Title page

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Successful management of aspiration pneumopathy without antimicrobial agents in 14 dogs

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Abstract

Objectives

To describe clinical cases of aspiration pneumonitis and pneumonia in dogs which were successfully managed without antimicrobials.

Methods

Retrospective case review of dogs presenting to a referral teaching hospital between February 2014 and February 2021. Cases were included when a clinical diagnosis of aspiration pneumopathy was made (requiring one or more of the following: radiographic evidence of an aspiration pneumopathy, endotracheal airway sampling consistent with aspiration, and/or a positive endotracheal airway sample culture) which was not treated with antimicrobial therapy.

Results

Fourteen cases were identified of which 9 had respiratory signs including increased respiratory rate or effort (n=8), arterial hypoxaemia (n=2), or a clinician-determined requirement for oxygen therapy (n=4). Where haematology was performed, 6/9 displayed a normal neutrophil count with toxic changes, 2 displayed neutrophilia, and 1 displayed neutropenia with toxic changes. Endotracheal airway sample cytology in 4 cases revealed neutrophilic inflammation with bacteria, plant material, yeasts and unidentified foreign material. Where respiratory signs were present, these resolved within 12-36 hours.

Clinical relevance

Immunocompetent animals sustaining aspiration events, even with classical evidence of pneumonitis or pneumonia, may be managed successfully without antimicrobials. Radiography alone cannot be used to determine the requirement for antimicrobials. Better characterisation of the trajectory of the aspiration pneumopathy may enable a significant reduction in antimicrobial prescription.

Introduction

The term 'aspiration' is generally used to refer to the inhalation of gastric or oropharyngeal contents into the respiratory tract beyond the larynx (Raghavendran et al., 2011). The exact constituents are variable though and may include gastric acid, bacteria, blood, saliva or food particles (Marik, 2001). Aspiration pneumonitis can be defined as pulmonary injury caused by inhalation of chemical irritants, while aspiration pneumonia refers to the bacterial infection that can develop after aspiration, (Goggs, 2014, Marik, 2001) although both direct bacterial inoculation and subsequent bacterial colonisation are possible explanations for a bacterial infection after an aspiration event. Clinically aspiration pneumonitis and pneumonia can be difficult to distinguish as the early phase of both disease courses can be dynamic, and the exact components of aspirated material are generally unknown (oropharyngeal flora, gastric contents, or a combination of the two). Bacterial colonisation, infection and any further lung injury are determined not simply by the pathogen, but also by the host response (Casadevall and Pirofski, 1999) and may well be prevented by the immune response, the mucociliary escalator and coughing. Patients in which aspiration pneumonia develops, alongside routine supportive care, may benefit from antimicrobials. Identification of those patients that will or will not benefit from antimicrobials alongside routine supportive care, however, has not been explored.

Inappropriate antimicrobial prescription habits in veterinary medicine are likely to be contributing to antimicrobial resistance and multidrug resistance (Rantala et al., 2004, Schmidt et al., 2018). Antimicrobial stewardship orientated consensus statements and the subsequent implementation of their recommendations are targeted at reducing antimicrobial prescriptions (Weese et al., 2015, Lappin et al., 2017, Singleton et al., 2021, BSAVA/SAMSoc,

2018) to promote the use of antimicrobials only in situations in which they are truly required, thus reducing our reliance on such agents and minimising selection for multidrug resistant organisms. In dogs with bacterial pneumonia the duration of antimicrobial therapy can often be reduced without clinical detriment (Wayne et al., 2017, Viitanen et al., 2017) but evidence of the management of such patients without the use of antimicrobial agents is lacking.

It is recognised that antimicrobials are not always required in dogs and cats that have sustained an aspiration event, even where cytological, microbiological or radiographic evidence suggests infection (Lappin et al., 2017). There is, however, a lack of published information to support this. The aims of this study were to review the management of patients with documented aspiration pneumopathy without the use of antimicrobial agents, and to generate hypotheses over which cases may be appropriately managed in this way.

