

Case Report

J Vet Intern Med 2017;31:550–555**Recurrent Obstructive Fibrinous Tracheal Pseudomembranes in a Young English Bulldog**

E. Robin, L.V. Guieu, and K. Le Boedec

Endotracheal intubation is a common procedure, rarely associated with life-threatening complications (e.g., tracheal rupture, necrosis, foreign body). A 1.5-year-old English Bulldog was presented for respiratory distress, with increased respiratory efforts and stridor, 2 days after endotracheal intubation. Cervical and thoracic radiographs disclosed a severe narrowing of the tracheal lumen associated with an intraluminal soft-tissue structure at the thoracic inlet. Tracheoscopy confirmed the presence of an obstructive fibrinous tracheal pseudomembrane (OFTP) creating a 1-way valve obstruction. Removal of the OFTP dramatically improved the dog's respiratory function, but the lesion reformed twice despite corticosteroid and antibiotic therapy PO, warranting repeated endoscopic removal of the OFTP. No additional recurrences were observed after treatment with inhaled heparin and N-acetylcysteine q4h. No respiratory signs were reported 9 months after discharge. Postintubation OFTP has been reported rarely in humans and never described in dogs. Unexplained signs of upper airway obstruction shortly after endotracheal intubation should prompt consideration of OFTP in dogs, even if intubation was uneventful. Unlike its counterpart in humans, OFTP in dogs can reoccur after endoscopic removal, warranting repeated endoscopic extraction. A combination of corticosteroid therapy PO and heparin and N-acetylcysteine inhalation q4h may be attempted if recurrence is observed.

Key words: canine; endotracheal intubation; plastic tracheobronchitis; tracheal casts.

A 1.5-year-old, 25-kg, male intact English Bulldog was referred to the Veterinary Hospital Fregis, Paris, for evaluation of acute severe respiratory distress. Four days before referral, the dog underwent general anesthesia for entropion surgery. The dog was premedicated with acepromazine^a (0.03 mg/kg IV), induced with propofol^b (5 mg/kg IV), and intubated. General anesthesia was maintained with isoflurane in oxygen. No proton pump inhibitor or metoclopramide was used. According to the referring veterinarian, a properly sized endotracheal tube was used (8 mm) and advanced without resistance into the tracheal lumen. Anesthesia lasted 1 h, and no anesthetic incidents were reported. Respiratory distress started the day after surgery, with increased inspiratory efforts and regurgitation observed by the owners. The dog was immediately presented back to the referring veterinarian. A lateral thoracic radiograph disclosed a severe narrowing of the tracheal lumen at the thoracic inlet. The dog was treated with prednisolone^c 10 mg PO q24h (0.4 mg/kg PO). Despite initial improvement for 2 days, respiratory distress recurred and the dog was referred.

From the Internal Medicine Unit, (Robin, Le Boedec) and Emergency and Critical Care Unit, (Guieu) CHV Fregis, Arcueil, France.

The case report was not supported by a grant.

No previous presentation of this case.

Corresponding author: K. Le Boedec, Internal Medicine Unit, CHV Fregis, 43 avenue Aristide Briand, 94110 Arcueil, France; e-mail: drleboedec@hotmail.fr

Submitted September 2, 2016; Revised November 4, 2016; Accepted December 6, 2016.

Copyright © 2017 The Authors. Journal of Veterinary Internal Medicine published by Wiley Periodicals, Inc. on behalf of the American College of Veterinary Internal Medicine.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

DOI: 10.1111/jvim.14650

Abbreviations:

NAC	N-acetylcysteine
OFTP	obstructive fibrinous tracheal pseudomembrane

On presentation, the dog was quiet, alert, and responsive. Rectal temperature was increased (103.8°F [39.9°C]; reference range, 99.5–102.5°F [37.5–39.2°C]). The dog showed respiratory distress with increased inspiratory and expiratory efforts as well as stridor. Respiratory rate was normal (28 breaths/min; reference range, 15–30 breaths/min). No adventitious lung sounds were heard during inspiration and expiration, but thoracic auscultation was difficult because of a substantial amount of referred upper airway noise.

