and thus difficult to document
- Cough may be unproductive, resonant, harsh, hacking during the day and productive during the evening or early morning hours
- Paroxysmal cough precipitated by exercise or excitement
- Obesity
- Cyanosis, collapse, exhaustion, and exercise intolerance
- Pronounced sinus arrhythmia
- Expiratory dyspnea
- Varying periods of remission followed by exacerbation of coughing (exacerbations may be in association with changes in weather, particularly cold weather)
- Systemic signs of illness may be seen during severe exacerbations or episodes of bronchopneumonia.[7]

The clinical diagnosis of chronic bronchitis requires fulfillment of three major criteria: (1) chronic cough on most days for at least 2 consecutive months during the preceding year; (2) evidence of excessive mucus or mucopus hypersecretion; and (3) exclusion of other chronic respiratory diseases.[8] The first two criteria may easily be established with a thorough and accurate history. The third criterion is established only after an exhaustive examination for other causes of chronic cough and dyspnea.

The most important differential diagnoses that must be ruled out are cardiac diseases (typically chronic mitral regurgitation), chronic bacterial pneumonia, pulmonary neoplasia, foreign body bronchitis, hypersensitivity airway disease, dirofilariasis, pulmonary parasites, fungal pneumonia, dysphagia, and megaesophagus.

The physical examination typically does not contribute significantly to the patient evaluation. Diligent auscultation of the chest is important because cardiac diseases (e.g., chronic mitral regurgitation or cor pulmonale) and pulmonary diseases (e.g., tracheal collapse or pneumonia) are often present as coexisting problems or secondary complications in patients with chronic bronchitis. Lung sounds may be normal or abnormal depending on the degree of airway involvement. Paninspiratory crackles and expiratory wheezes are the most commonly heard adventitious (abnormal) breath sounds. In those dogs with coexisting collapse of the intrathoracic trachea, an end-expiratory snap (click) may be heard during coughing or forced expiratory efforts. Nevertheless, it must be stressed that many dogs with chronic bronchitis have normal auscultation findings.

Dogs with severe obstructive lung disease also may show evidence of hyperinflation (barrel-chested appearance), a pronounced expiratory effort, and a prolonged expiratory phase of respiration. The presence of increased respiratory effort during the expiratory phase of breathing should be considered a significant clinical finding because chronic bronchitis is the only common respiratory disorder in dogs to cause expiratory dyspnea.

Differential Diagnosis

Chronic bronchitis is a diagnosis based on clinical exclusion of other chronic respiratory diseases. The presence of coexisting cardiopulmonary disease may, however, complicate the diagnosis of chronic bronchitis. Chronic respiratory diseases associated with either cough or exercise intolerance, or both, that should be excluded include congestive heart failure, tracheal collapse, hypersensitivity (allergic) lung disease, parasitic lung disease, dirofilariasis, neoplastic lung disease, eosinophilic or lymphomatoid granulomatosis, pneumonia, lung lobe abscess, foreign body, lung lobe torsion, diaphragmatic hernia, pleural space disease (e.g., hemothorax, chylothorax, pneumothorax, neoplasia), neuromuscular diseases with secondary aspiration pneumonia (e.g., megaesophagus, myasthenia gravis), laryngeal paralysis, and mediastinal disease (e.g., pneumomediastinum, neoplasia).

Diagnostic Tests

Since the diagnosis of canine chronic bronchitis is largely based on the history of chronic cough, diagnostic tests are performed to rule out other causes of chronic cough. A complete blood count (CBC), serum biochemical profile, and urinalysis are indicated if systemic disease is suspected. In dogs with respiratory abnormalities only, a CBC can be valuable, although it is often normal. An increased white blood cell count may indicate the presence of bronchopneumonia, whereas eosinophilia may suggest an allergic or parasitic pneumonitis. Arterial blood gas analysis may be indicated in some patients with severe obstructive lung disease. An increased Pa_{CO_2} due to hypoventilation is a grave finding that denotes the onset of ventilatory failure associated with increased work of breathing. All dogs with chronic cough from heartworm endemic areas should have an antigen test (or similar tests) performed to rule out dirofilariasis. A fecal examination (standard flotation and Baermann) should be performed to rule out the presence of lung parasites, if suspected.

Good quality thoracic radiographs are essential to rule out other causes of chronic cough or to disclose complicating conditions such as pneumonia, bronchiectasis, and cardiac disease. Thoracic radiographs from dogs with nonobstructive chronic bronchitis usually show bronchial wall thickening or generalized increased airway-oriented interstitial density or both (Figure 52-1). Bronchial wall thickening is recognized by "doughnut" shadows and "tram lines," which arise from either end-on or longitudinal projections of thickened bronchial walls, respectively. The existence of alveolar infiltrates may indicate concurrent pneumonia or pulmonary edema. Many dogs, however, have normal appearing lung fields; thus the finding of normal thoracic radiographs should not rule out the diagnosis of chronic bronchitis.

The presence of a mild to moderate peribronchial pattern in the thoracic radiograph of an older dog is significant and should not be dismissed as a change compatible with age. Peribronchial and interstitial densities in thoracic radiographs of older dogs have been shown to correlate with significant histologic abnormalities.[9] Likewise, similar changes in the chest radiograph of an older human would be considered a significant sign of peribronchial pathology.

Dogs with obstructive chronic bronchitis (e.g., chronic bronchitis and chronic obstructive pulmonary disease) have radiographic evidence of pulmonary hyperinflation in addition to bronchial wall thickening and a generalized increase in airway oriented interstitial density. Pulmonary hyperinflation is recognized by hyperlucency and enlargement of the lung fields, and by caudal displacement and flattening of the diaphragm. Bronchopneumonia and bronchiectasis may arise as complications of chronic bronchitis. Superimposed bronchopneumonia is recognized radiographically by patchy alveolar infiltrates. Bronchiectasis is identified by saccular or cylindrical dilation of bronchi.

Bronchoalveolar lavage or tracheal wash to collect material for cytology and microbiology should be considered in all dogs suspected of having chronic bronchitis. It is definitely indicated in any dog with chronic bronchitis that has an acute exacerbation of clinical signs. Bronchopulmonary cytology in dogs with chronic bronchitis typically reveals excess mucus with either normal or hyperplastic bronchial epithelial cells; and increased

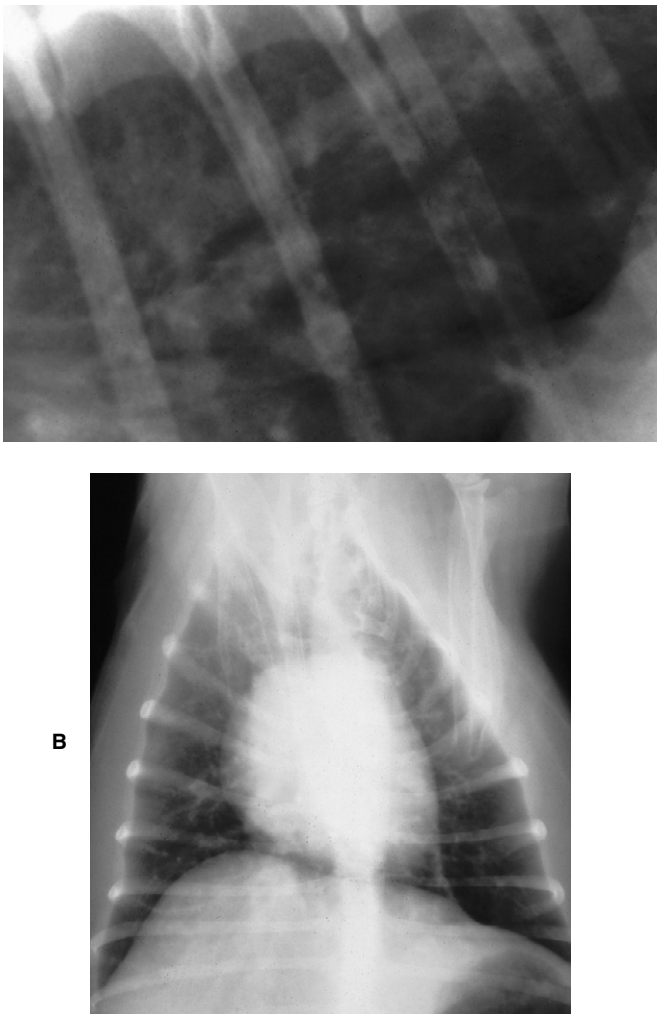

Figure 52-1. A, *Close-up view of the dorsocaudal lung lobes on a lateral thoracic radiograph.* ***B,*** *Ventrodorsal view of the same thorax. Both views are from a dog with nonobstructive chronic bronchitis and show bronchial wall thickening and a generalized increase in airway-oriented interstitial density.*

numbers of macrophages, goblet cells, neutrophils, and lymphocytes. Purulent material characterized by increased neutrophils with engulfed bacteria indicates an associated bronchial infection or bronchopneumonia. The presence of large numbers of eosinophils may suggest an underlying hypersensitivity disorder or parasitic disease.

Microbiological culture and sensitivity testing of the fluid obtained during bronchoalveolar lavage or tracheal wash may be indicated to rule out secondary bacterial infection. The airways and lungs of healthy dogs are commonly inhabited by a variety of bacterial flora.[10,11] Growth of small numbers of bacteria on culture does not necessarily imply the presence of infection. In many dogs with chronic bronchitis, bacteria cultured from the airways or lungs merely reflect innocuous colonization rather than infection. Tracheobronchial culture and sensitivity testing

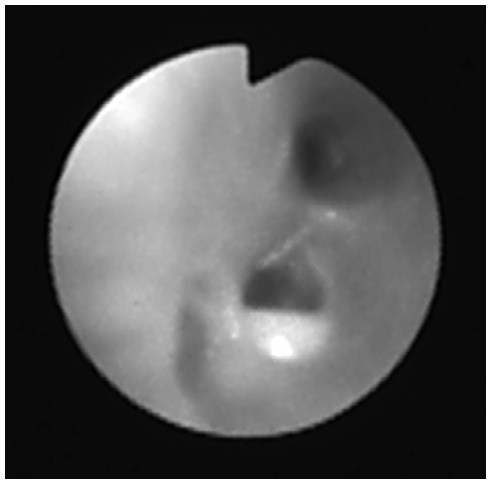

Figure 52-2. *Excessive, thick, tenacious mucus may be found in strands or small plaque-like accumulations within the airways. Small airways may be occluded by mucus plugs.*

is indicated in newly diagnosed dogs with chronic bronchitis that have radiographic or bronchoscopic evidence of bronchiectasis, and in dogs with an acute exacerbation of previously stable chronic bronchitis. In most of these situations, bronchopulmonary cytology supports the presence of infection based on the findings of intracellular bacteria or the toxic appearance of neutrophils. For the culture results to be meaningful it is essential that sample material for tracheobronchial culture and sensitivity testing is obtained from the lower airways and not the pharynx. The most common isolates are *Bordetella bronchiseptica, Streptococcus* spp., *Pasteurella* spp., *Escherichia coli, Pseudomonas* spp., and *Klebsiella* spp.

Bronchoscopy may be a useful procedure in helping to establish a clinical diagnosis of chronic bronchitis, especially in dogs lacking the typical radiographic findings of the disease. Bronchoscopy is also valuable in obtaining representative samples from the deeper airways for cytology and culture. The airways of dogs with chronic bronchitis are characterized by erythema and a roughened granular appearance.[3] The mucosa often appears thickened, irregular, and edematous. Occasionally polypoid or nodular proliferations are seen projecting into the bronchial lumen. Excessive thick tenacious mucus may be found in strands or small plaquelike accumulations within the airways. Small airways may be occluded by mucus plugs (Figure 52-2). Collapse of the dorsal tracheal membrane into the lumen of the airway is commonly observed in dogs with chronic bronchitis and indicates the presence of concurrent tracheal collapse. Principal bronchial collapse may be observed in some patients during passive tidal exhalation. These patients typically have a worse prognosis than those without evidence of principal bronchial collapse. Saccular and irregular dilation of secondary or tertiary bronchi indicates the presence of bronchiectasis.

Pathological and Histopathological Findings

Because chronic bronchitis is largely a clinical diagnosis, tissue biopsy is not required for confirmation. Fibrosis; edema; and cellular infiltration of the lamina propria by lymphocytes, plasma cells, macrophages, and neutrophils are seen histopathologically. A significant proportion of the tracheobronchial wall is occupied by mucous glands. There is both an increase in size and number (hypertrophy) of mucous glands, in addition to an overall increase (hyperplasia) in the number of epithelial goblet cells.[12] Focal ulceration, loss of cilia, and squamous metaplasia of the bronchial epithelium is also found. Extremely severe cases may have medial hypertrophy of the small pulmonary arteries and muscularization of the pulmonary arterioles,[13] associated with right ventricular hypertrophy as a result of chronic hypoxic pulmonary hypertension.

Bronchopulmonary cytology of deep lung samples obtained via bronchoalveolar lavage typically reveals excess mucus, with either normal or hyperplastic bronchial epithelial cells; and a preponderance of nondegenerate neutrophils.[14] Increased numbers of macrophages, goblet cells, and lymphocytes may be present. Bronchial casts of airway mucus (Curschmann's spirals) are sporadically recovered in lavage fluid samples. The presence of increased numbers of neutrophils does not necessarily indicate the presence of bacterial infection. Bacterial infection is not a clinical problem in many dogs with chronic bronchitis. The presence of large numbers of degenerate neutrophils or neutrophils with engulfed bacteria supports the presence of secondary bacterial bronchitis or bronchopneumonia.

Occasionally, dogs with chronic bronchitis have increased numbers of eosinophils in lavage fluid; this may indicate concurrent systemic hypersensitivity or parasitism by gastrointestinal parasites or ectoparasites, underlying hypersensitivity lung disease, or the stage of disease. Increased numbers of eosinophils may be recovered from humans with acute exacerbation of chronic bronchitis, signifying that noninfectious irritants, viruses, and *Mycoplasma* spp. should be considered as possible causes of acute inflammation.[15]

Management and Monitoring

The structural alterations in airway anatomy associated with chronic bronchitis are not readily reversible, if at all. Bronchiectasis, tracheobronchial collapse, and emphysema are permanent, irreversible changes that complicate the management of these patients. Because this disease is essentially incurable, client education is very important. There should be an understanding by the client of the natural history of the problem and the goals of therapy.