Materials and methods

Computerised records from the [redacted] were retrospectively reviewed for cases of dogs with aspiration pneumopathy between February 2014 and February 2021. Inclusion criteria were a clinical diagnosis of aspiration pneumopathy that had been managed without antimicrobials with at least 14 days of follow up clinical notes noting no antimicrobials being prescribed. Aspiration pneumopathy was defined as one or more of the following: radiographic or computed tomographic evidence of aspiration as reported by a board-certified specialist in diagnostic imaging (such as cranioventrally distributed increased attenuation, alveolar pattern, air bronchograms and consolidation with maintenance of lung volume)(**Fig 1**), endotracheal airway sampling consistent with aspiration pneumopathy (such as neutrophilic inflammation, the presence of foreign material, evidence of oropharyngeal contamination with or without presence of microorganisms), and/or a positive endotracheal airway sample culture. Data collected included signalment, cause for the pneumopathy, underlying disease, results of diagnostics performed (complete blood count, C-reactive protein (CRP), radiographic findings, airway sample analyses) and physical examination findings at the time of diagnosis of aspiration pneumopathy, including whether respiratory distress was noted in the clinical record. Respiratory distress was defined as an increase in respiratory effort, tachypnoea above a rate of 36 breaths per minute at rest, a clinician-determined requirement for oxygen therapy, documented pulmonary function impairment on arterial blood gas analysis (PaO_2 less than or equal to 80mmHg) or a combination thereof.

Results

Sixteen possible cases were identified for inclusion in the study. Two cases were excluded due to insufficient follow up, leaving 14 cases in the final study population. The study population comprised 7 females (of which 5 were neutered) and 7 males (of which 5 were neutered). The most frequently represented breeds were Labradors (4) and English bulldogs (2), and the median age was 30 months (range 4-164).

Seven dogs had an elevated rectal temperature (≥39°C) but two of these were suspected to be due to hyperthermia rather than genuine pyrexia. Those considered pyrexic had rectal temperatures of 39.1°C (n=2), 39.2°C (n=1), 39.7°C (n=1) and 39.8°C (n=1).

The cause of the aspiration event was an oesophageal foreign body in 5 cases. Other causes were tremorgenic mycotoxicosis (n=1), tremorgenic mycotoxicosis with cardiopulmonary arrest (n=1), brachycephalic obstructive airway syndrome (n=2), metaldehyde toxicity (n=1), pharyngeal stick injury (n=1), paroxysmal movement disorder (n=1) and vomiting (n=1). The cause of aspiration was unknown in one dog.

The aspiration pneumopathy was confirmed by radiography alone in 10 cases, and by endotracheal wash cytology and culture alone in 4 cases. Where the timescale from onset of aspiration to radiographic documentation of a pneumopathy was confirmed, these were after 6, 12, 22, 24 and 36 hours.

Respiratory distress was present in 9/14 dogs. These included dogs with increased respiratory rate (RR) (n=3), or increased effort (n=1) alone; increased RR and receipt of oxygen (n=2),

increased RR, increased respiratory effort and receipt of oxygen therapy (n=1), increased RR, receipt of oxygen and arterial hypoxemia (n=1), and increased RR and effort and arterial hypoxemia (n=1).

In the 2 dogs that were documented to be hypoxemic PaO_2 was noted to be 58.9mmHg and 74.9mmHg, PaO_2:FiO_2 280 and 356 and A-a gradient 43.6 and 38.5, respectively.

Of the 9 cases in which a contemporaneous complete blood count was performed, 6 displayed neutrophil toxicity without neutrophilia (median 11.05 x 10^9/L, range 3.83 – 14.97), 2 displayed neutrophilia (16.84 x 10^9/L (reference interval 3 - 11.5); 19.35 x 10^9/L (reference interval 6-17.1)) with unremarkable neutrophil morphology, and one displayed neutropenia (1.93 x 10^9/L, reference interval 3 - 11.5) with mild toxic changes.

Of the 8 cases in which serum CRP was measured contemporaneously, 5 were elevated (>30mg/L) at 351.5 mg/L, 143.5mg/L, 113 mg/L, 96.5 mg/L and 79.9mg/L. The other three dogs had serum CRP concentrations of 5 mg/L, 10.2 mg/L and 17.4 mg/L. Two patients were documented to be hypoglycaemic (3.9mmol/L and 4.6mmol/L (RI 4.7-7.3mmol/L)).

Endotracheal airway sample cytology from the four cases in which it was available revealed marked neutrophilic inflammation with extracellular bacteria, pollen and yeast (culture yielded *Streptococcus equi subsp. Zooepidemicus*); abundant heterogenous bacteria, yeasts and foreign material (plant material and suspected charcoal) with evidence of squamous epithelial cells (culture yielded all of the following: two types of *E. coli*, alpha-haemolytic *Streptococcus* spp, *Enterococcus faecium*, *Klebsiella pneumoniae*, another uncharacterised

gram negative bacilli, and a profuse growth of *Penicillium* spp); neutrophilic inflammation without evidence of bacteria (culture negative); and neutrophilic inflammation with extracellular rods and unidentified crystalline material (culture yielded bacterial growth but was not further classified or identified).