Based on the breed and loud stridor, laryngeal disease was suspected in addition to the tracheal narrowing observed on radiographs 2 days earlier. Because the dog was not stable, immediate care was provided, including sedation with butorphanol^c (0.2 mg/kg IV) and acepromazine^a (0.03 mg/kg IV) as well as supplemental oxygen via a blindly placed nasotracheal tube. A previously described technique was used to place the nasotracheal tube.^{1,2} A 6-French polyurethane tube was premeasured such that the tip would rest at the mid-tracheal level. The tube was covered with lidocaine gel, quickly introduced into the ventral nasal meatus, and passed into the trachea through the larynx by hyperextending the dog's neck and advancing the tube. Proper placement was confirmed by demonstrating a lack of negative pressure after aspiration with a 50-mL syringe and by obtaining a lateral cervical radiograph. The dog's breathing pattern improved overnight, but another episode of respiratory distress developed the next morning.

Cervical and thoracic radiographs identified a severe, 4-cm-long narrowing in tracheal lumen caused by a suspected intraluminal soft-tissue structure centered on the

thoracic inlet (Fig 1A). No pneumomediastinum was identified, and no clinically relevant abnormalities were noted in the pulmonary parenchyma. Lung overinflation was present.

Tracheal endoscopy was planned, and the patient was induced with propofol^b (5 mg/kg IV) before endotracheal intubation. Cardiorespiratory arrest occurred immediately after anesthesia induction. Cardiopulmonary resuscitation instantly was initiated with chest compressions (patient positioned in dorsal recumbency), endotracheal intubation, and IV administration of epinephrine (0.01 mg/kg IV) and atropine (0.04 mg/kg IV). A 1-cm-wide and 4.8-cm-long tracheal cast (Fig 2) was expelled through the endotracheal tube shortly after intubation and recovery of the patient, presumably secondary to repeated chest compressions. Tracheoscopy performed through the endotracheal tube identified an irregular and hyperemic mucosa from the end of the first third to the beginning of the last third of the tracheal length. No persistent intraluminal material was observed. Only a small amount of clear fluid was observed in the bronchi, which appeared morphologically normal. Cytological findings of a bronchoalveolar lavage were increased cellularity (8000 cells/ μ L; reference range, 50–450 cells/ μ L) and neutrophilic inflammation (90% hypersegmented neutrophils and 10% activated macrophages). No bacteria were cultured from the bronchoalveolar lavage fluid. Cytological analysis of the expectorated tracheal cast showed a large number of degenerated neutrophils engulfed in mucus without infectious organisms identified (Fig 3A), along with acellular proteinaceous material (Fig 3B). On histopathological analysis, abundant pale eosinophilic material consistent with a fibrinonecrotic cast was present, with a moderate amount of entrapped neutrophils (Fig 4A,B).

The dog's respiratory distress immediately improved after expectoration of the tracheal cast. Oxygen supplementation was continued via the nasotracheal tube. The dog was treated with butorphanol^d (0.2 mg/kg IV q2h), amoxicillin/clavulanic acid^e (20 mg/kg IV q12h), enrofloxacin^f (5 mg/kg IV q24h), dexamethasone^g (0.27 mg/kg once, then 0.14 mg/kg IV q24h), and