Therapy is based on an assessment of the nature and severity of the individual animal's problems. Basically, management of patients with chronic bronchitis is divided into five major categories:

1. Avoidance of exacerbating factors and control of body weight
2. Relief of airway obstruction and inflammation
3. Control of cough
4. Control of infection
5. Oxygen therapy

Factors initiating chronic bronchitis are rarely identified. If an offending agent is identified and exposure continues, cure is rarely achieved and control is simply more difficult. In the unusual situation where exposure to the initiating factors can be curtailed, there are reduced airway inflammatory changes and return of the airway anatomy towards normal. It is recommended that dogs with chronic bronchitis be kept in a clean, cool environment. Exposure to inhaled irritants (e.g., oven and household cleaners, dust or smoke, heat, and humidity) should be avoided. If concurrent airway collapse is present, events promoting stress or excitement should be avoided to reduce paroxysmal bouts of coughing. These dogs, as well as those with marked tracheal sensitivity for cough, should be fitted with a harness rather than a collar.

Many dogs with chronic bronchitis are overweight. The excessive accumulation of extrathoracic, intrathoracic, and intraabdominal fat restricts the respiratory system and thereby decreases lung volume.[3] Obesity decreases thoracic wall compliance, increases the work of breathing, and increases intraabdominal pressure on the diaphragm. A low resting lung volume is present, predisposing the animal to small airway closure, which thereby decreases the efficiency of normal pulmonary defense mechanisms and reduces pulmonary ventilation. Weight reduction improves ventilation, promotes increased exercise capability, enhances arterial oxygenation, and reduces stress on the cardiovascular system. In some dogs, a significant improvement in clinical signs is seen with weight loss alone.

Relief of airway obstruction is generally accomplished by patient-specific combinations of three types of therapy: antiinflammatory medications, bronchodilator medications, and treatments that promote removal of accumulated airway secretions.

Antiinflammatory therapy is the most important aspect of treatment of chronic bronchitis. Chronic bronchial inflammation results in mucus hypersecretion, mucosal bronchial wall thickening, and variable degrees of airway smooth muscle constriction. Weeks to months of therapy may be required to achieve a reduction in airway inflammation, and in some instances control of airway inflammation is never attained.

Because most cases of canine chronic bronchitis do not have a defined cause, the primary basis of medical treatment is to control airway inflammation. Glucocorticoids appear to benefit dogs with chronic bronchitis, presumably by alleviating chronic airflow obstruction by reducing airway inflammation and mucus production, and by decreasing cough by diminishing stimulation of airway sensory nerves responsible for initiating cough.[7,14] Glucocorticoids are the most effective drugs and form the basis of chronic therapy for managing dogs with chronic bronchitis. However, glucocorticoids should not be given to patients with secondary bronchopulmonary infection.

Studies to determine the specific bioavailability of the various glucocorticoid preparations for lung tissue have not been established in the dog. In humans, hydrocortisone seems to have the greatest penetrability for lung tissue, followed by methylprednisolone and prednisone. Oral or parenteral glucocorticoid therapy is typically used in dogs. Many adverse side effects can develop with chronic oral or parenteral glucocorticoid therapy. Short-acting glucocorticoids such as prednisone and prednisolone are associated with fewer side effects than the long-acting preparations such as dexamethasone, methylprednisolone, and triamcinolone. Inhaled glucocorticoid therapy is preferred in human medicine because it allows direct absorption of the drug into the lung and diminishes systemic side effects; however, this route of administration is not feasible for many canine patients.

A 10- to 14-day therapeutic trial using oral prednisone or prednisolone at a dosage of 0.5 to 1 mg/kg every 12 hours is initially recommended. If remission of clinical signs is induced, the dosage should be reduced by half every 10 to 14 days. The dosage of medication should gradually be reduced to the absolute minimum required to maintain improvement of clinical signs (i.e., reduction in cough and improved exercise tolerance). Prolonged alternate or every third day therapy is beneficial in some patients. If the sole administration of prednisone or prednisolone does not bring about significant clinical improvement, combination therapy with a bronchodilator such as albuterol should be undertaken. After 2 to 4 months of maintenance therapy, an attempt should be made to gradually stop treatment entirely. Some dogs may not have worsening of clinical signs for months after stopping therapy. Glucocorticoid therapy should be reinstituted using the guidelines above if exacerbation of disease is observed.

The use of nonsteroidal antiinflammatory drugs has not been evaluated in the treatment of dogs with chronic bronchitis. While thromboxane TXA2 and prostacyclines PGF2 and PGD2 cause bronchoconstriction under experimental conditions, they are not considered at this time to play an important role in the pathogenesis of bronchoconstriction in dogs with chronic bronchitis.

Bronchodilators are widely prescribed in humans to relieve bronchoconstriction associated with chronic bronchitis. Their use in dogs with chronic bronchitis is predicated on the assumption that bronchoconstriction is present and is a significant component of airway obstruction. There is evidence to suggest that $beta_2$-agonist therapy can increase expiratory airflow, reduce wheezing, increase exercise tolerance, reduce cough, and partially resolve radiographic changes when given to some dogs with chronic bronchitis.[7] However, it is difficult to confirm the presence and reversibility of bronchoconstriction in a given dog with chronic bronchitis because pulmonary function tests such as tidal breathing flow volume loops are not widely used. Despite this limitation, probably all dogs with chronic bronchitis should be given the benefit of trial therapy with bronchodilators. The efficacy of bronchodilator therapy should be judged in terms of clinical improvement because relatively few dogs with chronic bronchitis have reversible bronchoconstriction. The sole use of bronchodilators is not advised in dogs that demonstrate clinical improvement with bronchodilator therapy. The inflammatory nature of chronic bronchitis is chronic and progressive, so concurrent use of glucocorticoids is advised.

$Beta_2$-agonists (e.g., albuterol and terbutaline) may be the most effective bronchodilator drugs for use in dogs with chronic bronchitis.[7] These drugs also appear to act synergistically with glucocorticoids to control airway inflammation. Therefore, dogs that demonstrate a positive clinical response to $beta_2$-agonist therapy may have control of their clinical signs with a reduced dosage of both drugs when given in combination. $Beta_2$-agonist therapy should be considered in dogs with exercise intolerance, wheezing on chest auscultation, or failure of adequate response to glucocorticoids. Common side effects of $beta_2$-agonists include restlessness and skeletal muscle tremors. These side effects usually resolve within 2 to 5 days of initiating therapy. Albuterol syrup is recommended at a starting dosage of 0.02 mg/kg PO every 12 hours for 5 days. After 5 days, if a positive response to the initial dosage was not appreciated, the dosage may be increased to 0.05 mg/kg PO every 8 to 12 hours providing that the dog is tolerating the medication. If a positive response to therapy is appreciated, the lowest effective dosage of albuterol that minimizes cough and improves exercise tolerance should be found. Should a positive response not be established within 2 weeks of instituting therapy, further bronchodilator treatment will likely not be effective. The effective dosage for terbutaline has not been clearly defined; however, a dosage of approximately 1 mg/kg PO every 12 hours has been recommended.

The methylxanthine derivatives (e.g., theophylline and aminophylline) previously were most commonly used in the management of canine chronic bronchitis.[16] Although the pharmacokinetics of theophylline in the dog are well established,[17] only anecdotal reports address the occasional effectiveness of this drug for dogs with chronic bronchitis. Like beta-agonists, methylxanthine derivatives seem to act synergistically with glucocorticoids to control airway inflammation.[14] Theophylline is reported to cause relaxation of bronchial smooth muscle, increase mucociliary transport rates, stabilize mast cell membranes, decrease bronchovascular leak, and increase contractibility of fatigued diaphragmatic muscle.[14] Adverse side effects of methylxanthines are likely related to adenosine antagonism and include gastrointestinal distress, tachycardia, and hyperexcitability. The preferred theophylline preparations for dogs are long-acting, slow-release tablet formulations (Theo-Dur Tablets [Key Pharmaceuticals], 20 mg/kg PO every 12 hours; Slo-Bid Gyrocaps [Rhone-Poilenc Rorer], 20 to 25 mg/kg PO every 12 hours).

Anticholinergic agents (e.g., atropine and ipratropium bromide) are potent bronchodilators.[14] Anticholinergic drugs relax airway smooth muscle and reduce mucus production through blockage of vagal nerve transmission to airway smooth muscle and submucosal gland and goblet cells. Atropine has not proven to be an effective bronchodilator in dogs with chronic bronchitis be-

cause increased vagal tone is only a minor contributing factor to airway narrowing in this disease. Ipratropium bromide is administered only by inhalation and is not at present a practical alternative for dogs.

Some dogs with chronic bronchitis benefit from methods to facilitate removal of accumulated airway secretions. The inhalation of humidified air via steam inhalation or nebulization moistens thick, tenacious bronchial secretions and thereby facilitates their movement from the airways. An ultrasonic nebulizer is best because it produces the very small particles of water needed to penetrate deep in the airways. Aerosol therapy for hospitalized patients may be accomplished by placing a portable nebulizer in an enclosed cage with the animal. A more expensive alternative is the use of an oxygen cage with humidification and temperature controls. Therapy may be attempted at home by compelling the dog to breathe aerosolized vapors from a portable nebulizer. Treatment in either situation requires a minimum of 15- to 30-minute treatments three or four times daily in order to be effective.

Light exercise after aerosol therapy assists in dislodging bronchial mucus and helps open small airways by promoting increased lung volumes associated with a standing posture. Chest physiotherapy is also beneficial following aerosol therapy to aid in dislodging bronchial mucus. Chest percussion (coupage) is achieved by using a cupped hand to generate vibrations on the patient's thoracic wall, and should be performed three or four times daily for 5 to 10 minutes per session. The success of treatment is judged by the induction of a bout of productive coughing following therapy.

Expectorants may be tried to promote removal of bronchial secretions. Theoretically, these drugs enhance the secretion of less viscous bronchial mucus, but their efficacy is questionable. Medications containing a combination of cough suppressants and expectorants should not be used if the cough is productive because an intact cough reflex is desirable to expel bronchial secretions. Mucolytics such as acetylcysteine are drugs capable of breaking the disulfide bonds that are partially responsible for the viscid nature of airway mucus. Unfortunately, aerosolized acetylcysteine is irritating to bronchial epithelium and can trigger bronchoconstriction.[6] Antiinflammatory therapy, maintenance of normal hydration, and aerosol therapy are probably the most beneficial methods to reduce production and viscosity of airway mucoid secretions.

Cough is an important pulmonary defense mechanism. Effective removal of viscid airway secretions is of great importance in patients with chronic bronchitis. Suppression of cough before resolution of inflammation may result in mucus trapping, which may perpetuate airway inflammation. Once clinical signs suggest that inflammation is resolving (e.g., improved exercise tolerance, improved thoracic radiographs, chronic nonproductive cough), cough suppressants may be advantageous to resolve cough because chronic coughing can lead to repeated airway injury and syncope.[6] The use of antitussives should be restricted to those dogs with periods of nonproductive cough, dogs with chronic cough who are unable to sleep, and dogs with chronic cough due to airway collapse. Narcotic antitussives such as hydrocodone bitartrate and butorphanol are much more effective than over-the-counter anti-tussives such as dextromethorphan. In some dogs, however, dextromethorphan may be effective in controlling cough. The primary side effects of the narcotic antitussives are sedation or drowsiness and constipation. Hydrocodone bitartrate may be given at a dosage of 0.22 mg/kg PO every 6 to 12 hours, or butorphanol at a dosage of 0.05 to 1 mg/kg PO every 6 to 12 hours, both as needed without inducing excessive sedation. Long-term therapy may be required in dogs with severe airway collapse. It is important not to indiscriminately suppress coughing, especially if productive cough or bronchopulmonary infection is present. The cause of an acute exacerbation of cough should be found, if possible, before recommending cough suppressants.

Bacterial infection does not usually play a significant role in the cause or exacerbation of clinical signs in dogs with chronic bronchitis.[14] The signs of bronchial disease typically wax and wane in severity and frequency. Reports describing the therapeutic effect of antibiotics in controlling chronic cough were likely consistent with the waxing and waning nature of untreated cases of chronic bronchitis. Likewise, a positive culture does not necessarily imply infection but may be a result of normal airway contaminants. The use of antibiotics should only be based on demonstrated evidence of bronchial infection. Prompt effective treatment of any bacterial bronchial infection is essential in dogs with chronic bronchitis in order to prevent further perpetuation of airway damage and the development of bronchopneumonia. Culture and sensitivity of lavage fluid from the lungs or lower airways should be considered in dogs with documented evidence of bronchiectasis (either via radiographs or bronchoscopy) or those with an acute exacerbation of symptoms associated with mucopurulent nasal discharge, fever, or radiographic signs of lobar consolidation.

Antibiotic choice should be based on sensitivity results when possible. Broad-spectrum antibiotics are indicated due to the diversity of bacteria commonly isolated in the lung. Lipophilic antibiotics should be employed due to the presence of the blood-bronchus barrier, which limits penetration of many antibiotics into bronchial tissue.[6] Antibiotics of choice include chloramphenicol (50 mg/kg PO every 8 hours), doxycycline (2.5 to 5 mg/kg PO every 12 hours), and enrofloxacin (5 to 10 mg/kg PO every 12 hours or 10 to 20 mg/kg PO every 24 hours); or ciprofloxacin (10 to 20 mg/kg PO every 12 hours or 20 to 40 mg/kg PO every 24 hours). Fluoroquinolones such as enrofloxacin inhibit the metabolism of theophylline, and the combination of the two drugs can result in toxic plasma levels of theophylline.[18] A reduction in the dosage of theophylline by at least 30% is advised if fluoroquinolones are required. Chronic or severe infections may involve various organisms and may require a combination of chloramphenicol, trimethoprim-sulfa (15 mg/kg PO every 12 hours), or clindamycin (11 mg/kg PO every 12 hours) with enrofloxacin or ciprofloxacin to facilitate resolution of the infection.

Oxygen therapy can be used for temporary support during treatment of dogs with severe hypoxemia as a result of acute decompensation of disease or the presence

of severe bronchopneumonia.[3] The inhaled air should be humidified to help liquify tenacious bronchial secretions and prevent drying of the airways. Periodic suctioning of the airways with a soft rubber catheter (if the dog is intubated and receiving temporary ventilatory support) or chest physiotherapy (if the patient is mobile) should be attempted to remove accumulated secretions. Animals receiving oxygen therapy and suffering severe obstructive disease should be frequently monitored for hypoventilation because their hypoxic drive stimulus for respiration may be removed by the inhalation of oxygen rich air.

