Is inhaled immunotherapy more effective than environmental management when treating equine asthma?

A Knowledge Summary by

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KNOWLEDGE SUMMARY

PICO question

In horses with severe equine asthma syndrome, is inhaled immunotherapy compared to environmental reduction of allergen exposure more effective in disease modification?

Clinical bottom line

Category of research question

Treatment

The number and type of study designs reviewed

12 papers were critically reviewed. Nine clinical trials; one crossover study; one split-plot design study; and one cross-sectional study

Strength of evidence

Low

Outcomes reported

Four studies found inhaled immunotherapy to improve the clinical signs associated with equine asthma and the lung function of horses with asthma. Three papers found environmental modification improved lung function and the clinical signs associated with equine asthma but two studies provide moderate evidence that environmental management alone is insufficient to permanently cure asthma

Conclusion

There is a low level of evidence to support the use of inhaled immunotherapy as a treatment for equine asthma

How to apply this evidence in practice

The application of evidence into practice should take into account multiple factors, not limited to: individual clinical expertise, patient's circumstances and owners' values, country, location or clinic where you work, the individual case in front of you, the availability of therapies and resources.

Knowledge Summaries are a resource to help reinforce or inform decision making. They do not override the responsibility or judgement of the practitioner to do what is best for the animal in their care.

Clinical Scenario

You have recently diagnosed a 10-year-old pony with severe equine asthma syndrome. The owner would like to know more about inhaled immunotherapy as an option for treating equine asthma and if inhaled immunotherapy will result in better disease modification compared to environmental management alone for the pony.

Abbreviations:

$AaDO_2$	alveolar-arterial oxygen gradient
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
CBC	complete blood count
CpG	cytosine-phosphate-guanosine
CpG-ODN	cytosine-phosphate-guanosine oligodeoxynucleotides
GNP	gelatin nanoparticle
HPW	highly purified water
HPW-GNP	highly purified water bound to gelatin nanoparticle
IFN-γ	interferon gamma
IL	interleukin
MMP	matrix metalloproteinase
$PaCO_2$	arterial partial pressure of carbon dioxide
PaO_2	arterial partial pressure of oxygen
TIMP	tissue inhibitor of matrix metalloproteinase

Summary of the evidence

The papers appraised include a number of different terms previously used for severe equine asthma. The original terms used in the paper can be found in the population section of each individual appraisal, otherwise the term equine asthma is used.

Klier et al. (2019)	
Population:	Adult horses with equine asthma Case selection: • Resting respiratory rate (RR) (>16/min) on contact to dusty hay and straw • Increased abdominal breathing effort • Abnormal thoracic auscultation • Increased neutrophilic granulocyte percentage in BALF (>25%) • Reduced partial oxygen pressure at rest (<90 mmHg) • Increased interpleural pressure (>15 cmH_2O) • No concurrent respiratory disease • No medication in the 8 weeks prior to/during study
Sample size:	29 horses
Intervention details:	Horses assigned into treatment groups considering age, housing management and breed Treatment groups, each received a total of 10 inhalations: • CpG single dose, 187.5 µg CpG-ODN (n= 11): One inhalation q 48 h for 20 days

	• CpG double dose, 375 µg CpG-ODN (n= 9): One inhalation q 48 h for 20 days • Beclomethasone, 1600 µg (n=9): One inhalation q 24 h for 10 days • Technique: standardised Horses were assessed at the following time points: • Time point I: before treatment • Time point II: immediately after treatment period • Time point III: 8 weeks after final inhalation
Study design:	Double-blinded clinical field trial
Outcome studied:	Subjective Assessments: • HOARSI: standardised horse owner assessed respiratory signs index (Time points I and III) • Bronchoscopy: evaluation of mucus, redness or swelling of nasal mucosal membranes (Time points I, II and III) Objective Assessments: • Clinical examination scores (Time points I, II and III) • Lung function testing (Time points I, II and III) • BAL for cytokine assay and immunalysis (Time points I, II and III) • Blood sample: CBC and fibrinogen (Time points I, II and III) Horses were also clinically observed daily
Main findings: (relevant to PICO question):	Single dose CpG: • Improvement in resting RR (clinical examination score) at Time points II and III • Improvement of 82% clinical parameters at Time point II • Improvement in 100% clinical parameters at Time point III Beclomethasone: • No improvement in resting RR • Improvement in 72% clinical parameters measured at Time point II • Improvement in 50% clinical parameters measured at Time point III Double dose CpG: • Did not result in improvement compared to single dose CpG Single dose CpG vs beclomethasone: • CpG single dose improved HOARSI scores at Time point III compared to beclomethasone group • No difference in cytokine analysis at Time points II or III • No difference in CD4+ lymphocyte analysis No adverse effects of CpG treatment were noted