omeprazole^h (1 mg/kg PO q12h). The next day, respiratory distress with inspiratory effort and stridor recurred and cervicothoracic radiographs identified relapse of the intraluminal tracheal obstruction. Because recurrence was thought to be caused by endotracheal intubation, tracheoscopy was repeated without intubation. A pseudomembrane, with the same appearance as the tracheal cast expectorated the day before, was visualized at the thoracic inlet and was creating a dynamic 1-way valve obstruction during inspiration (Fig 5A,B). The pseudomembrane was in continuity with a semicircumferential, 3-cm-long tracheal cast covering the ventral aspect of the tracheal mucosa. Foreign body forceps were passed through the biopsy channel to gently remove the cast in 1 block. Because the dog's breathing pattern became normal immediately after relieving the obstruction, the nasotracheal tube was removed to avoid further tracheal injury. Nebulization was added to the treatment regimen, with 5000 units of heparinⁱ and 3 mL of a 20% N-acetylcysteine^j (NAC) solution aerosolized every 12 h, adapted from a method previously described in human pediatric medicine.³ Another episode of respiratory distress with inspiratory efforts required endoscopic removal of a pseudomembrane 2 days after starting nebulization therapy. Aerosolized heparin and NAC therefore were given q4h to prevent recurrence of cast formation. No additional endoscopic interventions were necessary after intensification of nebulized therapy. The dog was discharged with a 15-day course of prednisolone^c (0.5 mg/kg PO q12h initially) 8 days after admission. An intraluminal tracheal soft-tissue opacity could no longer be observed on cervicothoracic radiographs (Fig 1B) at the time of discharge. Nine months later, the dog was still clinically normal and had not experienced any respiratory problems since discharge.

In the dog of this report, tracheal pseudomembranes developed after tracheal intubation and caused life-threatening upper airway obstruction.

Pseudomembranous tracheobronchitis is a rare medical condition in humans that can be infectious or traumatic in origin.^{4,5} Infections that have been associated with tracheobronchial pseudomembranes include croup,

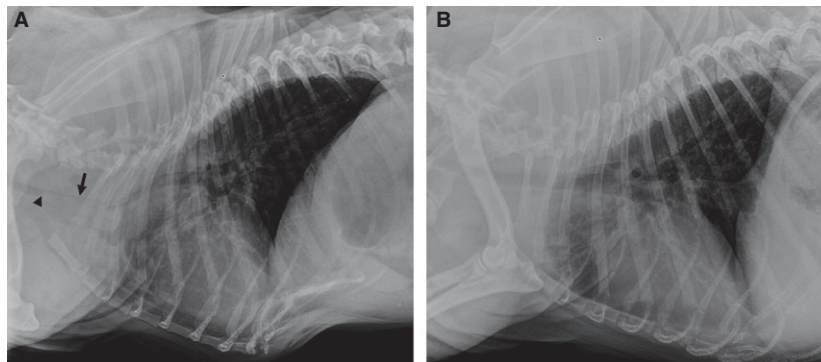


Fig 1. Right lateral radiographic views of the thorax at admission (A) and at discharge (B). A severe tracheal narrowing is observed from the thoracic inlet to the third intercostal space (arrow). An intraluminal obstructive structure is suspected based on the rounded margin (arrowhead). Overinflation of the lungs is present. At discharge, the trachea and the lungs appeared normal.



Fig 2. Thick, tubular, rubber-like, whitish tracheal pseudomembrane, measuring 4.8×1 cm, and expectorated during cardiopulmonary resuscitation.

staphylococcal tracheobronchitis in infants, and invasive pulmonary aspergillosis in immunosuppressed patients.^{4,6,7} Sterile tracheal pseudomembranes have been reported as a rare complication arising 3 hours to 9 days (mean delay, 59 ± 27 hours) after endotracheal intubation.⁵ The mechanism involved in the formation of these lesions is not clear. They may represent an

early stage of tracheal ischemic damage related to endotracheal cuff overinflation, leading to superficial necrosis of the tracheal wall and intense inflammation with profuse fibrinous exudate infiltrated by polymorphonuclear cells.⁵ Endoscopic evidence of tracheal wall ischemia can be seen with cuff pressure >30 cm H_2O in human beings.⁸ However, postintubation tracheal pseudomembranes were diagnosed in people with cuff pressure <15 cm H_2O , suggesting that other causative factors may be involved.⁹ Systemic hypotension and caustic injury by aspirated gastric content have been suspected as other potential causes.^{9,10} Regardless of their origin, tracheal pseudomembranes always appear as tube-like lesions consisting of fibrin, inflammatory cells, and desquamated necrotic tracheal epithelium, firmly adhered to the tracheal wall, a description that matches perfectly the appearance of the lesion in our dog.⁵