Outcome and Prognosis

Chronic bronchitis is a common, progressive, and chronic airway disorder that can often be managed but is essentially incurable. The prognosis is improved when the airway inflammation can be effectively controlled and exposure to environmental respiratory irritants is reduced. Periods of exacerbation, nevertheless, often characterize the chronic, progressive clinical course of disease in these patients. Fortunately, most dogs are only affected by a recurrent cough. All dogs with chronic bronchitis should have periodic examinations to evaluate the effectiveness of any current therapy and to ensure that secondary bronchopulmonary infections are not present.

The major complications associated with chronic bronchitis are the development of COPD, bronchopneumonia, bronchiectasis, and, in severely affected dogs, cor pulmonale. Bronchopulmonary infections should be treated promptly and effectively. Dogs with bronchiectasis should be inspected regularly (every 3 to 6 months) for the development of bronchopneumonia. Cor pulmonale (right heart failure) is a serious consequence of chronically increased pulmonary vascular resistance. This is a direct complication of advanced chronic bronchitis and indicates a grave prognosis for the patient.

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CHAPTER 53

Feline Bronchial Disease/Asthma

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Definition and Etiology

Feline bronchial disease (feline asthma or bronchitis) is one of the most common respiratory diseases in cats. It is recognized clinically by various combinations of cough, wheeze, exercise intolerance, and respiratory distress and is characterized pathologically by inflammation of the lower airways without an obvious identifiable cause. Young- to middle-age cats are most commonly affected. The Siamese breed may be overrepresented, although cats of any breed are susceptible.

Pathophysiology and Pathogenesis

Like asthma in humans, the pathophysiology of feline bronchial disease is not altogether known. However, considerable research has been completed on these syndromes in recent decades, and the disease in cats has been better characterized by the use of an experimental model of antigen-induced inflammatory bronchial disease.[1-5] Clinical signs range from intermittent cough to severe respiratory distress; these are attributable to airway obstruction caused by bronchial inflammation, with subsequent smooth muscle constriction, epithelial edema, and mucous gland hypertrophy and hyperactivity.[6-9] These changes are reversible in some cats that have primarily hyperresponsive, inflamed airways; however, chronic inflammation may lead to permanent pathology in other cats and is evidenced by airway fibrosis or emphysema.[10]

Decreased airflow in the small airways is caused by excessive mucus secretion, airway edema, cellular infiltrates, and smooth muscle hypertrophy and constriction. Following Poiseuille's law, airflow through a bronchus or bronchiole is proportional to the radius of the tube raised to the fourth power.[11] Therefore, a 50% reduction in airway luminal size results in a sixteenfold increase in resistance to airflow, and airway mucus, edema, or bronchoconstriction can reduce airway diameter and diminish airflow significantly. Correspondingly, therapy that leads to small increases in airway lumen diameter can dramatically increase airflow and reduce clinical signs.

Severe lower airway obstruction in cats with asthma can lead to lung hyperinflation because they are unable to exhale completely past the narrowed airways, resulting in air trapping. Lung hyperinflation may cause an enlarged, barrel-chested appearance; or can be appreciated by a flattened, caudally-displaced diaphragm and increased pulmonary radiolucency on thoracic radiographs of cats with bronchial disease. Chronic airway inflammation and obstruction in this manner can induce such dramatic intraluminal pressure for significant periods that permanent airway dilation (bronchiectasis) and loss of pulmonary elastic support structures (emphysema) may result. Bronchiectasis and emphysema have been noted radiographically and histopathologically in some cats with chronic bronchial disease.[6,7,10,12] In contrast, complete obstruction of a mainstem bronchus may cause atelectasis of the corresponding lung lobe because air is unable to enter or exit and residual air is resorbed. For unknown reasons, this process seems to affect the right middle lung lobe in cats with bronchial disease more often than other lobes, as noted in radiographic series of these patients.[7,8]

Coughing may be initiated by a variety of factors in cats, including airway compression; the presence of foreign material, noxious gases, tissue, mucus, or fluid in the tracheobronchial tree; airway inflammation; or airway smooth muscle contraction. Cough in cats with bronchial disease may result from stimulation of irritant receptors due to the presence of excess mucus or inflammatory mediators in inflamed and constricted airways. Cough is seen more commonly in cats with airway disease than in those with pulmonary parenchymal disease or congestive heart failure because cough receptors are located in the airways, but not in the alveoli.[13]

Asthma is characterized by localized accumulation of inflammatory cells in the airway, particularly eosinophils and activated lymphocytes. Eosinophils appear to be primary effector cells in the development of asthmatic airway pathophysiology in cats as well as in humans. Highly charged cationic proteins found within eosinophil granules may be released into airways, causing epithelial disruption and sloughing, and smooth muscle hyperreactivity.[14] Studies in mice have shown that local interleukin-5 (IL-5) secretion from activated T

lymphocytes plays a pivotal role in causing migration of activated eosinophils into airways, participating in the pathogenesis of bronchial hyperreactivity and lung damage.[15] These events may also take place in cats with bronchial disease.

Adhesion molecules contribute to selective cellular recruitment responses and permit cell-cell and cell-substratum attachments.[16] Intercellular adhesion molecule-1 (ICAM-1) is found on vascular endothelium and epithelium. Interaction of ICAM-1 with eosinophils is important for cell recruitment to human airways and for the eventual development of bronchial inflammation and hyperresponsiveness.[17] Interactions of intercellular adhesion molecules could be an important target for therapeutic intervention, although the role of these agents in the pathogenesis of feline bronchial disease has not yet been confirmed.

In vitro studies have suggested that serotonin, a primary mediator released from feline mast cells, contributes to airway smooth muscle contraction in the cat.[5] Smooth muscle cell responsiveness of tracheal and bronchial smooth muscle tissue from immune-sensitized cats was examined in the presence and absence of serotonin receptor blockade with cyproheptadine. The strength of contraction was attenuated in the presence of cyproheptadine,[5] implicating a role for serotonin in the bronchoconstriction that occurs in this model of antigen-stimulated airway hyperresponsiveness. Whether serotonin plays a role in naturally occurring disease has not been established. In this same study, prevention of leukotriene production with an inhibitor of 5-lipoxygenase had no effect on contraction of airway smooth muscle *in vitro*, suggesting that leukotriene metabolites might not play a role in feline bronchoconstriction.

Epidemiology and Risk Factors

In human asthma, allergens are risk factors for development and expression of disease, and aeroallergens are also important triggers of the inflammatory process.[18,19] The role of allergens and nonspecific airway irritants in feline bronchial disease is unknown; however, irritants may exacerbate or initiate the inflammation and airway obstruction of asthma. Conditions that might be identified as stimulants of clinical signs in cats with bronchial disease include allergens, air pollution, and aerosolized irritants.

Viral, bacterial, mycoplasmal, or parasitic respiratory tract infections also have the potential to trigger airway inflammation. Viral (e.g., rhinovirus, influenza, and respiratory syncytial virus) respiratory infections are the most common cause of asthma exacerbations in children,[20] and infections early in life may play a role in asthma development.[21] Respiratory infections increase airway hyperresponsiveness, possibly by causing or enhancing bronchial inflammation via stimulation of local cytokine secretion. Some respiratory infections may be protective for the development of asthma in humans, possibly by stimulating a T helper 1 cytokine profile (i.e., gamma interferon) that shifts the balance away from allergic inflammation.[22] In cats, the relationship between upper respiratory tract infections and asthma remains unclear, although in a recent study, 25% of cats evaluated for signs of asthma had clinical signs consistent with upper respiratory tract infection.[6]

The role of Mycoplasma in initiation or exacerbation of clinical signs associated with feline bronchial disease remains speculative. *Mycoplasma* spp. were isolated from airway washings in 4 of 9 cats with bronchial disease,[7] and *Mycoplasma* spp. have not been recovered from the airways of healthy cats.[23,24] If present within the airway, Mycoplasma could potentially increase bronchoconstriction and airway edema by prolonging the activity of Substance P. In rodent studies, *Mycoplasma* spp. have been reported to degrade neutral endopeptidase, an enzyme responsible for Substance P degradation.[25,26]

Historical Findings and Clinical Signs

Clinical signs most often apparent in cats with bronchial disease include a combination of cough, wheeze, and abnormal or difficult respiration. Decreased airflow is responsible for the clinical signs of cough, wheeze, and lethargy. These signs are often chronic or slowly progressive; however, cats with severe exacerbations may present acutely with open mouth breathing, dyspnea, and cyanosis due to bronchoconstriction. Mildly affected cases may only have occasional and brief episodes of bronchoconstriction and cough separated by long periods without symptoms. Exacerbation or induction of clinical signs may occur in association with exposure to potential allergens or irritants such as new litter (possibly perfumed), cigarette or fireplace smoke, perfumed household items (e.g., carpet cleaners, air fresheners, deodorants, and hair spray), dust associated with remodeling, or seasonal pollens. Clinical signs commonly worsen with stress or exercise. Weight loss may be apparent in cats suffering from chronic bronchial disease; however, cats that have restricted activity due to respiratory disease can be overweight.

Differential Diagnosis

Cough is fairly specific for tracheobronchial disease in the cat because cats with pulmonary edema due to heart disease do not typically cough. Airway foreign bodies are rare but should be ruled out. Pulmonary parasitic infestation with *Paragonimus, Aelurostrongylus,* or *Capillaria,* although uncommon, may cause many of the same clinical findings as those present in cats with asthma (e.g., local and peripheral eosinophilic inflammation and bronchoconstriction). Infection with *Bordetella* can lead to upper respiratory tract signs, and occasionally coughing is noted.[27] Parenchymal diseases (e.g., bacterial pneumonia) are relatively uncommon in cats, and cats usually display a less pronounced cough than dogs. Occasionally, cats with chylothorax cough intermittently; however, the cough that occurs with bronchial disease is more frequent. Dyspnea or respiratory distress is common in cats

with acute congestive heart failure and is often found in cats with pleural effusion or pneumothorax. Physical examination findings are helpful in distinguishing among these various disorders.

Diagnostic Tests

PHYSICAL EXAMINATION

Many asthmatic cats can appear normal at rest, and thoracic auscultation may be unremarkable. Because bronchial disease is an obstructive disease of the small, lower airways, most affected cats exhibit a prolonged expiratory phase of respiration, and audible wheezes or crackles may be heard with or without the aid of a stethoscope, usually during expiration. Air trapped distal to obstructed airways can lead to diminished thoracic wall compressibility and a barrel-shaped appearance to the chest. Many cats exhibit increased tracheal sensitivity and cough with cervical tracheal palpation.

BLOODWORK

Approximately 20% of cats with bronchial disease have a peripheral eosinophilia,[6-8] and the likelihood of eosinophilia may increase as disease severity worsens.[6] This finding is not specific however because several other possible diagnoses (e.g., lungworm or heartworm infections, gastrointestinal parasitism, or ectoparasites) may also cause peripheral eosinophilia. A stress leukogram may be apparent. Chronic hypoxemia could potentially cause a compensatory increase in hematocrit, although this is relatively uncommon. Biochemical profiles rarely yield information specific to bronchial disease. Some cats have hyperglobulinemia, suggestive of chronic immunological stimulation. Heartworm antibody and antigen serology is recommended for cats that exhibit respiratory symptoms and reside in a heartworm-endemic region.

FECAL EXAMINATION

Airway parasitic infestations with *Paragonimus, Aelurostrongylus,* or *Capillaria* can occur. Therefore fecal examination, including a flotation with or without centrifugation (to find *Paragonimus* and *Capillaria* eggs), and a Baermann sedimentation (to detect *Aelurostrongylus* first-stage larvae) is recommended as part of the diagnostic work-up.

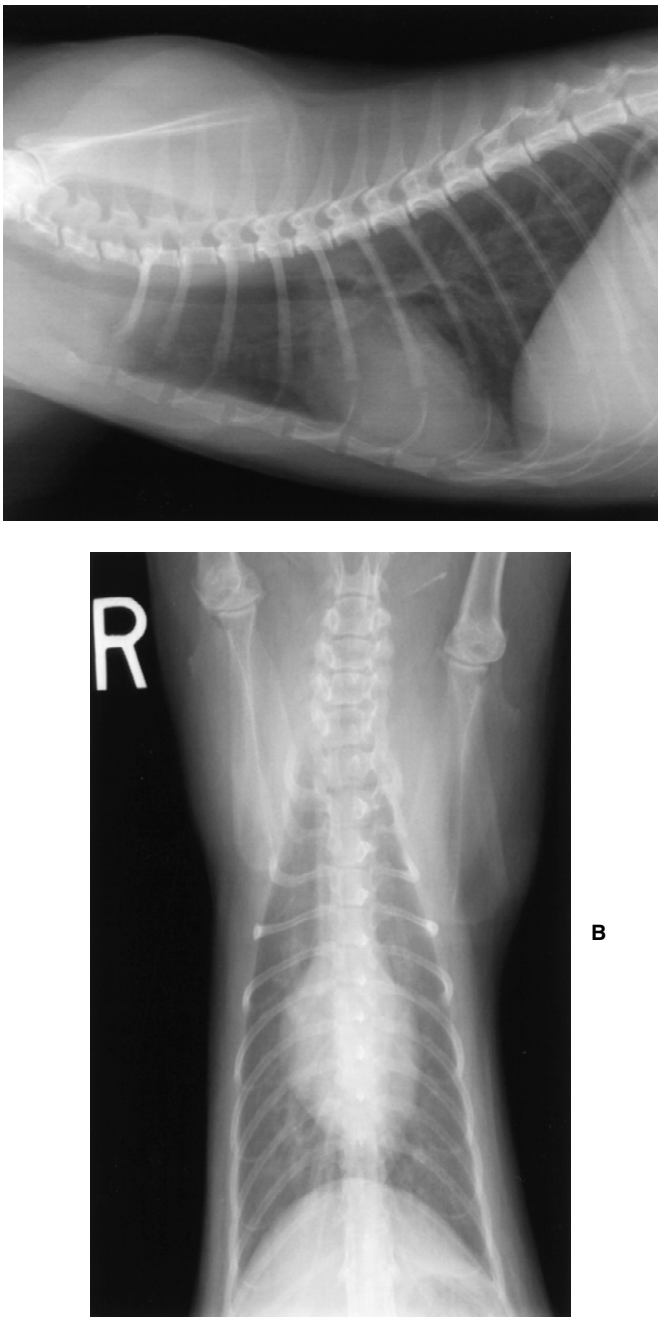

Figure 53-1. A, *Lateral and* ***B,*** *ventrodorsal thoracic radiographs of a cat with bronchial disease. Notice the prominent bronchiolar radiographic pattern, especially in the caudal lung fields, seen as multiple doughnuts and railroad tracks.*