Limitations:	• Environment and management were not standardised which may have influenced horses' response to treatment • No placebo group • Small sample size • Owner bias

Klier et al. (2015)	
Population:	Adult horses with severe equine asthma (chronic recurrent airway obstruction (RAO)) Case selection: • Increased resting RR on contact to dusty hay/straw • Increased abdominal breathing effort • Abnormal thoracic auscultation • Increased neutrophil percentage in BALF (>25%) • Reduced partial oxygen pressure at rest (<90 mmHg) • Increased interpleural pressure (>15 cmH_2O) • No additional medication for 2 months prior to/during study
Sample size:	24 horses
Intervention details:	Inhaled CpG or placebo Treatment groups, one inhalation q48 hours for 10 days: • CpG group (n=16) – 187.5 µg CpG-ODN • Placebo group (n=8) – HPW-GNP • Technique: Standardised Horses were assessed at the following time points: • Time point I: before treatment • Time point II: immediately after treatment period • Time point III: 4 weeks after final inhalation
Study design:	Randomised, double-blinded, placebo-controlled clinical trial
Outcome studied:	Subjective Assessments: • Bronchoscopy (Time points I, II and III) Objective Assessments: • Clinical examination scores (Time points I, II and III) • Lung function testing (Time points I, II and III) • BAL and cytology (Time points I, II and III) Horses were also clinically observed daily

Main findings: (relevant to PICO question):	CpG:
	• Improvement between Time points I and II in:
	  ○ breathing pattern
	  ○ lung auscultation
	  ○ partial oxygen pressure
	  ○ $AaDO_2$
	  ○ neutrophil percentage

	○ nasal discharge ○ tracheal secretion quantity and viscosity • Improvement between Time points I and III in: ○ breathing pattern ○ lung auscultation ○ $AaDO_2$ ○ nasal discharge ○ tracheal secretion quantity and viscosity CpG vs placebo: • Improvement in RR after CpG compared to placebo • Placebo resulted in no improvement of any parameters measured • CpG inhalation improved 70% of clinical, endoscopic and cytological variables evaluated between Time points I and III No adverse effects to CpG inhalation were detected during the study
Limitations:	• The environment and management of horses in study was not standardised • Small sample size

Klier et al. (2012)	
Population:	Adult horses with equine asthma (moderate RAO) and healthy adult horses
Sample size:	12 horses
Intervention details:	Healthy – placebo or CpG RAO – CpG Treatment groups: • RAO group (n=4) – 187.5 µg CpG-ODN: One inhalation q 48 hours for 10 days • Compatibility group (n=4) – 187.5 µg CpG-ODN: One1 inhalation q 48 hours for 6 days • Placebo group (n=4) – HPW-GNP: One inhalation q 48 hours for 6 days All horses were assessed at: • Time point I: before treatment • Time point II: after third inhalation The RAO group were also assessed at: • Time point III: after five inhalations Technique: Inhalations were administered with the same nebuliser equipment
Study design:	Placebo-controlled clinical trial

Outcome studied:	Subjective assessment: • Bronchoscopy Objective assessment: • RR • Blood gas analysis and PaO_2 • BALF cytology and cytokine analysis Horses were also clinically observed daily
Main findings: (relevant to PICO question):	CpG inhalation in RAO horses: • Increased IL-10 and IFN-γ in BALF between Time points I and III • Increased PaO_2 between Time points I and III • Decreased RR between Time points I and III • Decreased BALF neutrophil percentage between Time points I and III • No difference in BALF neutrophil percentage between RAO group after treatment and healthy horses after placebo No adverse effects of treatment with CpG were detected
Limitations:	• RR was the only clinical examination parameter measured • Small sample size • The assessors were not blinded to the treatment protocols • Management and environmental conditions are unspecified • Signalments of horses is not divulged