Although tracheal pseudomembranes have never been reported in dogs to the authors' knowledge, the tracheal vasculature in dogs is very sensitive to pressure exerted by the endotracheal tube and cuff, because measurable tracheal injury invariably can be identified after intubation, even with meticulous selection of cuff size and careful inflation.¹¹ Although clinical signs rarely are observed, nearly complete ciliary denudation always follows endotracheal intubation in dogs and takes at least 7 days to heal.¹¹ Excessive pressure caused by overinflation of the endotracheal cuff has resulted in tracheal

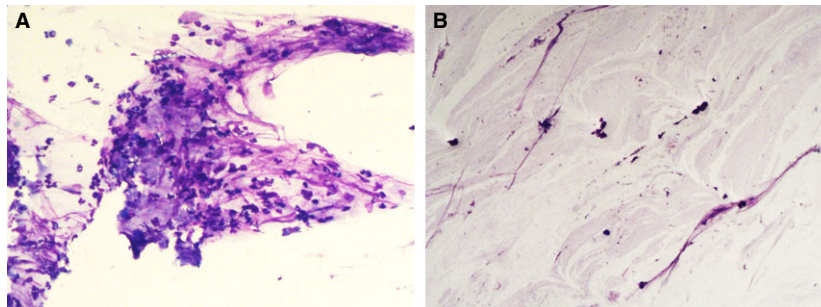


Fig 3. Impression smear of the expectorated tracheal pseudomembrane, showing a large number of degenerated neutrophils engulfed in mucus (A), as well as areas of acellular proteinaceous material (B). No infectious organisms were identified. Diff-Quick stain, $\times 10$ objective.

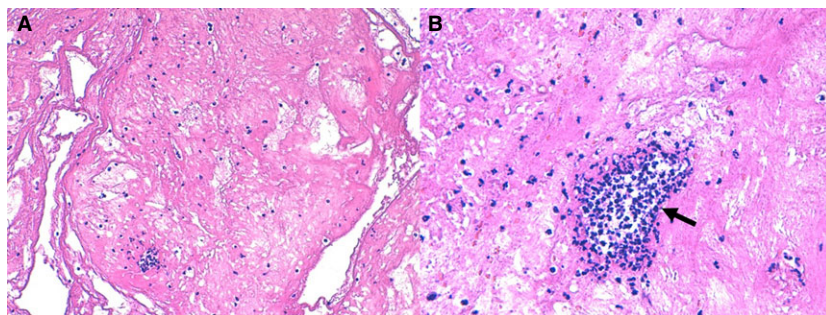


Fig 4. At $\times 200$ magnification, histological analysis of the tracheal pseudomembrane revealed an abundant pale eosinophilic material consistent with a fibrinonecrotic cast (A). At higher magnification ($\times 400$), moderate amount of entrapped neutrophils (arrow) can be observed (B). Hematoxylin and eosin stain.

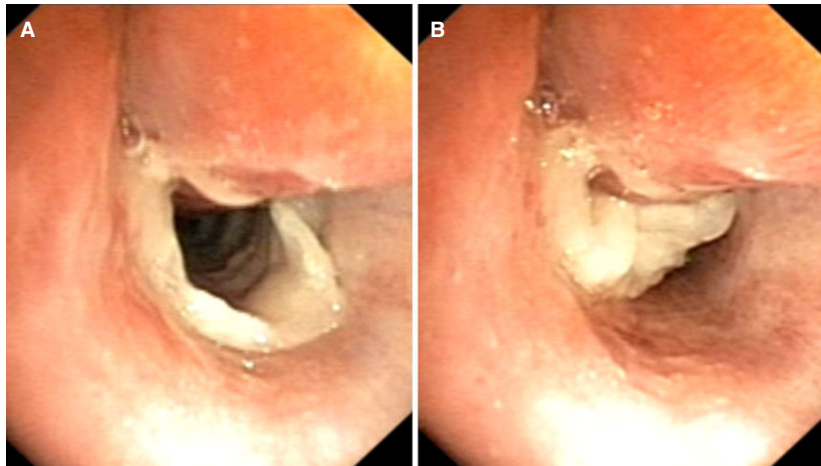


Fig 5. Endoscopic views of a tracheal pseudomembrane at the level of the thoracic inlet during expiration (A) and inspiration (B). The pseudomembrane was creating a dynamic 1-way valve obstruction during inspiration.