RADIOLOGY

Routine thoracic radiographs can be within normal limits in some cats with bronchial disease, and the diagnosis should not be ruled out based solely upon these results. The classic lung pattern in a cat with bronchial disease includes evidence of bronchial wall thickening (doughnuts or railroad tracks) because of airway inflammation (Figure 53-1). Air trapping may also be evident in the peripheral lung fields. Signs suggestive of lung hyperinflation and air trapping include increased lucency to the lungs and flattening or caudal displacement of the diaphragm (Figure 53-2). A small percentage of cats may have evidence of right middle lung lobe atelectasis, indicated by opacity in this lobe and a right mediastinal shift.[7,8] Rarely, cats with bronchial disease may develop pneumothorax or rib fractures secondary to chronic airway compromise and respiratory distress.[28]

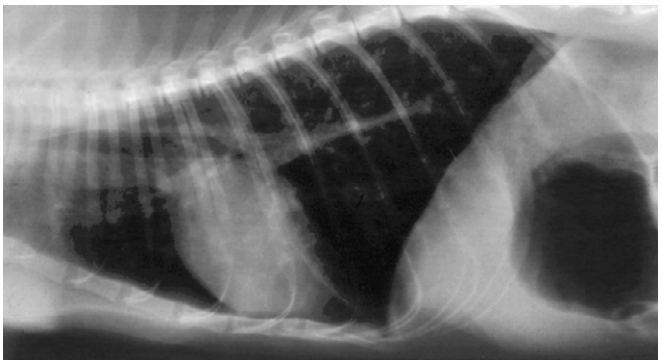

Figure 53-2. *Lateral thoracic radiograph of a cat with bronchial disease. Notice the lung hyperinflation as evidenced by the flattened, caudally-displaced diaphragm. A gas-filled stomach, caused by aerophagia, can be seen on this view.* (Courtesy Dr. John D. Bonagura, The Ohio State University, Columbus, Ohio.)

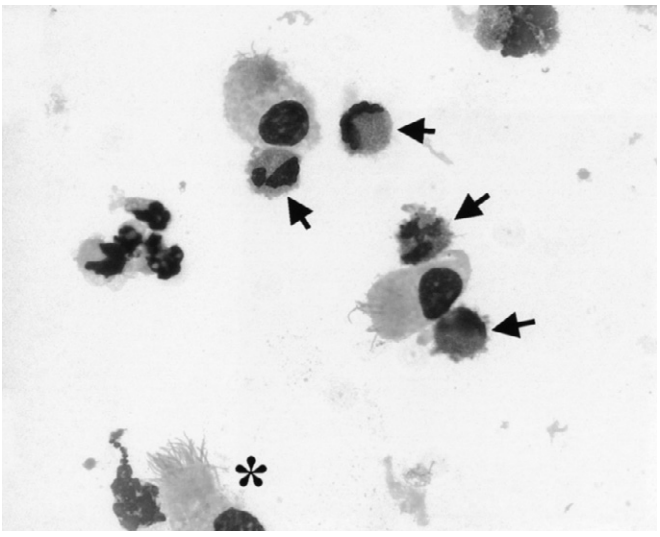

Figure 53-3. *Photomicrograph of transtracheal wash fluid cytology obtained from the cat described in Figure 53-1. Several ciliated, columnar epithelial cells (*) are seen, along with many eosinophils* (arrows) *(100×). The cytological differential count revealed 45% eosinophils and 40% neutrophils, and no evidence of infectious agents.*

ENDOTRACHEAL WASH (ETW)/ BRONCHOALVEOLAR LAVAGE (BAL)

Cytologic examination of airway samples from asthmatic cats generally provides evidence of airway inflammation, with increased numbers of eosinophils and/or neutrophils (Figure 53-3). A preponderance of eosinophils may be found in tracheobronchial washings from healthy cats,[23,29-31] therefore eosinophilic airway washes are not pathognomonic for asthma or bronchial disease. In a recent study, the number of eosinophils and neutrophils in BAL samples of cats with bronchopulmonary disease correlated well with disease severity.[6]

Despite the fact that a role of infectious agents in the pathogenesis of bronchial disease has not been established, aseptically handled samples of ETW or BAL fluid should be submitted for culture of aerobic bacterial and mycoplasmal organisms and for antibacterial susceptibility testing. A mixed population of aerobic bacteria has been cultured from cats with asthma, but similar bacteria can be cultured from the airways of healthy cats, so the significance of a positive culture is unknown at this point.[6] These bacteria may be colonizing the airways rather than causing true pulmonary infection. A positive culture result could be considered more meaningful if a pure culture with a large number of organisms is grown on primary culture plate media (not enrichment broth), or if intracellular bacterial organisms or a preponderance of one type of bacterium are visualized upon ETW or BAL cytology. Since oropharyngeal bacteria can contaminate samples, cytology should be carefully evaluated for the presence of squamous cells, indicating that oropharyngeal contents have likely been deposited in the sample.

Isolation of *Mycoplasma* spp. is difficult and requires specialized growth media. Therefore, before collection of samples, it is recommended that the laboratory be contacted for information on proper submission of airway specimens. The role of *Mycoplasma* in feline respiratory disease remains unknown; however, these species are potentially important because *Mycoplasma* has been cultured from airways of cats with respiratory disease[7] but not from healthy cats.[23,24]

PULMONARY FUNCTION TESTS

Pulmonary function testing is commonly utilized in human medicine for the evaluation of respiratory disease, including use in the diagnosis and monitoring of therapeutic response in patients with asthma or chronic bronchitis. Parameters such as vital capacity, airway resistance, total lung capacity, and forced expiratory volume can be measured to evaluate airway disorders and to assess response to therapy.[32] Because patient cooperation with pulmonary function tests is limited in veterinary species, identical evaluations cannot be completed; however, some methods have been developed to examine airway mechanics in anesthetized or awake cats. In awake animals, measurement of flow-volume loops during tidal breathing can be used as a noninvasive means of evaluating pulmonary function. The use of tidal breathing flow volume loops has confirmed that cats with bronchial disease have an increased ratio of expiratory time to inspiratory time, decreased area under the expiratory curve, lower expiratory flow rates, decreased tidal breathing expiratory volumes, and increased mean lung resistance.[33] These changes in resistance during the expiratory phase of respiration are compatible with lower airway obstructive disease.

Additional techniques are being investigated that would allow noninvasive measurements of pulmonary mechanics, and use of a whole-body plethysmograph has proven useful in assessing airway reactivity in normal cats.[34] Application of this technique to cats with bronchial disease would allow confirmation of airway

hyperresponsiveness and quantification of the response to bronchodilators. Other measures of airway responsiveness and pulmonary mechanics require anesthesia and therefore have not been applied to a wide number of clinical cases. However, one study of cats with bronchial disease showed that lung resistance increased with disease severity, providing an objective means for assessment of disease.[6]

Pathological and Histopathological Findings

Eosinophilic and/or neutrophilic bronchial inflammation with smooth muscle hyperplasia are common histopathological findings in cats with bronchial disease. Hyperplasia and hypertrophy of goblet cells and submucosal glands are also common features, as is subsequent mucus accumulation with inflammatory cellular debris in the bronchial lumen (Figures 53-4 and 53-5). Epithelial erosion can be seen, especially in severe cases. Lobular and bullous emphysema, which may occur as a possible consequence of chronic obstructive airway disease, has been described in a small number of cats with bronchial disease.[10] Similarly, bronchiectasis has been reported in some cats with chronic bronchial disease.[10,12]

Treatment

There is no consistently reported strategy for the treatment of bronchial disease in cats, and very little research has been completed to evaluate specific treatments in cats. An expert panel has determined four components of asthma treatment in humans:

1. Use of objective measurements of lung function to assess asthma severity and to monitor the course of therapy
2. Establishment of environmental control measures to avoid or eliminate factors that precipitate asthma symptoms or exacerbations
3. Utilization of comprehensive pharmacologic therapy for long-term management of disease that is designed to reverse and prevent airway inflammation and to manage asthma exacerbations
4. Employment of patient education that fosters a partnership among the patient, his or her family, and clinicians[35]

A similar approach modified for veterinary patients and clients would be recommended in the treatment of cats with bronchial disease.

EMERGENCY MANAGEMENT

In cats that present with acute, severe respiratory distress (e.g., cyanosis and open mouth breathing), diagnostic tests should be delayed, stress should be minimized, and an oxygen enriched environment (oxygen cage with Fio_2 of at least 40%) should be provided. Initially, bronchodilator therapy (e.g., terbutaline 0.01 mg/kg IV, IM, or SC) should be used to combat acute bronchoconstriction. Inhaled bronchodilator medication (e.g., albuterol) may be used if the equipment is available and if the patient tolerates this method of administration. Visual inspection of respiratory rate and effort

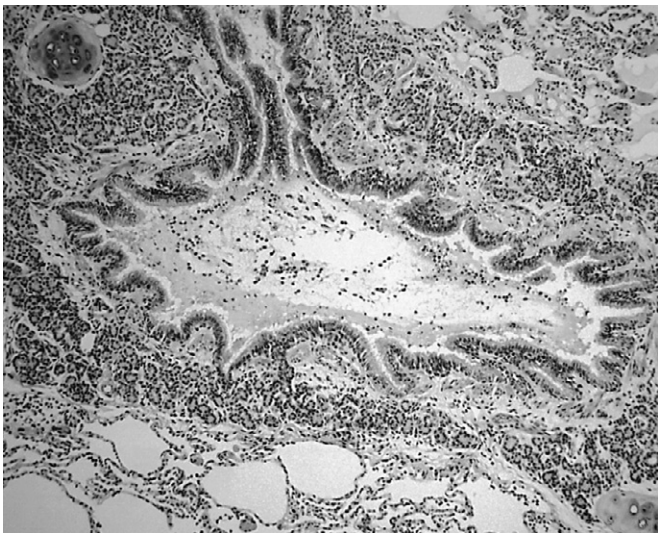

Figure 53-4. *Histological section of a bronchus from a cat with bronchial disease. Note accumulation of mucus and inflammatory cells in the lumen, epithelial hyperplasia and folding, smooth muscle hypertrophy, and increased numbers of mucous glands (200×).* (Courtesy of Dr. Margaret A. Miller, University of Missouri, Columbia.)

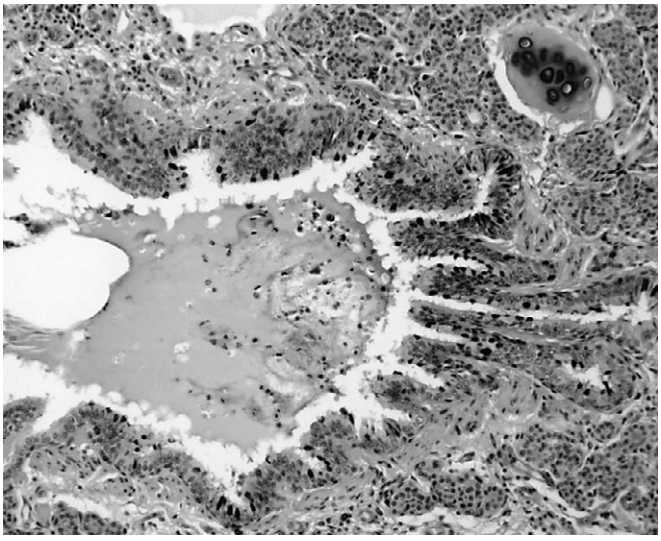

Figure 53-5. *Histological section of a bronchus from a cat with bronchial disease. Note accumulation of mucus and inflammatory cells in the lumen, epithelial hyperplasia and folding, smooth muscle hypertrophy, and increased numbers of mucous glands. The Alcian blue/PAS stain (pH 2.5) highlights the numerous epithelial goblet cells (400×).* (Courtesy of Dr. Margaret A. Miller, University of Missouri, Columbia.)

during the first hour of therapy will allow assessment of the therapeutic response. A positive response is expected within 30 to 45 minutes, and is indicated by a decrease in respiratory frequency and effort. If the cat does not respond favorably in that time, a repeated dose of bronchodilator medication is warranted and a rapidly acting corticosteroid (e.g., dexamethasone 0.25 to 2 mg/kg IV or IM) should be administered. If no response is seen to this combination of drugs, alternate causes for dyspnea should be investigated. If the cat remains severely dyspneic, intubation and positive pressure ventilation with 100% oxygen may be needed to facilitate diagnostic testing, including radiography, cardiac evaluation, and respiratory tract cytology and bacteriology.

Once the patient is stable, a complete diagnostic evaluation for feline asthma as outlined above is recommended. If corticosteroids have been administered to control respiratory distress, airway cytology may lack the classic inflammatory response and may therefore be of diminished benefit.

Atropine is an effective bronchodilator; however, its anticholinergic effects can cause tachycardia and inspissation of bronchial mucus that might worsen airway obstruction. Epinephrine is also a potent bronchodilator, but it should only be used in cats that are dying or those in which cardiac disease has been ruled out because its alpha and beta-1 agonist activities may cause arrhythmias, vasoconstriction, and systemic hypertension. Aminophylline exhibits weaker bronchodilatory activity than terbutaline and is not recommended as the first choice in emergency situations. Beta-blockers (e.g., propranolol and atenolol) should not be administered to cats in which bronchial disease is a possible cause for respiratory distress. Cats rely heavily on sympathetic tone for bronchodilation, and inhibition of beta-agonist activity may have dire consequences in these patients.

Initiation of emergency medications at home may be recommended in cats with a previous diagnosis of asthma that experience frequent asthma attacks. An injection of terbutaline or a dose of inhaled albuterol can be given by the owner at the onset of acute dyspnea; however, emergency veterinary attention should be sought if no response is seen within 15 to 30 minutes. It is important to stress that proper diagnosis and chronic therapy should be pursued in such cases.

CHRONIC THERAPY

Decrease Allergen/Irritant Exposure

Because environmental allergens and nonspecific irritants may be important risk factors in the initiation and exacerbation of asthma in cats, asthma care may be improved by identification of offending allergens and institution of steps to avoid these in the environment. A therapeutic trial of isolation in one room where allergens are minimized may help determine the degree of effect that allergens play in an individual cat's bronchial disease. Similarly, switching the cat's litter, especially eliminating dust and perfumes, may assist in diminishing clinical signs of asthma.