Where respiratory signs were documented, these normalised in 12-36 hours in all cases. The dog with arterial hypoxemia of 58.9mmHg had a PaO_2 of 76.1mmHg (PaO2:FiO2 362) documented 48 hours later. The other dog with documented hypoxemia was not sampled again due to clinical improvement. All dogs were discharged with normal respiratory rate and effort after a median of 2 (range 1-5) days.

Discussion

This study documents the concept that aspiration events can induce a spectrum of clinical scenarios including clinically silent but radiographically and cytologically evident inflammation and infection. Furthermore, even when a more classical clinical picture of an aspiration pneumopathy is present, including respiratory distress, hypoxemia, pyrexia and evidenc of systemic inflammation, that antimicrobials are not always required.

The decision-making and patient selection for withholding of antimicrobials in such patients is an emerging field, without clear recommendations available. Without clinical signs, or with documentation of a purely inflammatory insult, antimicrobials are not justified (Raghavendran et al., 2011). Several of the cases described here would appear to bridge the gap between purely a chemical pneumonitis and an established pneumonia which may normally be considered to require antimicrobials.

In people, where a pneumonitis is suspected or diagnosed, antimicrobials do not tend to be prescribed, but are considered in more severe cases, in patients receiving gastric acid suppressant medications or in those with small bowel obstruction due to the greater risk of a larger or more pathogenic bacterial load. (Mandell and Niederman, 2019). Similar caveats may be applicable in veterinary medicine considering the known, albeit poorly characterised, alteration of gastrointestinal flora by proton pump inhibition (Garcia-Mazcorro et al., 2012, Sullivan et al., 2016).

At the authors' hospital the criteria utilised when considering antimicrobial therapy in cases of aspiration pneumopathy include the patient's systemic stability, the underlying cause, the subjective severity of any respiratory distress, and the time after which the aspiration was suspected to have occurred that the patient is being evaluated. For example, a systemically well patient with recent (<12 hours) suspicion or documentation of an aspiration event and a transient disease process such as oesophageal foreign body or intoxication, even if displaying mild to moderate respiratory clinical signs, would be considered a candidate for monitoring further rather than immediate prescription of antimicrobials. Should the patient fail to improve or show signs of deterioration during monitoring, antimicrobials could then be instituted. This would especially be the case where culture is outstanding, and is based on the pathophysiology of sterile aspiration events, which experimentally includes biphasic inflammation (at approximately 1 and 4 hours)(Kennedy et al., 1989) but which is maximal at 6-8 hours and occurs independently of the presence or proliferation of any bacterial isolates (Knight et al., 1993).

The authors' approach is not novel practice. The International Society for Companion Animal Infectious Diseases (ISCAID) guidelines suggest that 'no treatment' is an option in acutely affected patients after aspiration events where there is no evidence of systemic sepsis (Lappin et al., 2017). However, this study is the first documentation of such a practice in clinical veterinary medicine for aspiration pneumopathy. In the current climate of antimicrobial prescription tendencies, it is likely that many practitioners would have prescribed antimicrobials in many of these cases, and indeed it is likely many cases excluded due to use of antimicrobials could also have been managed without such agents. In people, it is similarly difficult to distinguish between aspiration pneumonitis and aspiration pneumonia, and

211 despite recommendations, prescription of broad-spectrum antimicrobials for patients that
212 are likely only to have pneumonitis appears common, at least while bacterial culture results
213 are outstanding (Rebuck et al., 2001, Son et al., 2017), although it has specifically been
214 appreciated that anaerobic cover appears less important than aerobic (Marik and Careau,
215 1999).
216
217 In addition to the volume of material aspirated, the two variables that appear most significant
218 in inducing an inflammatory response are the acidity and the particulate matter content of
219 the aspirated material. Both a pH <2.5 and the presence of particulate matter resulted in a
220 more extensive inflammatory response in an experimental rabbit model than delivery of fluid
221 with a higher pH or filtered fluid into the lungs. The presence of particulate matter in
222 particular appearing to propagate a macrophagic infiltration on top of the initial neutrophilic
223 component (Teabeaut, 1952, Knight et al., 1993). It is possible that dogs with a pneumonitis
224 originating from aspiration of saliva develop less of an inflammatory response owing to the
225 alkalinity of the material aspirated, but this cannot be safely assumed without more
226 information.
227
228 Antimicrobial resistance is, rightfully, of great concern in both human and veterinary
229 medicine. Reducing both the frequency with which antimicrobials are prescribed, and the
230 length of time for which they are prescribed, is expected to be of benefit to both disciplines
231 and is a core tenet of antimicrobial stewardship in both human and veterinary healthcare.
232 (Lappin et al., 2017, Weese et al., 2015)