necrosis in some dogs, presumably by occlusion of the capillaries in the tracheal wall.^{12,13}

Several features support a cuff-related origin for the tracheal pseudomembranes described in our case. First, the acute onset of respiratory distress the day after anesthesia in a dog that had never experienced any respiratory issues in the past parallels the delayed clinical expression of tracheal pseudomembranes reported in human medicine.⁵ Second, the pseudomembranes were repeatedly observed at the same localization, which likely corresponds to the site where the endotracheal cuff was inflated. Finally, bacterial culture of bronchoalveolar lavage fluid was negative, and no infectious organisms were seen either cytologically or histologically within the extracted pseudomembranes. Furthermore, brachycephalic breeds are predisposed to gastroesophageal reflux, which could have contributed to mucosal injury of the trachea during anesthesia in our dog, as has been reported to occur in dogs, mice, and humans.^{9,14–16}

One major difference between the postintubation OFTP described here and those observed in human medicine is the recurring aspect of the lesion in our dog. Indeed, 3 episodes of respiratory distress that required endoscopic intervention to relieve airway obstruction occurred. In birds, in which postintubation tracheal pseudomembranes are also recognized, and in humans, mechanical ablation of the lesion typically leads to full recovery without relapse.^{5,9,17–19} Experimental models in rabbits suggest that the same tissue reaction and subsequent tracheal obstruction can be seen not only with endotracheal cuff-related injuries but also with trauma or irritation of the tracheal mucosa without pressure necrosis.^{20–22} Several obstructive bronchial diseases associated with smoke inhalation injury or cardiovascular surgery (i.e., Fontan-related plastic bronchitis) have been described in humans and are characterized by formation of casts inside the airways that are very similar to tracheal pseudomembranes in composition.^{23,24} Unlike postintubation OFTP disease,

obstructive smoke inhalation injury and Fontan-related plastic bronchitis require medical therapy to stop cast formation.^{25,26} The use of inhaled or systemic corticosteroids, aerosolized NAC, tissue plasminogen activator, or IV and aerosolized heparin has been reported.^{25,26} The rationale for using inhaled anticoagulation therapy is to decrease airway fibrin deposition and obstruction, and improve oxygenation and ventilation.²⁵ The addition of NAC to nebulized heparin acts as a co-agent to prevent or minimize formation of obstructive casts by promoting mucolysis.²⁷ Although some studies failed to show a survival benefit for a nebulized heparin and NAC protocol in patients with smoke inhalation injury and even suggested an increase in pneumonia rates, 2 recent systematic reviews suggest an overall favorable effect of such treatment on survival.^{25,27,28} Moreover, no increase in prevalence of pneumonia was reported in an experimental study conducted in sheep.²⁹ Although systemic absorption of heparin could lead to bleeding as a complication, no hemorrhage was reported with nebulized heparin with doses ranging from 50,000 to 400,000 IU of unfractionated heparin in people.^{27,28} An irritating effect of NAC on airway mucosa, presumably associated with acidity (pKa of 2.2) and the foul sulfur odor of the compound, has been suspected in humans and cats, but no data are available in dogs to the authors' knowledge.^{30,31}

Because the relapsing OFTP in our dog was life-threatening, and based on the similarities between the recurring airway casts in this patient and the relapsing casts described in human smoke inhalation injury and plastic bronchitis, inhaled heparin and NAC therapy was attempted. However, to minimize adverse effects, and although the aerosolized heparin and NAC protocol described in humans recommends nebulization q4h, nebulized therapy initially was administered q12h in our dog as a precautionary measure. Despite an apparent longer delay before recurrence, tracheal obstruction eventually relapsed, which required intensification of the nebulized heparin and NAC therapy to q4h. It is

unclear whether the lack of further relapses resulted from spontaneous healing of the tracheal mucosa, delayed beneficial effects of corticosteroid treatment, intensified aerosol therapy, or some combination of these factors.