Corticosteroids

The most consistent, reliable, and effective treatment for feline asthma or bronchitis is high-dose (initially), long-term, oral corticosteroids. Reduction of underlying inflammation is recommended even in relatively asymptomatic cats because human asthmatics often have evidence of chronic airway inflammation even when clinical signs are not present.[36] Inhaled corticosteroids are utilized principally in humans, thereby allowing the topical use of an extremely effective drug without the degree of harmful side effects that systemic corticosteroids can induce. Cats can be treated with inhaled corticosteroids using pediatric spacers and aerosolization chambers, but administration can be expensive, labor-intensive, and may not be well tolerated. Fortunately most cats are relatively resistant to the health-threatening side effects of systemic corticosteroids, which can be used safely in the majority of cats. Oral prednisone or prednisolone (1 to 2 mg/kg PO BID for 7 to 10 days) is recommended, with a slow taper of the dose over 2 to 3 months in cats that respond. No benefit has been reported for the use of longer-acting oral corticosteroids. Long-acting repository glucocorticoids can be used as an alternative when owners are unable to medicate the cat orally. Methylprednisolone acetate (Depo-Medrol®) can be given at a dose of 10 to 20 mg/cat IM or SC every 2 to 4 weeks.

Bronchodilators

Bronchodilators seem to be most useful in human and feline patients during acute exacerbations caused by bronchoconstriction. These agents may also be utilized in chronic management in an attempt to decrease the dose of corticosteroids needed to control clinical signs, especially if corticosteroid-induced side effects (e.g., diabetes mellitus or concurrent infectious diseases) become problematic. The primary goal of therapy, however, should be to control the underlying airway inflammation, and substitution of systemic corticosteroids by inhalant corticosteroids may be more appropriate in these situations. Bronchodilators may also be added to chronic therapy if corticosteroid administration alone does not induce a sufficient decrease in symptoms.

Bronchoconstriction can be reversed using beta-2 adrenergic agonists (e.g., terbutaline 0.625 mg PO BID) in some cats with asthmatic signs that have airway hyperreactivity or increased airway resistance.[6,37] Cats that have airway obstruction due to remodeling of the airways are less likely to show a positive response. Beta-agonists are effective for quick relief of bronchospasm because of their direct action to induce smooth muscle relaxation, and injectable terbutaline is recommended for management of acute exacerbations of asthma. Potential side effects of terbutaline administration include tachycardia, agitation and hypotension due to slight beta-1 agonist activity.

Methylxanthine derivatives (e.g., theophylline and aminophylline) have been used extensively, and may be useful in some cats with bronchopulmonary disease. This class of drug appears to cause bronchodilation via

a combination of mechanisms. Theophylline may inhibit a phosphodiesterase isoenzyme, increasing cAMP concentrations and causing bronchodilation; it may inhibit adenosine, a mediator of bronchoconstriction; or it may interfere with intracellular calcium mobilization. Other positive effects on the respiratory tract include inhibition of mast cell degranulation and increased strength of respiratory muscles. Pharmacokinetic studies have established a dose for long-acting oral preparations of theophylline (Theo-Dur® tablets or Slo-Bid® gyrocaps) of 20 to 25 mg/kg PO every 24 hours in the evening.[38,39] These drugs are not currently on the human market, and it is not known whether generic long-acting theophylline products are bioequivalent in the cat. A suggested initial dosage of generic sustained-release theophylline is 10 mg/kg PO once daily in the evening.

Cyproheptadine

In vitro studies have shown that serotonin, a mediator released from mast cells, contributes to airway smooth muscle contraction; and that cyproheptadine, a serotonin antagonist, significantly attenuates this response.[5] Reports have not been published to corroborate this response in the clinical setting; however, it is possible that blockade of serotonin might alleviate clinical signs in vivo. A trial of cyproheptadine (1 to 4 mg/cat PO BID) can be utilized in cats in which high doses of corticosteroids and bronchodilators are not effective in eliminating the clinical signs of cats with bronchial disease. Potential side effects of cyproheptadine are related to its other antiserotonin effects, and include lethargy and increased appetite. Approximately $2^1/_2$ days are required to reach steady-state drug concentrations, and several more days may be required to appreciate a clinical response.[40]

Cyclosporine

With knowledge of the role activated T cells play in the pathophysiology of asthma, it can be theorized that cyclosporine, a potent inhibitor of T cell activation, may be effective in asthma therapy. In cats with experimentally-induced asthma, cyclosporine therapy diminished structural derangements in airway histopathology and attenuated functional changes in airway reactivity.[3] Cyclosporine therapy might be indicated for those cats with especially severe or end-stage bronchial disease, or for those that are unresponsive to more standard medical management, although no clinical trials have been carried out to date. Based upon studies in experimentally-induced feline asthma,[1,3] the initial recommended dose is 10 mg/kg PO BID (olive oil-based Sandimmune®) or 3 mg/kg PO BID (microemulsion Neoral®); however, cyclosporine blood levels should be checked weekly until a stable, therapeutic dose (500 to 1000 ng/ml whole blood trough level) is achieved, and then evaluated monthly thereafter. Experience with cats receiving renal transplants indicates that lower doses of cyclosporine and whole blood trough levels between 250 and 500 ng/ml may achieve immunosuppression.[41] Continued monitoring of blood levels is important because the oral absorption of cyclosporine is unpredictable. Feeding a high-fat meal at the time of cyclosporine administration may increase its oral bioavailability.

Leukotriene Modifiers

Leukotrienes are inflammatory mediators that may contribute to the pathophysiology of certain forms of asthma in humans and in some animal models by causing airway smooth muscle contraction, increased microvascular permeability, stimulation of mucus secretion, decreased mucociliary clearance, and by acting as eosinophil chemoattractant agents.[42] The role of leukotrienes in the pathogenesis of feline bronchial disease has not been established, and contradictory results have been reported with measurement of urine leukotriene metabolite concentrations in cats with asthma.[43,44] While several clinical studies have shown modest clinical improvement in asthmatic people using leukotriene receptor antagonists[45] or inhibitors of 5-lipoxygenase,[46] an *in vitro* study using feline airways demonstrated no decrease in airway contraction in response to a 5-lipoxygenase inhibitor.[5] Therefore, until more research is completed in cats, these medications cannot be recommended at this time.

Antiinterleukin-5 Antibody

Interleukin-5 (IL-5), a cytokine secreted from activated T cells, appears to participate in asthma pathology by inducing eosinophil migration into the airways and bronchial hyperreactivity.[14] The IL-5 gene of cats has been sequenced[47]; however, the role of this mediator in feline bronchial disease has not yet been elucidated. Preliminary research in cats with experimentally induced asthma treated with a nebulized anti-IL-5 antibody appears promising,[48] but more information is required before its use can be recommended.

Antibiotics

Respiratory bacterial infections are rarely associated with clinical bronchial disease in cats, and bacteria may be cultured from tracheobronchial washes in healthy cats.[6] Therefore, antibiotics are rarely indicated or effective for the treatment of asthma in cats. Exceptions include cats in which a pure, heavy growth of bacteria is grown on the primary culture plate; and those in which Mycoplasma spp. is cultured. Mycoplasma spp. have not been found to colonize the lower respiratory tract of healthy cats[23,24]; therefore, a trial of doxycycline or other anti-mycoplasma antibiotics might be considered pending culture results.

Inhaled Medications

Medications for respiratory conditions given via inhalation offer the advantage of high drug concentrations within the airways while attenuating systemic side effects. Inhaled corticosteroids and bronchodilators are the current standard of care for human asthmatic patients. Controlled clinical trials on the use of inhaled medications in cats have not yet been reported; however, anec-

dotal recommendations have been presented.[43] The primary disadvantage of utilizing this method of treatment in feline patients is their lack of tolerance of the face mask that is placed over the nose and mouth, especially when symptoms of respiratory distress are present. The use of inhalant medications in cats requires three pieces of equipment:

1. The metered dose inhaler (MDI) that contains the medication
2. A spacer into which the medication is sprayed so that activation of the MDI does not need to be coordinated with inhalation
3. An anesthetic face mask that connects the spacer with the cat's mouth and nose.

This type of apparatus is used to treat infants or children suffering from asthma. The recommended protocol for cats entails fitting the three pieces of equipment together, actuating (spraying) the MDI to fill the spacer with medication, then placing the face mask over the cat's nose and mouth for 7 to 10 inspirations.[43] Recommended inhaled medications include albuterol (Ventolin®, Proventil®), a short-acting beta-2 agonist bronchodilator used for acute worsening of symptoms; salmeterol (Serevent®), a long-acting beta-2 agonist bronchodilator; and/or fluticasone propionate (Flovent®, 110-220 μg/puff), a corticosteroid utilized as chronic therapy.[43] Future clinical reports on the response to inhaled medication will help guide therapy. In general, the type of medication and frequency of administration need to be tailored to each patient's symptoms and concurrent oral medications, and adjusted based upon response.

Monitoring

Evaluation of clinical response to treatment is the usual and most practical means of monitoring cats with bronchial disease. Effective therapy should eliminate or significantly minimize the clinical signs. Repeating thoracic radiographs to compare with those taken prior to therapy provides an objective means to evaluate the response to treatment. The diagnosis of bronchial disease should be questioned if a significant response is not appreciated within 1 to 2 weeks of initiating proper treatment. Ensuring that the owner has been able to medicate the cat at home is imperative in the evaluation of clinical response to therapy. If a cat has not responded to proper therapy and other diseases have been ruled out, a trial of injectable methylprednisolone acetate should be considered. Measurement of lung function, if available, would provide an objective evaluation of both initial disease severity and response to therapy.

Outcome and Prognosis

The majority of cats with bronchial disease respond to appropriate therapy, yet it should be assumed that lifelong treatment may be required. Spontaneous resolution of asthma is relatively common in children that grow out of their asthma as they become adults. Although this scenario has not been documented in cats, some feline patients with bronchial disease can be tapered off their medications with no apparent return of symptoms. A small percentage of cats may succumb to acute, severe bronchoconstriction and subsequent respiratory distress, especially when proper emergency therapy is delayed. Some owners may choose euthanasia for cats that do not quickly respond to chronic therapy, those that do not tolerate the administration of medications, or those that experience severe drug side effects.

Areas for Further Research

No clinical studies have been published comparing different treatment modalities for bronchial disease in cats. Most of the information in this area is extrapolated from research in human patients, and opinions regarding therapy in cats are shared from veterinarian to veterinarian via anecdotal reports. One difficulty causing the shortfall of research is the lack of an easily obtained, readily available, objective method for obtaining a definitive diagnosis.

Asthma appears to be more prevalent in some families, and children that have a close relative with asthma or allergies have a higher incidence of asthma. Identification of genes associated with asthma will allow further understanding of its pathophysiology, and can improve diagnostic capabilities and early therapeutic intervention.

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CHAPTER 55

Bronchopulmonary Dysplasia

John P. Hoover • Michael S. Davis

Definition and Etiology

Dysplasia is defined as abnormal cellular or tissue development. Bronchopulmonary tissues that may become dysplastic include those in the tracheobronchial tree (i.e., cartilage, fibrous connective tissue, elastin, collagen, and smooth muscle), mucosa (i.e., respiratory epithelium and bronchial glands), alveoli, interstitium (i.e., fibrocytes and elastin) and vessels (i.e., endothelium, elastin, and smooth muscle).

In human medicine, the term bronchopulmonary dysplasia (BPD) refers to a specific syndrome in neonates originally described in 1967 as a chronic, noninfectious respiratory insufficiency (i.e., hypoxia, hypercapnia, increased pulmonary resistance, and decreased pulmonary compliance) caused by prematurity, oxygen toxicity, and barotrauma.[1] This condition is a sequela to respiratory distress syndrome (RDS), in which there is abnormally high surface tension within the alveoli, resulting in alveolar collapse and filling with fluid. In some patients with RDS a thickened, glassy, hyaline-like membrane consisting of clotted exudate[2] covers the alveolar walls and respiratory airways, leading to the term hyaline membrane disease (HMD). The formation of hyaline membranes begins within hours in the injured neonate lung.[3]

The term BPD has been associated in human medicine with short-term life-threatening pulmonary disease.[4,5] With increasing survival of patients with BPD, a new definition has evolved to encompass any chronic lung disease (CLD) of neonates resulting from incomplete or inappropriate repair of inflamed and injured lung tissue.[3,4] RDS has been recognized in foals, calves, and piglets,[6] and a clinical syndrome analogous to human neonatal BPD could theoretically follow in the lungs of animals.

Pathogenesis

BPD is multifactorial, but the factors of greatest importance in its development are prematurity, barotrauma, and oxygen toxicity.[3-5] Neonate lungs, especially preterm, are not fully developed at birth.[4,5] In humans, immaturity of pulmonary cell junctions,[7] low levels of protective antioxidant enzymes,[8] decreased surfactant levels,[9] and decreased factors that promote lung differentiation and regeneration[10] appear to contribute to the development of BPD. Immature lungs in premature neonates are deficient in alveolar surfactant phospholipids, which increases airway surface tension leading to alveolar collapse and development of hyaline membrane disease.[11,12] BPD in humans has been primarily associated with preterm infants that develop respiratory distress and have been treated with high levels of inspired oxygen (Fio_2) and positive pressure ventilation (PPV).[3-5,12,13]

PPV expands collapsed alveoli in the atelectatic surfactant-deficient lung of neonates with severe RDS. However, overdistention of the small terminal airways is a source of ongoing barotrauma, bronchiolar ischemia, and necrosis.[3,14] BPD has also been seen in term human infants that received PPV for pneumonia, aspiration, and patent ductus arteriosus (PDA).[15] Damage to the lung by oxygen free radicals due to oxygen toxicity[3,13] may be more important than barotrauma in producing lung damage in newborn piglets.[16] High inspired oxygen concentrations facilitate increased generation of oxygen free radicals through the hypoxanthine-xanthine oxidase system.[4,17-21] Both surfactant production and function are altered by these reactive oxygen species, making the lungs more vulnerable to injury.[21] Therefore, oxidative stress appears to play a pivotal role in the development of CLD or BPD.[3] Damage by peroxidation can also occur in the absence of oxygen toxicity from oxygen radicals that are produced by activated phagocytes.[22] Regardless of the source, oxygen radicals increase the damage to many different cellular compounds and exacerbate preexisting pulmonary dysfunction.[4]

With pulmonary endothelial damage from inflammation, there is leakage of plasma albumin, as well as leakage and activation of coagulant proteins into the airways, interstitium, and alveoli.[23] Increased hyaluronan and decreased available plasminogen favor fibrin deposition in the damaged pulmonary tissues and airways.