Klier et al. (2017)	
Population:	Adult horses with equine asthma Case selection: • Increased resting RR (>16/min) • Increased abdominal breathing effort • Abnormal thoracic auscultation • Increased neutrophilic granulocyte percentage in BALF (>25%) • Reduced partial oxygen pressure at rest (<90 mmHg) • Increased interpleural pressure (>15 cmH_2O) • No additional medication in the 8 weeks prior to study or during study
Sample size:	20 horses
Intervention details:	Inhaled CpG or CpG with specific allergen Treatment groups: • CpG inhalation, 187.5 µg CpG-ODN (n=9): One inhalation q48 hours for 14 days • CpG + two individually selected allergens (n=11): One inhalation q48 hours for 14 days

	Allergen selection: • Functional in vitro test on whole blood was carried out on horses and two allergens were selected for each horse based on geographical location, seasonality of clinical signs and results of blood test Technique: • All inhalations were administered with the same nebuliser equipment All horses were assessed at the following time points: • Time point I: Prior to treatment • Time point II: Immediately after last inhalation • Time point III: 6 weeks after inhalational therapy
Study design:	Prospective, randomised clinical trial
Outcome studied:	Objective assessments: • Arterial blood gas measurements: PaO_2 and $PaCO_2$ • $AaDO_2$ • Maximum interpleural pressure differences • Cytology of tracheobronchial secretion: neutrophil percentage Subjective assessments: • Clinical examination scores • Endoscopy Horses were also clinically observed daily
Main findings: (relevant to PICO question):	CpG only vs allergen group: • No difference was found at any time point, of any parameter or cytokine measured, between the groups In both groups there were significant improvements between time point I and III in: • Resting RR • Breathing type score • PaO_2 • Nasal discharge score • Lung auscultation score • Tracheal mucous and viscosity • Tracheal wash (TW) and serum IL-4
Limitations:	• Environmental and management conditions of horses were not standardised • No control group • Small sample size • Assessors were not blinded to the treatment interventions

Barton et al. (2019) (Follow on paper from Klier et al. 2017)	
Population:	Adult horses with equine asthma
Sample size:	20 horses
Intervention details:	Inhaled CpG or CpG with specific allergen Treatment groups: • CpG inhalation, 187.5 µg CpG-ODN (n=9): One inhalation q48 hours for 14 days • CpG + two individually selected allergens (n=11): One inhalation q48 hours for 14 days Allergen selection: • Functional in vitro test on whole blood was carried out on horses and two allergens were selected for each horse based on geographical location, seasonality of clinical signs and results of blood test Technique: • All inhalations were administered with the same nebuliser equipment All horses were assessed at the following time points: • Time point I: Prior to treatment • Time point II: Immediately after last inhalation • Time point III: 6 weeks after inhalational therapy
Study design:	Randomised clinical trial
Outcome studied:	Objective assessments: • IFN and IL enzyme-linked immunosorbent assay (ELISA): serum and tracheal wash (TW) fluid • MMP and TIMP ELISA from BAL
Main findings: (relevant to PICO question):	• Higher TW concentrations of MMP-2, MMP-9, TIMP-1 and TIMP-2 in horses with severe asthma vs mild asthma • Both groups – MMP-2 and TIMP-2 reduced at Time point II and III • In both groups, MMP-9 and TIMP-1 were reduced at Time point III • In both groups TW IL-4 was reduced at Time point II No adverse effects of inhalational therapy detected
Limitations:	• Environmental and management conditions were not standardised • No control group • Small sample size