In conclusion, unexplained occurrence of respiratory failure with signs of upper airway obstruction shortly after endotracheal intubation should prompt consideration of OFTP in dogs, even if intubation was uneventful. The findings described here are particularly relevant because endotracheal intubation is a common procedure and this complication, although rare, may be life-threatening. Based on our experience, we recommend immediate endoscopic removal of the OFTP after stabilization with oxygen. In case of relapse, corticosteroid therapy PO and inhaled unfractionated heparin and NAC treatments q4h may be attempted. The patient should be kept in the hospital for 2 days after removal of the tracheal pseudomembrane to detect potential relapses and avoid life-threatening tracheal obstruction at home.

Footnotes

- ^a Calmivet, Vetoquinol, Lure, France
^b Propovet, Axience, Pantin, France
^c Dermipred, CEVA, Libourne, France
^d Torbugesic, Zoetis, Paris, France
^e Augmentin, Glaxo Smith Kline, Marly-le-roi, France
^f Baytril, Bayer Health care, Loos, France
^g Dexadreson, MSD Santé animal, Beaucauze, France
^h Inexium, AstraZeneca, London, UK
ⁱ Heparine choay, Sanofi aventis, Gentilly, France
^j Mucomystendo, UPSA, Bristol-Myers Squibb, Rueil-Malmaison, France
-

Acknowledgments

The authors thank Dr. Fine for his help with the histological examination, as well as Dr. Julie Danner for assisting with preparation of the manuscript.

Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References

- Grimm KA, Lamont LA, Tranquilli WJ, et al. Veterinary Anesthesia and Analgesia. Ames, IA: John Wiley & Sons; 2015:1074 p.
- Bojrab MJ, Waldron DR, Toombs JP. Current Techniques in Small Animal Surgery, 5th ed. Jackson, WY: CRC Press; 2014: 1185 p.
- Desai MH, Mlcak R, Richardson J, et al. Reduction in mortality in pediatric patients with inhalation injury with aerosolized heparin/N-acetylcysteine [correction of acetylcysteine] therapy. J Burn Care Rehabil 1998;19:210–212.
- Salamone FN, Bobbitt DB, Myer CM, et al. Bacterial tracheitis reexamined: Is there a less severe manifestation? Otolaryngol-Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg. 2004;131:871–876.
- Deslée G, Brichet A, Lebuffe G, et al. Obstructive fibrinous tracheal pseudomembrane. A potentially fatal complication of tracheal intubation. Am J Respir Crit Care Med 2000;162: 1169–1171.
- Françoise M, Sandre D, Gouyon JB. Necrotizing tracheo-bronchitis in ventilated newborn infants. Arch Pédiatrie Organe Off Société Fr Pédiatrie 1994;1:1106–1110.
- Argüder E, Şentürk A, Hasanoğlu HC, et al. Unique case of pseudomembranous aspergillus tracheobronchitis: Tracheal perforation and horner's syndrome. Mycopathologia 2016;181:885–889.
- Seegobin RD, van Hasselt GL. Endotracheal cuff pressure and tracheal mucosal blood flow: Endoscopic study of effects of four large volume cuffs. Br Med J Clin Res Ed 1984;288: 965–968.
- Kang HH, Kim JW, Kang JY, et al. Obstructive fibrinous tracheal pseudomembrane after tracheal intubation: A case report. J Korean Med Sci 2010;25:1384–1386.
- Bunegin L, Albin MS, Smith RB. Canine tracheal blood flow after endotracheal tube cuff inflation during normotension and hypotension. Anesth Analg 1993;76:1083–1090.
- Klainer AS, Turndorf H, Wu WH, et al. Surface alterations due to endotracheal intubation. Am J Med 1975;58:674–683.
- Alderson B, Senior JM, Dugdale AHA. Tracheal necrosis following tracheal intubation in a dog. J Small Anim Pract 2006;47:754–756.
- Knecht CD, Schall WD, Barrett R. Iatrogenic tracheostenosis in a dog. J Am Vet Med Assoc 1972;160:1427–1429.
- Poncet CM, Dupre GP, Freiche VG, et al. Prevalence of gastrointestinal tract lesions in 73 brachycephalic dogs with upper respiratory syndrome. J Small Anim Pract 2005;46:273–279.
- Leverment JN, Pearson FG. Tracheal damage associated with cuffed tracheostomy tubes. Aspiration of gastric content as a cause of local damage in tracheotomised dogs. Anaesthesia 1977;32:603–613.
- Wynne JW, Ramphal R, Hood CI. Tracheal mucosal damage after aspiration. A scanning electron Microscope study. Am Rev Respir Dis 1981;124:728–732.
- Sykes JM, Neiffer D, Terrell S, et al. Review of 23 cases of postintubation tracheal obstructions in birds. J Zoo Wildl Med Off Publ Am Assoc Zoo Vet 2013;44:700–713.
- Nakwan N. Obstructive fibrinous tracheal pseudomembrane: A rare condition in postextubation stridor. Respir Care 2014;59:e91–e93.
- Rice BL, Culver DA, Santacruz JF, et al. Obstructive fibrinous tracheal pseudomembrane. Ann Thorac Surg 2011;92:e115–e117.
- Marfatia S, Donahoe PK, Hendren WH. Effect of dry and humidified gases on the respiratory epithelium in rabbits. J Pediatr Surg 1975;10:583–592.
- Nakagishi Y, Morimoto Y, Fujita M, et al. Rabbit model of airway stenosis induced by scraping of the tracheal mucosa. Laryngoscope 2005;115:1087–1092.
- Star EG, Caselitz J, Löning T. [The effect of ethylene oxide and chemical disinfectant residues upon the larynx- and tracheal mucosa of rabbits (author's transl)]. Zentralblatt Für Bakteriologie 1 Abt Orig B Hyg Krankenhaushygiene Betriebshygiene Präventiv Med 1980;170:539–547.
- Singhi AK, Vinoth B, Kuruvilla S, et al. Plastic bronchitis. Ann Pediatr Cardiol 2015;8:246–248.
- Miller AC, Rivero A, Ziad S, et al. Influence of nebulized unfractionated heparin and N-acetylcysteine in acute lung injury after smoke inhalation injury. J Burn Care Res Off Publ Am Burn Assoc 2009;30:249–256.

25. Miller AC, Elamin EM, Suffredini AF. Inhaled anticoagulation regimens for the treatment of smoke inhalation-associated acute lung injury: A systematic review. *Crit Care Med* 2014;42:413–419.
26. Madsen P, Shah SA, Rubin BK. Plastic bronchitis: New insights and a classification scheme. *Paediatr Respir Rev* 2005;6:292–300.
27. Kashefi NS, Nathan JI, Dissanaik S. Does a nebulized heparin/N-acetylcysteine protocol improve outcomes in adult smoke inhalation? *Plast Reconstr Surg Glob Open* 2014;2:e165.
28. Monagle K, Ryan A, Hepponstall M, et al. Inhalational use of antithrombotics in humans: Review of the literature. *Thromb Res* 2015;136:1059–1066.
29. Enkhbaatar P, Esechie A, Wang J, et al. Combined anticoagulants ameliorate acute lung injury in sheep after burn and smoke inhalation. *Clin Sci Lond Engl* 2008;114:321–329.
30. Reiner CR, Lee-Fowler TM, Dodam JR, et al. Endotracheal nebulization of N-acetylcysteine increases airway resistance in cats with experimental asthma. *J Feline Med Surg* 2011;13:69–73.
31. Rubin BK. Aerosol medications for treatment of mucus clearance disorders. *Respir Care* 2015;60:825–829.