Polymorphonuclear leukocytes (PMNs) play an important part in the development of lung injury.[24-26] Activated PMNs generate oxygen free radicals, release secretory hydrolases[27-30] and elastase,[31,32] partially inactivate the primary pulmonary proteinase inhibitor alpha-1 proteinase,[33,34] and generate arachidonic acid metabolites.[35,36] The resulting inflammation is associated with pulmonary epithelial leakage of albumin and activated

coagulant proteins, and may exaggerate the repair process and promote development of pulmonary fibrosis.[22] PMN elastase is the main proteolytic enzyme for pulmonary interstitial, bronchial, and vascular elastin. Elastin is a critical component of the lung interstitium, participates in the maintenance of elastic recoil and stabilization of alveolar volume, and helps to maintain small airway and blood vessel patency during breathing.[37,38] Elastase-proteinase inhibitor imbalance has been associated with destruction of lung connective tissue and fibrosis characteristic of BPD.[39-43]

Other cells (e.g., mast cells and alveolar macrophages) may also play a role in the initiation of oxidative stress and BPD. Tryptase is a serine protein specific to mast cells that has been shown to be a potent fibroblast mitogen.[44] Tryptase-positive mast cell hyperplasia in BPD suggests a role of mast cells, as well as tryptase in the pathogenesis of the disease.[44] Pulmonary alveolar macrophages (PAMs) are potent sources of free radicals.[22,45,46] Endothelin-1 synthesized and secreted by the tracheal epithelial cells and/or PAMs in rabbits has a priming effect on PAMs to produce superoxide anion and may be correlated with the development of BPD.[47] Activated PAMs produce fibronectin, which is a potent chemoattractant, attachment factor and growth factor for fibroblasts.[22] Fibronectin is increased in adults that develop fibrotic lung disease and in the tracheal effluent of infants that develop BPD.[48] Overstimulation of PAMs and increased fibronectin release is associated with pulmonary fibrosis.[22]

Endogenous antioxidant compounds such as vitamins A, C, E, and glutathione normally scavenge free radicals.[49] Vitamin A (retinol) also promotes epithelial regeneration during recovery from lung injury in BPD.[50] Vitamin A deficiency results in lung histopathology similar to BPD.[51] Magnesium deficiency increases the susceptibility of cells and tissues to peroxidation, exacerbates inflammation, decreases the immune response, exaggerates release of catecholamines in stress, and decreases energy metabolism.[52] Many of the chemical compounds vital to the antioxidant systems (e.g., vitamin E and Mg) are transferred from dam to offspring very late in gestation and thus may be deficient in neonates, particularly premature neonates.[3] Maintenance of these compounds is highly dependent on nutrition, and inadequate food intake may make premature neonates more susceptible to lung injury by free radicals.[53]

Polyunsaturated fatty acids (PUFAs) and plasmalogens are the two main substrates for lipid peroxidation in surfactant.[54] Neonatal animals contain triglycerides that are richer in PUFAs than older animals.[55,56] Supplementation with n-3 PUFAs may suppress synthesis of cytokines (e.g., IL-1β and TNF-α) and appears to improve tolerance to oxygen toxicity in animals.[57,58]

Pathology

The pathological lesions of BPD appear to result from disordered growth and repair. The structural immaturity of the neonatal lung is a key component in the development of BPD. Lung maturation occurs late in gestation and progresses through the neonatal period.[59] Elastin production and normal deposition is necessary for the development of alveoli, and elastin metabolism is altered in experimental models of BPD.[37] At term birth, the alveoli are simple saccules that mature to more complex alveolar acini during the first few days to weeks of life.[59] Inflammation during this period can disrupt normal alveolar development, and persistence of the relatively inefficient saccular architecture.[59,60]

BPD consists of an early inflammatory reaction with proliferation and hypercellularity that is followed by variable healing and fibrosis.[22] An abnormal balance between elastin production and breakdown[39,40,43] by elastase from PMNs,[22] along with abnormal distribution and deposition of elastin and collagen in the immature lung, contributes to the abnormal pattern of alveolar growth and differentiation.[61-63]

BPD in humans is currently divided into three phases with different but overlapping pathologic and histologic patterns[5,61,64]: (1) an early inflammatory phase, followed by (2) a subacute or reparative phase, and then (3) a chronic phase with remodeling of airways (Table 55-1).

EARLY INFLAMMATORY PHASE

This phase is characterized by an irregular distribution of hyperinflation and atelectasis. Interstitial edema and inflammation occur, with epithelial necrosis of the small conducting and terminal airways. This is followed by interstitial and bronchiolar fibrosis, and then prominent areas of hyperinflation. Histologically there is resorption of fibrotic tissue without complementary alveolization, which leads to hyperexpanded or oversimplified alveoli.[5,61]

SUBACUTE FIBROPROLIFERATIVE (REPARATIVE) PHASE

This phase is characterized histologically by an irregular pattern of atelectasis and hyperinflation with hyperplasia of type II pneumocytes, hypertrophy of bronchial and bronchiolar smooth muscle, and interstitial and perialveolar fibrosis. During this phase the pulmonary tissues may undergo a repair process[5] involving platelets, PMNs, and alveolar macrophages.[22] Normal saccules and alveoli are interposed between foci of alveoli with thickened overexpanded saccular walls, increased collagen, and myofibroblasts.[5]

CHRONIC FIBROPROLIFERATIVE (REMODELING) PHASE

This phase is characterized by hyperexpansion and cystic-looking lungs with areas of emphysema, thickening and fibrosis of the interstitium, and replacement of type I pneumocytes by type II cells.[12] Airway remodeling may occur histologically[5] and tracheo- and bronchomalacia with airway collapse is a common finding in infants.[65,66]

The changes in developing alveoli and the interstitium are most severe, characterized by areas of atelectasis and hyperinflation that can lead to emphysematous

TABLE 55-1 **Progression of Radiographic, Gross, and Histological Findings with Bronchopulmonary Dysplasia (BPD)***

Phases of BPD	Radiographic Findings	Gross Findings	Histological Findings
Acute Inflammatory	Atelectasis	Atelectasis	Atelectasis and hyperinflation of alveoli
(Less than 1 week)	Reticulogranularity	Pulmonary edema	Peribronchial and perivascular edema
	Air bronchograms		Interstitial and bronchiolar inflammatory infiltrates
	Pulmonary interstitial edema		
Subacute Fibroproliferative	Areas of atelectasis	Irregular pattern of atelectasis and emphysema	Hypertrophy of bronchial smooth muscle
(Reparative)	Areas of hyperinflation		Interstitial, bronchial and perialveolar fibrosis
(1 to 3 weeks)	Increased air bronchograms		Hyperplasia of type II pneumocytes and decreased alveoli
	Alveolar densities		
			Airway epithelial necrosis and squamous metaplasia
Chronic Fibroproliferative	Cystic-appearing lungs	Hyperinflated lungs	Interstitial thickening and fibrosis
(Remodeling)	Hyperexpansion (hyperlucency)	Bullae and cyst formation	Replacement of type I with type II pneumocytes
(1 month or longer)	Cardiomegaly (in some)	Airway collapse	Tracheobronchomalacia

*Modified from reports of human infants with BPD.[5,12,71]

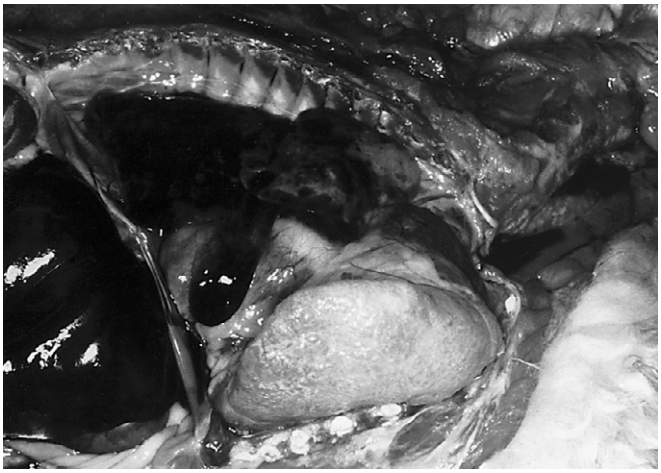


Figure 55-1. *Gross postmortem showing a hyperinflated cranial portion of the left cranial lung lobe with bullae formation projecting to the right side, and atelectasis of the right middle and caudal lung lobes in a 5-month-old chow chow with bronchial cartilage dysplasia.* (From Hoover JP, Henry GA, Panciera RJ: Bronchial cartilage dysplasia with multifocal lobar bullous emphysema and lung torsions in a pup, *J Am Vet Med Assoc* 201(4):600,1992.)

blebs.[3] Alveolar interstitial support (elastin) is disordered and replaced by fibrosis.[38,39,41,42,63] The alveoli are markedly decreased in number and enlarged[14] due to the failure of normal sacculation postnatally[59] and septal destruction with fibrosis.[14] With septal distraction there may be bullae formation[43] (Figure 55-1).

In the large airways, there is submucosal glandular hypertrophy, increased smooth muscle, squamous metaplasia of the mucosal epithelium, submucosal fibrosis, inflammatory infiltrates, and granulation tissue.[14,67] In severe cases of BPD airway necrosis occurs with intraluminal debris accumulation.[68] The bronchioles have marked smooth muscle hypertrophy, focal mucosal squamous metaplasia, and marked chronic inflammatory infiltrates with fibrosis.[14,67] Peribronchiolar and perivascular edema and fibrosis occur, and commonly, bronchiolar collapse.[65,66]

Muscular hypertrophy of the medial layer and endothelium of the arterioles is accompanied by fibrosis. Irreversible destruction of the capillary bed decreases vascular cross-sectional area[14] and leads to increased pulmonary vascular resistance and cor pulmonale.[3] The collective result is loss of capillary surface area and pulmonary hypertension, and thickening of the airways (smooth muscular hypertrophy and fibrosis) with luminal narrowing.[69]

Pathophysiology

Initially, neonates with RDS have widespread areas of atelectasis. Consequently the overall surface available for gas exchange is reduced and the lung is stiff, resulting in hypoxia and hypercapnia. With PPV, especially with increased Fio_2, the small airways are damaged and areas of hyperinflation and emphysematous blebs develop.[3] Surfactant deficiency results in areas of alveolar collapse and atelectasis, and development of hyaline membrane disease.[11] Oxidative stress can lead to damage to surfactant and membrane phospholipids, resulting in the release of arachidonic acid and eventual production of proinflammatory eicosanoids.[70] Free radicals can inactivate surfactant, causing an increase in the work of breathing, and can impair the nonspecific immune functions of surfactant.[4,21]

In the early inflammatory phase of BPD, mechanical and oxidative stress injury to the respiratory epithelium and vascular endothelium facilitates plasma transudation into the airways, obstructing the lumen and interstitium, and contributing to perivascular, peribronchiolar and interstitial pulmonary edema.[2,14] Atelectasis with increased lung water in the form of interstitial edema

further decreases lung compliance, compromises gas diffusion, and promotes extension of the ongoing inflammatory processes in the alveolar interstitium.

BPD progresses into the subacute healing or reparative phase with bronchial gland and smooth muscle hypertrophy, airway epithelial metaplasia and granulation following necrosis, peribronchial and perivascular edema, and intraluminal airway debris. Airway smooth muscle hypertrophy and excess mucus production lead to increased pulmonary resistance, particularly at the level of the small bronchioles,[5] which is complicated by decreased capacity for mucociliary clearance because of the squamous metaplasia of the airway epithelium.[3] Areas of atelectasis and hyperinflation result in decreased lung compliance. Airway narrowing and obstruction results in increased respiratory effort, especially on expiration.

In the chronic remodeling phase of BPD the interstitium in both the atelectatic and overinflated areas is widened and contains undifferentiated mesenchymal cells, myofibroblasts, and relatively fewer cells and more collagen and elastin around expanded and enlarged alveoli,[60,63] resulting in low lung compliance.[71] Hyperreactivity of airway smooth muscle is a common feature of BPD in humans.[3] Therefore, airway resistance is increased in BPD, resulting in greater residual volume (RV) and RV/total lung capacity ratio consistent with air trapping.[5]

Ventilation distribution is abnormal in BPD. Areas of atelectasis (perfused but not ventilated) alternate with areas of hyperinflation (ventilated but not perfused), leading to marked ventilation/perfusion (V/Q) mismatch.[71] V/Q mismatch is the primary reason for the hypoxemia often found in BPD.[3] Hypercapnia is also common because of alveolar hypoventilation, increased functional dead space, and increased V/Q mismatch.[5] A persistent increase in the work of breathing may lead to a compensated respiratory acidosis.[71]

BPD affects the function, growth, and development of the lung and heart because of the fibroproliferative repair of damaged pulmonary and vascular tissues.[72] Chronic hypoxia and periarteriolar thickening[12] may lead to pulmonary hypertension[3,5,12,71,72] and, eventually, right heart failure.[3,5,72]

Incidence/Prevalence

The clinical incidence of classic BPD secondary to oxygen toxicity or barotrauma in animals is unknown but is likely quite low because of the rarity of such management in veterinary medicine. In addition to RDS in horses, calves, and piglets,[6] numerous animal species are used for modeling BPD in humans.[3,73-75] It is clear that many animal species are susceptible to RDS and the development of CLD with neonatal lung inflammation. If the definition of BPD were expanded to include *any* acquired bronchopulmonary dysplasia secondary to the incomplete or inappropriate repair of inflamed and injured tissue, the incidence of heretofore unrecognized BPD in animals would likely become considerably greater. There have been a few reports of BPD-like disease in the veterinary literature.