Many of the recommended treatment protocols for antimicrobial use in veterinary medicine have little or no evidence base. Although stated in many reference texts, it is out-dated to administer antimicrobials for 3-4 weeks to patients with aspiration pneumonia or until 1 week after radiographic resolution. Significantly shorter prescription lengths will usually suffice (Wayne et al., 2017, Viitanen et al., 2017) and the ISCAID guidelines suggest antimicrobial use be re-evaluated within 10-14 days, being extended, adjusted or ceased based on the clinical response (Lappin et al., 2017). In people with aspiration pneumonia, courses of 5-7 days in length are recommended where no extrapulmonary foci of infection exist, and where a good response to initial treatment has been demonstrated (Mandell and Niederman, 2019).

According to the American College of Veterinary Internal Medicine (ACVIM) consensus statement on therapeutic antimicrobial use in animals and antimicrobial resistance "a common misconception is the need to complete a minimum duration of an antimicrobial drug to prevent the emergence of resistance". The committee also goes on to state that antimicrobials should never be continued once there is clinical and microbiological evidence that an infection has been eliminated simply because of a perceived need for a minimum duration of administration (Weese et al., 2015).

Another common misconception that has been partly addressed by the cases described herein, is that radiographic evidence of aspiration pneumonia or pneumonitis lags significantly behind the aspiration event. Whilst this can happen, two of the dogs described had radiographic evidence of aspiration pneumonitis within 12 hours of the onset of clinical signs, one after just 6 hours. If the patient has clinical signs of aspiration, and radiography would help in the decision-making process, then pursuing radiography early should be

considered, without concern for a false negative result. If alternative confirmation of aspiration is required whilst the lesion is radiographically silent, then airway sampling, clinicopathological variables, and point of care ultrasound examinations may also be used. Ultrasonographic findings are not reported in this study but would be particularly useful in any prospective evaluation. It is interesting to note that an inflammatory leukogram and (in some cases quite markedly) elevated CRP were present in many of these patients, suggesting these parameters are not necessarily useful in determining whether antimicrobial therapy is required, which is consistent with human medicine (Raghavendran et al., 2011).

This study is inherently limited by its retrospective nature, with cases expected to have been lost due to inadequate data capture. Also, many patients which may have been successfully treated without antimicrobials are likely to have been prescribed them, reducing the number available for the study. There may also have been patients in which this approach was initially attempted but was unsuccessful. The importance of careful monitoring of patients treated in this manner, to identify any deterioration or progression of respiratory distress which would likely indicate the need for more aggressive therapy including administration of antimicrobials, should therefore be emphasised.

Reviewing these cases serves two main purposes; to challenge the blanket prescription of antimicrobials in dogs with aspiration, and as a starting point for interrogation of the criteria that ought to be satisfied for justification of antimicrobial prescription in such cases. Further investigations into the incidence and clinical relevance of aspiration events are required, including improved stratification and identification of those subsequently requiring

antimicrobials. The recommended course length of antimicrobial prescription for dogs with aspiration pneumonia also requires a more evidence-based approach.

Incidental documentation of aspiration without the presence of clinical signs does not require antimicrobial treatment and simply monitoring of those patients would be appropriate. In patients with clinical signs of pneumonia, but which are systemically stable, the utility of a 'delayed prescription' may also be considered, i.e., antimicrobial provision if the patient fails to improve in the expected timeframe or displays more overt or concerning clinical signs referable to pneumonia. There is very likely a subpopulation of immunocompromised animals in which this approach is undesirable. Characterisation of the canine pulmonary microbiome and interactions between that and the gastrointestinal microbiome may also be prerequisites to truly comprehending the pathogenesis of aspiration events (Mandell and Niederman, 2019).

296 **Figure Legend**

297

298 **Fig 1**

299 Representative examples of radiographs displaying aspiration pneumopathy affecting the

300 right middle (a) and left cranial lung lobes (b and c).

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