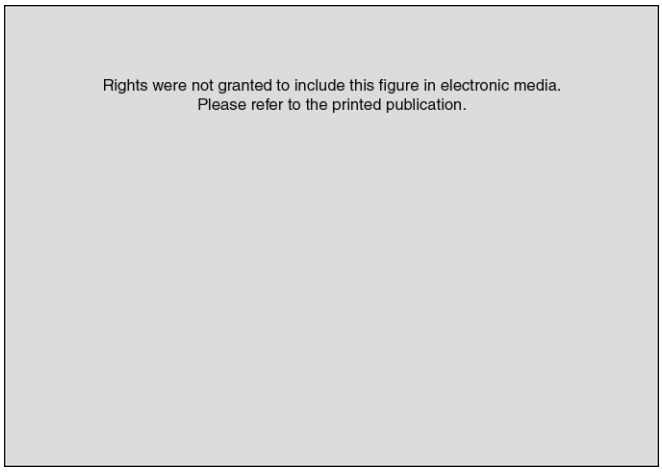


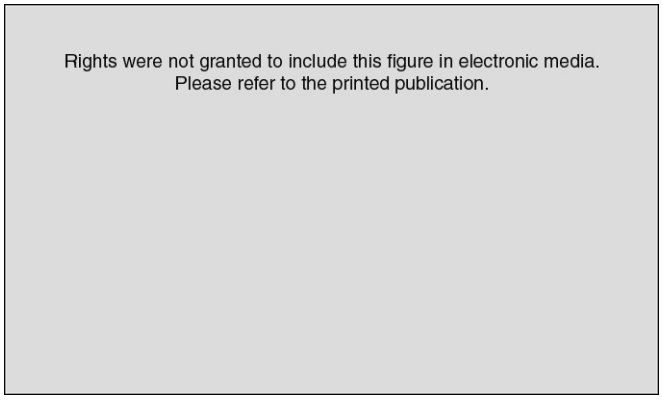
Figure 55-2. *Lungs and heart removed at necropsy from a 5-month-old chow chow with bronchial cartilage dysplasia. Notice the lobar emphysema and 180-degree torsion of the cranial portion of the left cranial lobe, with fibrous adhesion to the atelectic left caudal portion of the left cranial lobe* (arrow), *and atelectasis of the caudal lung lobe* (arrow head). *Bullous emphysema with torsion of the right accessory lung lobe is also present.* (From Hoover JP, Henry GA, Panciera RJ: Bronchial cartilage dysplasia with multifocal lobar bullous emphysema and lung torsions in a pup, *J Am Vet Med Assoc* 201(4):600, 1992.)

In a 1989 report, Freeman and colleagues[76] described lesions consistent with BPD in a foal that had received supplemental oxygen by nasal insufflation. A later correspondence[77] indicated that when tissues from this foal were reanalyzed, they contained equine arteritis virus. They suggested that the viral infection may have played a pivotal role in the development of the foal's clinical disease.

In a 1992 report, Hoover and colleagues[78] described a case of bronchial cartilage dysplasia (BPD-like) in a pup with no history of supplemental oxygen or mechanical ventilation. This animal developed collapse of bronchial lumens, multiple lung lobe torsions, and lobar bullous emphysema (Figure 55-2) secondary to the widespread bronchial cartilage dysplasia. In addition, there was small airway collapse and air trapping in the lung parenchyma (Figure 55-3). The term bullous emphysema was used in this case to be consistent with previous reports.[79-84] In reality, this was a bronchial cyst characterized by septal breakdown, confluence of alveoli, and loss of tethering support of the noncartilaginous airways without the alveolar inflammation associated with true emphysema.[85] No history of any neonatal disease was reported in this patient, so it remains unclear whether the etiology of the lesions in this young dog were congenital or acquired. Retrospectively, the authors suspect that an acquired insult played a major role in the disease.

Collapse of hypoplastic bronchi,[86] bronchogenic cyst,[87] and lung lobe torsion[88] have been associated with BPD in children. Similar conditions have been described in young dogs,[79-81] adult dogs,[82,83] and a cat.[84] Congenital bronchial cartilage aplasia[80] and hypoplasia[82,83] have been associated with lobar emphysema in dogs. Therefore, it appears plausible that analogous conditions

A



B

Figure 55-3. *Photomicrograph* **(A)** *H&E stain, bar = 1,100 μm) of a section of the cranial portion of the left cranial lung lobe in the 5-month old Chow Chow. Notice discrete area of emphysema with loss and displacement of alveolar walls, compression of adjacent pulmonic constituents, and a thin walled bronchus* (arrow) *that contains ciliated pseudostratified columnar epithelium and submucosal glands but lacks cartilage* **(B)** *Inset, bar = 225 μm).* (From Hoover JP, Henry GA, Panciera RJ: Bronchial cartilage dysplasia with multifocal lobar bullous emphysema and lung torsions in a pup, *J Am Vet Med Assoc* 201(4):601, 1992.)

to BPD of human neonates, or to the chronic lung disease (CLD) of children, may also exist in neonatal and juvenile animals.

Epidemiology and Risk Factors

Known risk factors include prematurity of the lung, RDS, mechanical ventilation injury, and the use of high oxygen concentrations.[3,5,13] Lung defenses and the ability to tolerate hyperoxia, repair, and continued growth can be compromised by undernutrition and deficiencies in micronutrients such as vitamins A and E, copper, zinc, iron, magnesium, selenium, and essential fatty acids.[3,89] Impaired immune function and reduced phospholipids and surfactant may present an additional risk for infection.[89-91]

Acquired infections during the perinatal period may contribute to the development of BPD. Human respiratory syncytial virus has been associated with CLD in humans.[3,92] Nosocomial infections represent an important cause of morbidity and mortality among human infants with BPD. Hyperoxic injury (100% oxygen) of airways and lungs colonized by *Pseudomonas aeruginosa* or a coagulase negative *Staphylococcus epidermitis* resulted in 100% mortality by day 10 in baboons.[93,94] Parainfluenza infection in young rats has been shown to induce airway growth abnormalities associated with persistent pulmonary dysfunction and hyperresponsiveness.[95] These, together with the report of signs consistent with BPD in a foal infected with equine arteritis virus, support the contention that BPD in animals may be associated with some neonatal pulmonary infections.

Recognition of Clinical BPD

Recognition of BPD in veterinary patients depends on a history of bronchopulmonary insult or development of acute RDS with progressive clinical signs, and the general lack of response to treatment. Unfortunately, BPD is difficult to confirm antemortem.

DIFFERENTIAL DIAGNOSIS

The clinical signs of BPD are similar to the diseases that can increase the risk for developing BPD. Therefore the differential diagnosis for BPD could include RDS and HMD in premature neonates; congenital defects such as airway hypoplasia and aplasia in term neonates; and acquired inflammatory conditions such as bronchitis, bronchiolitis, bronchiectasis, bronchopneumonia, and pneumonitis in juveniles.

HISTORY

Patients developing BPD are expected to have a history of lower respiratory tract inflammation, whether it is due to oxygen toxicity, barotrauma, noxious (inhaled or aspirated) or infectious agents. Prematurity and a protracted course of respiratory insult increase the likelihood of BPD.

CLINICAL SIGNS

The clinical signs vary as BPD progresses from the acute inflammatory phase to the chronic fibroproliferative remodeling phase. Respiratory distress, cough, changes in breathing pattern, and auscultation abnormalities may occur. Clinical signs of RDS include increased respiratory rate and effort. As inflammation develops, areas of pul-

monary interstitial edema and decreased lung compliance[96] result in a restrictive breathing pattern.[97] As BPD progresses, a breathing pattern more consistent with lower airway obstruction may develop. This pattern features prolonged expiration and low flow rates, caused by compression and collapse of dysplastic lower airways, and eventually leading to air trapping.[97] Because of the hyperinflation, there is often maximal expansion of the thorax and an increased abdominal component to breathing. RDS may become so severe that distress may be characterized by orthopnea.[78] Terminally, ventilation efforts may diminish to apnea. Most veterinary patients will present in the acute inflammatory phase of BPD. The transition from inflammation to dysplasia may be subtle, and in many cases, the first indication that BPD is developing or has developed in an animal with RDS is a lack of continued improvement despite therapy.

Cough is a hallmark sign of lower airway inflammation, but it may not be seen in neonates with early BPD. When a cough develops, it is expected to be productive because of excess mucus transudation and exudation into the airways, and decreased mucociliary clearance.

Initially, breath sounds may be decreased due to atelectasis. As areas of lung inflate and pulmonary edema develops, inspiratory crackles may occur. With chronicity, airway compression and collapse may cause expiratory wheezes and coarse expiratory crackles.

Severe hypoxemia is caused by hypoventilation from airway obstruction, or by increased venous admixture from lung parenchymal disease. The patient may be only partially responsive to increased Fio_2, especially in advanced cases of BPD. This is because of significant right-to-left shunting from regional (lobar) atelectasis and pulmonary hypertension from hypoxia and increased vascular resistance.[3,5,61] Cyanosis of mucous membranes may be seen, although it does not always occur. Animals with BPD can be expected to have decreased Pao_2 (often 75 mm Hg or less) and may have increased $Paco_2$ (45 mm Hg or greater). Intermittent episodes of oxygen desaturation may be associated with apnea, bradycardia, or cyanosis,[3] occurring primarily while the patient is eating or sleeping.[98,99]

Radiography is essential for evaluation of animals with respiratory disease accompanied by a restrictive[100] or obstructive pattern.[101] Radiographs may reveal lower airway obstruction (i.e., airway collapse/compression), or a bronchial, interstitial, vascular, or alveolar pattern. Care must be exercised to stabilize the patient, provide oxygen if necessary, and minimize stress prior to making thoracic radiographs. Compromises in patient positioning may be necessary, and horizontal beam lateral projection should be considered if the animal is in respiratory distress. Other diagnostic procedures may be considered if the animal is stable enough.

Early radiographic signs of BPD in humans may be indistinguishable from other diffuse neonatal lung diseases (see Table 55-1). Initially, the radiographic findings may be indistinguishable from RDS[5] with diffuse atelectasis, reticulogranularity, and air bronchograms. Reticulogranularity represents hyperexpanded alveoli against a background of lung edema, fibrosis, and atelectasis.[71] In the advanced stages of BPD, irregularly distributed atelectasis and emphysema may be apparent.

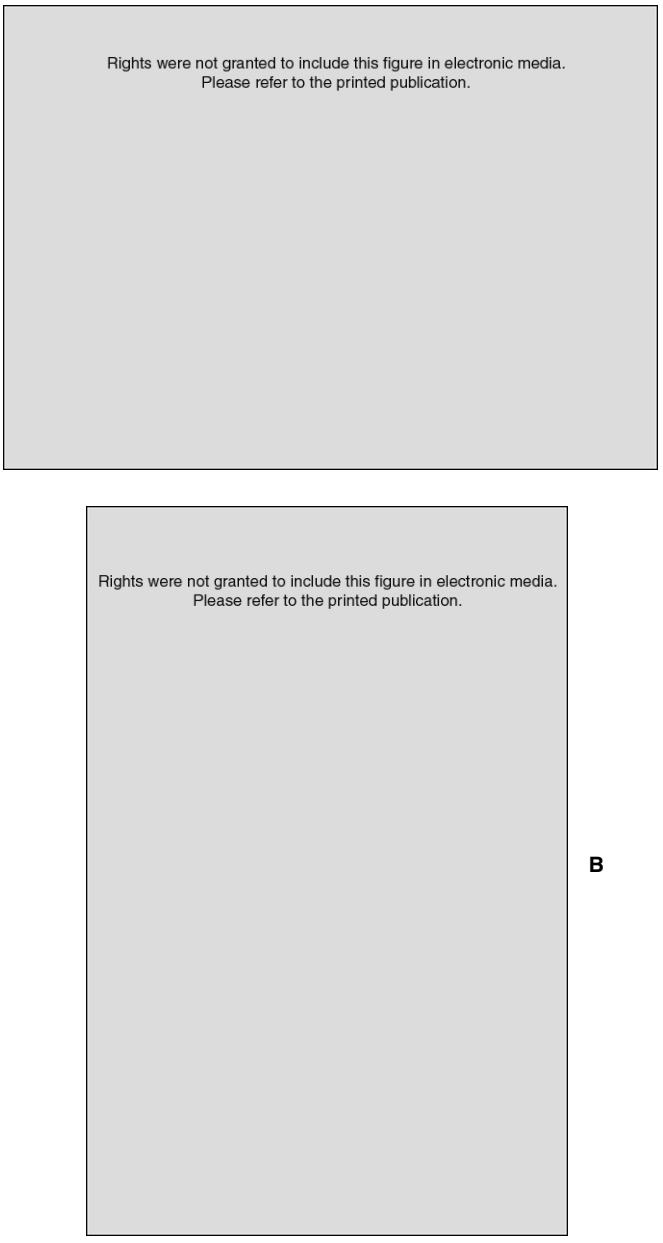


Figure 55-4. *Thoracic radiographs of a 5-month-old chow chow with a history of exercise intolerance, progressive dyspnea, and episodic cough. Hyperinflation of the lungs and flattening of the diaphragm* (arrow) *are evident in a right lateral radiograph* ***(A)*** *obtained using a horizontal beam. Hyperinflation of the left cranial lung lobe, with displacement of the mediastinum and heart to the right, and atelectasis of the right lung are evident in the dorsoventral view* ***(B)****.* (From Hoover JP, Henry GA, Panciera RJ: Bronchial cartilage dysplasia with multifocal lobar bullous emphysema and lung torsions in a pup, *J Am Vet Med Assoc* 201(4):601, 1992.)

In a canine patient with bronchial cartilage dysplasia, lung hyperlucency with hyperexpansion and flattening of the diaphragm, cystic lungs with bullae or bronchial cyst, and collapse of airways on expiration were all consistent with air trapping (Figure 55-4).

PATHOLOGY

Confirmation of BPD is usually achieved at necropsy and on histopathology. The pup reported by Hoover and colleagues[78] had clinical and radiographic signs, as well as gross necropsy (see Figure 55-1) and histologic findings (see Figure 55-3) consistent with the chronic fibroproliferative phase of BPD and airway remodeling. The foal reported with BPD-like lesions by Freeman and colleagues[76] was more consistent with the radiographic and histologic findings of the late acute inflammatory or early subacute fibroproliferative reparative phase of BPD.

Treatment and Management

The primary pathophysiologic problems are increased work of breathing and decreased efficiency of gas exchange. In BPD, however, often little can be done to alleviate these conditions because of the inherent structural damage that is the hallmark of the disease. Although some respiratory improvement might occur over time in the chronic phase,[61] most veterinary patients will likely succumb during the acute phase.[3] In many respects, management of veterinary BPD cases is not very different from management of human cases.

PREVENTATIVE TREATMENTS IN HUMANS

Therapies intended to prevent BPD in infants include steroids (e.g., antenatal and early postnatal), thyrotropin-releasing hormone to induce antioxidant enzymes, early postnatal surfactant, and antioxidants (e.g., superoxide dismutase and vitamins A and E). Other treatments include inositol and fatty acid supplementation (long-chain n-3 PUFAs).[13] Careful fluid restriction may minimize pulmonary edema and improve lung compliance.[3,13] Whenever ventilation with supplemental oxygen is necessary, high-frequency oscillatory ventilation[13,102] or synchronized (patient-triggered) ventilation[3,13] should be used. Permissive hypercapnea may promote early weaning from mechanical ventilation[13] and thereby reduce barotrauma.

MANAGEMENT OF INFANTS WITH BPD

Therapy includes supplemental oxygen, nutritional support, diuretics, corticosteroids, bronchodilators, and treatment of any infectious agents.[3,13] Other treatments include inhaled nitric oxide (NO) to vasodilate the ventilated areas of the lung, thereby reducing V/Q mismatching and pulmonary hypertension.[103-106] Improvement was reported in some studies of infants with BPD,[107,108] but in other reports infants failed to improve or could not be weaned off the inhaled NO.[103] Several medications (e.g., furosemide, beta-2 agonists, dexamethasone) are being administered to human infants by inhalation; however, variable doses are actually delivered and the mechanism of delivery requires that the patient is ventilated.[13]

PREVENTIVE TREATMENT OF BPD IN ANIMALS

Corticosteroids play important roles in normal prenatal lung maturation,[13] in decreasing inflammation mediated by cells (PMNs and PAMs),[3,13] and in improving the protease-antiprotease ratio.[109] As a result, these drugs are administered before birth in humans to prevent BPD in infants. However, the antenatal use of corticosteroids is controversial because their administration can induce premature parturition in domestic animals. Thus these hormones are not recommended for use in animals unless it is certain that preterm parturition is unavoidable. Proper nutrition of dams during late gestation (especially those with a history of premature births) and avoidance of breeding dams predisposed to premature parturition is recommended. Exercising caution with the use of PPV, avoiding high levels of Fio_2 and neonatal exposure to airway irritants and allergens, and responding quickly to neonatal respiratory infections are all also recommended.

MANAGEMENT OF BPD IN ANIMALS

Treatment is presented in three categories: (1) *supportive,* to maintain the patient and promote homeostasis; (2) *symptomatic,* to relieve clinical signs; and (3) *specific,* to prevent, control or eliminate the definitive cause. If a causal agent can be identified, early treatment may ameliorate this progressive condition. Patients with BPD have impaired pulmonary defense mechanisms and often have a relative inability to clear intraluminal mucus and exudate. Periodic airway suctioning may become necessary, especially if tracheal intubation becomes necessary to ventilate the patient. Any lower respiratory tract infection may exacerbate inflammation[110] and should be treated aggressively.

Antioxidants

Superoxide dismutase (SOD), administered intratracheally in newborn piglets exposed to 100% oxygen for 48 hours, mitigated the inflammatory changes of oxidative lung injury but did not appear to improve surfactant function.[111] Improved oxygenation and pulmonary blood-flow occurred when intratracheal SOD was combined with inhaled NO in a lamb model of persistent pulmonary hypertension.[112] Vitamin A promotes epithelial regeneration[50] and surfactant synthesis in rats,[113] and ventilated preterm human infants,[114] reducing the risk of BPD. Oral or IM administration on alternate days[13] may be worth considering. Human studies suggest that the earlier vitamin A supplementation is started in BPD, the better the response.[115]

Deferoxamine

Deferoxamine, an iron chelator, may protect the neonatal lung from the effects of oxygen exposure. It also appears to allow normal alveolar septation by reducing

elastin fiber length and density in hyperoxic neonatal rats[116] and lambs.[63] However, clinical use of deferoxamine in the treatment of BPD in humans or animals has not been established.

Surfactant

In rescue studies where human infants were given exogenous natural surfactant there was reduced mortality and development of BPD.[117] Decreased development of BPD and pulmonary interstitial emphysema was seen using modified bovine surfactant 100 mg/kg IT in baboons[118] and humans.[119] Synthetic protein-free and natural surfactants were compared in a metaanalysis of six human infant studies, revealing clear evidence of the superiority of natural surfactant.[117] Therefore, administration of 100 mg/kg of aerosolized IT natural exogenous surfactant may be considered in animal neonates, especially preterm neonates, with RDS.

Diuretics

Both furosemide and thiazides have been used to treat interstitial pulmonary edema in the early stages of BPD.[13] Diuretics, particularly furosemide, appear to increase lung compliance, decrease airway resistance, and improve V/Q mismatch.[3,13,120,121] There may be an additive effect with theophylline to increase dynamic lung compliance.[122] Improvement in pulmonary function of human infants with BPD given furosemide orally at 1 mg/kg appears to be rapid (less than 1 hour) but lasts less than 6 hours.[123] Furosemide at 2 mg/kg PO daily produced continued improvement in patient oxygenation (pulmonary function) after 1 week of therapy.[124] Inhaled aerosolized furosemide at 1 to 2 mg/kg improved pulmonary function for several hours in preterm neonates without any side effects.[125] Administration of medications by inhalation is problematic in animals, especially when the patient is not intubated. The application, dosages, and routes of administration of these drugs in clinical veterinary patients with BPD are largely unknown. Neonates may respond to and metabolize these medications differently than adults. A suggested guideline for treatment of veterinary patients is summarized in Table 55-2. Clinical veterinary recommendations suggest that furosemide should be administered IV, IM, or PO at 1 to 2 mg/kg, and repeated as needed based on clinical response.

Supportive Treatment

Oxygen supplementation is indicated for hypoxemic patients,[3] but administration should be minimized to avoid increased local oxidative stress.[12,21] The therapeutic goal in human infants is to maintain pulse oximetry readings of 93% to 96%.[3] Maintenance of patient Sa_{O_2} greater than 88% may be difficult using a nasal cannula, and tracheal intubation for PPV may become necessary.[3,13,102,126] When PPV is employed in veterinary patients, either high frequency oscillating ventilation (HFOV)[3,102] or patient synchronized ventilation[13] is recommended, using lower TV at peak inspiratory pressures less than 20 cm H_2O initially, and then weaning the patient as response permits.[3,13,102] Permissive hypercapnia may allow earlier weaning of veterinary patients with BPD.[13,127]

Fluid Therapy

Respiratory distress and hypoxia may preclude oral fluid intake and increase insensible fluid losses via the respiratory tract.[128] Adequate colloid osmotic pressure is essential to maintain intravascular fluid volume, but transudation of plasma proteins from the pulmonary vessels and increasing inflammatory proteins within the interstitium in BPD favor edema formation. Excess interstitial water exacerbates BPD, especially during the acute inflammatory phase. Relative fluid restriction of preterm infants at risk for BPD decreased BPD rates and mortality.[129,130] Thus careful restriction of water may be prudent in veterinary patients with RDS and BPD. Colloids should be administered only when needed. Balanced electrolyte crystalloid solutions[128] should be administered IV in sufficient volumes to maintain intracellular water and the minimum plasma volume for organ perfusion while avoiding exacerbation of pulmonary edema.

Nutritional Support

Growth failure is common in infants with severe BPD[3,13] because of increased energy expenditure with decreased intake in RDS. Veterinary neonatal patients with RDS and BPD will likely not nurse, and require nutritional support. Even neonates that are able to eat on their own may tire during feedings, and oxygen supplementation may improve their feeding performance.[3] Nutritional support may best be supplied by alimentary tube feeding using the gastrointestinal tract, but alternatively it can be supplied by parenteral nutrition. Frequent small feedings of a high-calorie, high-lipid diet with supplemental vitamin A, magnesium, and possibly n-3 PUFAs might be considered.

Anti-Tussive Drugs

Airway compression during coughing episodes may cause mechanical irritation to the airways.[131] Centrally acting antitussives may suppress the respiratory control centers as well as the cough. If a productive cough is present, it should not be suppressed because of its vital role in airway clearance. Therefore, centrally acting antitussives should be avoided in neonates, especially if they have BPD. Bronchodilators may act as mild peripheral antitussives by reducing airway compression, thereby avoiding exacerbation of airway inflammation.[131]

Bronchodilators

BPD patients develop airway obstruction due to smooth muscle hypertrophy and airway hyperreactivity.[3,5] Thus bronchodilators and antiinflammatory drugs may be in-

TABLE 55-2 **Suggested Treatments for Bronchopulmonary Dysplasia in Small Animals***

Prevention	Specific Treatments	Supportive Treatments	Symptomatic Treatments
1. Good nutrition for dam: Consider vitamin A and n-3 long-chain fatty acids 2. Avoid breeding dams prone to premature parturition 3. Caution when using O_2 supplementation in neonates (especially when premature): Fio_2 ≤60% 4. Antenatal dexamethasone 0.5 mg/kg to dam if premature parturition is imminent	1. Treat any lower airway infections aggressively 2. Administer antioxidants: a. Superoxide desmutase (rhSOD): 5 mg/kg IT q 48 hrs (≤7 doses) b. Vitamin A: 400-800 U/kg PO q 24-48 hrs c. Natural surfactant (Survanta®): 100 mg/kg IT d. Furosemide: 1-2 mg/kg PO, IV, IM prn	1. Oxygen supplementation: a. Nasal cannula—Fio_2 ≥ 60%; if flow rate >0.5 L/min, humidify O_2 with in-line bubbler. Maintain Sao_2 ≥88% b. Intubation/ventilation: 1) Spontaneous 2) Assisted: a) Patient triggered—Tidal volume 6-10 ml/kg, rate 60 bpm b) Continuous—High frequency oscillatory 3) Monitor and maintain Sao_2 ≥93%; Pao_2 ≥100 mm Hg; $Paco_2$ 45-55 mm Hg 2. Nitric oxide: Tracheal-bronchial catheter 5-80 ppm 3. Fluids—Minimum necessary. Consider reduced sodium isotonic crystalloid maintenance with 2.5% dextrose and KCl (20 mEq/l) ≤66 ml/kg/24 hours 4. Nutrition—Stomach tube, naso-esophageal or gastrotomy tube—high calorie, high lipid with vitamin A 400 U/kg ± n-3 long chain PUFAs	1. Bronchodilators: a. Beta-2 agonists: 1) Albuterol metered inhalant: 100 μg/activation prn 2) Terbutaline: 0.05-0.10 mg/kg PO b. Methylxanthines: theophylline 1-2 mg/kg IV q 6-8 hrs 2. Corticosteroids: Dexamethasone 0.5 mg/kg IV or IM q 12-24 hrs and taper off as improves

* Modified from human and animal model studies of bronchopulmonary dysplasia.
IT, Intratracheal; *PUFAs,* polyunsaturated fatty acids.

dicated to decrease the work of breathing. Inhaled beta-2 agonists such as albuterol,[132] metaproterenol,[133] and terbutaline[134] have been shown to increase lung dynamic compliance and reduce pulmonary resistance. Administration is usually by a metered dose inhaler or via jet nebulizer into the inspiratory circuit of a ventilator.[13] Beta-2 and methylxanthine bronchodilators both have some inotropic effect on the diaphragm.[135] Theophylline may have an additive effect with diuretics to improve pulmonary function and patient oxygenation.[123] Concurrent use of antiinflammatory drugs may potentiate bronchodilation by beta-2 agonists and allow reduction in the doses of both.[136,137] Finally, some beta-2 agonists and methylxanthines also have central nervous system stimulatory effects, which might be beneficial for stimulation of respiration in animal neonates that are failing with RDS or BPD. Albuterol can be administered by metered inhalation at 100 μg per activation for intubated veterinary neonates, and terbutaline can be given orally or by injection. Administration should be only as needed, and adjustments in drug dosages should be anticipated because of the immaturity of the neonatal liver.

Antiinflammatory Drugs

Although beta-2 agonists and methylxanthines have some antiinflammatory effects,[138-140] corticosteroids are the mainstay of antiinflammatory therapy. Exogenous steroids improve both pulmonary resistance and lung compliance, decrease oxygen requirements, and may facilitate extubation of ventilator dependent human infants with BPD.[13]

Dexamethasone systemically and by inhalation has been used most commonly for BPD in human medicine. Beclomethasone has also been administered by inhalation with similar effects.[141,142] Studies of inhaled dexamethasone indicated temporary improvement in respiratory function in infants with CLD, and fewer side effects compared with systemic administration.[143] Systemic administration of dexamethasone may be considered in veterinary patients with BPD at 0.5 mg/kg daily, and then tapered if there is continued clinical improvement in respiratory function. Nonsteroidal antiinflammatory drugs have not been effective in reducing the inflammation in the lung with respiratory disease, with the possible exception of heartworm infection.[131,144]

Surgery

In rare instances, surgical intervention may afford some relief from respiratory distress caused by compromised airways or a diseased or torsed lung lobe. Dysplasia of the tracheobronchial cartilage in humans or animals contributes to tracheobronchial chondro-

malacia. This results in airway collapse and narrowing from lack of structural support during inhalation (extrathoracic airways) and exhalation (intrathoracic airways), and in air trapping in the lung. Tracheal chondrodysplasia seen with BPD in infants has been amenable to surgical stenting.[145] Unfortunately, the primary lesions in BPD are often in the smaller, intrathoracic airways that are not amenable to direct surgical intervention.

Bronchial chondrodysplasia with bronchomalacia can also lead to lung lobe torsion and an acute respiratory crisis, as illustrated in the reported case of canine BPD.[78] The disease was too advanced in this animal to permit surgical intervention. In less severely affected cases with only single lung lobe torsion, a lobectomy might be considered after stabilization of the patient.

Outcome and Prognosis

The likelihood of BPD in animals resolving sufficiently to allow them to have normal activity without respiratory distress appears remote. Recovery from BPD, when it occurs, is a protracted process. In survivors the lung gradually remodels, but the process requires prolonged support and vigilance against additional acquired pulmonary disease. Most human survivors of BPD demonstrate stunted growth, reduced respiratory capacity, and are prone to recurrent infections.[5,71,146] For many veterinary patients, euthanasia because of unresponsive or minimally responsive pulmonary insufficiency is likely to be the predominant outcome.

BPD in its broadest sense may represent a largely unrecognized clinical entity in veterinary medicine. It could be elicited by a variety of severe or prolonged insults that set up a progressive inflammatory condition, resulting in improper lung development of premature neonates and inadequate or inappropriate bronchopulmonary repair.

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