Couëtil et al. (2005)	
Population:	Adult horses with equine asthma (RAO) Case selection: • History of chronic respiratory disease >2 years • Increased respiratory effort when fed hay • Management unchanged for 6 months prior to the study • Horses were grouped as mild, moderate or severe asthma • Horses in each group were then randomly assigned to a treatment group
Sample size:	28 horses
Intervention details:	Inhaled or oral corticosteroid treatment or inhaled placebo Treatment groups: • Inhaled fluticasone (n=10): 9 puffs (1980 µg) q12 hours for 2 weeks, then 5 puffs (1100 µg) q24 hours for 1 week, then 5 puffs (1100 µg) q48 hours for 1 week • Oral prednisone (n=9): 500 mg q12 hours for 2 weeks, then 200 mg q24 hours for 1 week, then 200 mg q48 hours for 1 week • Inhaled placebo (n=9): Nine puffs q12 hours for 2 weeks, five puffs q24 hours for 1 week, five puffs q48 hours for 1 week All horses managed outdoors with a completely pelleted diet for duration of study. Half the horses were managed by their owners at home during the study. Technique: • Inhaled substances were delivered using the same inhaler • Prednisone crushed and delivered directly by dosing syringe Horses were assessed: • Prior to treatment (day 0) • After 2 weeks of treatment (day 14) • After 4 weeks of treatment (day 28)
Study design:	Double-blinded, controlled clinical trial
Outcome studied:	Objective assessments: • Pulmonary function tests • Clinical examination score • BALF cytology
Main findings: (relevant to PICO question):	Clinical examination: • Clinical examination score of all horses improved during the study, independent of treatment Lung function tests: • Severely classed horses treated with fluticasone had improved pulmonary function and pulmonary resistance after 2 weeks

	• No difference in lung function between the oral prednisone and the control group • Improvement of all forced expiration values regardless of treatment group at 4 weeks BAL cytology • No improvement for any variable measured in any treatment group
Limitations:	• Half the horses were managed by their owners at home during the study. Treatment may have been incorrectly administered and environment may have differed • Small sample size • Short study time

Vandenput et al. (2010)	
Population:	Adult horses with asthma (chronic obstructive pulmonary disease (COPD)) and healthy adult horses Case selection: • Asthma horses: clinical history of asthma, positive response to hay and straw challenge with clinical signs reversible by administration of atropine (0.02 mg/kg IV) • Healthy controls: no history of respiratory disease, no respiratory abnormalities on clinical exam or pulmonary function tests, no response to hay and straw challenge
Sample size:	12 horses
Intervention details:	Changing environment Environments for asthma group (n=6): • At pasture, no access to barn or hay (Period A – 2 months) • In barn, wood shavings and grass silage (Period B – 6 weeks) • In barn, straw and grass silage (Period C – 6 weeks) • In barn, straw and dry hay (Period D – <6 weeks) Control horses (n=6): • Kept in Period D environment for 6 weeks Management: • Frequency and time of mucking out was standardised • Horses were fed twice daily at the same times • Horses were exercised for 30 minutes every morning COPD horses were assessed at the end of: • Period A, B and C • After they developed clinical signs of COPD during Period D Control group were assessed: • After 6 weeks in Period D environment

Study design:	Prospective, controlled clinical trial
Outcome studied:	Objective assessments: • Lung function tests • RR • Arterial blood gas Horses were also clinically observed each day
Main findings: (relevant to PICO question):	• Asthma horses – no clinical signs of asthma until Period D • After period D, the asthma group had increased pulmonary resistance, maximum change in pleural pressure and significantly decreased dynamic compliance and PaO_2 • No difference in RR between the control group and the asthma group in period D
Limitations:	• Small sample size • Hay exposure without straw should also have been assessed to determine if the development of asthma clinical signs was due to dry hay contact

Leclere et al. (2011)	
Population:	Adult horses with asthma (heaves) Age-matched healthy control horses Case selection of asthma horses (n=6): • 3–10 year history of asthma • Reversible airway obstruction when exposed to hay • Otherwise healthy based on clinical exam, CBC and biochemistry Selection of controls (n=5): • Age-matched clinically normal horses
Sample size:	11 horses
Intervention details:	All horses were maintained at pasture for > 3 months prior to the start of the study Horses were then stabled with hay for the duration of the study Each horse was examined at three time points: • Time point I: prior to stabling • Time point II: day 1 of stabling • Time point III: day 30 of stabling
Study design:	Prospective clinical trial
Outcome studied:	Objective assessments: • pulmonary function • endobronchial and peripheral lung biopsy histology and morphometric analysis/ airway smooth muscle mass measurements • BALF cytology

Main findings: (relevant to PICO question):	• Prior to stabling there was no significant difference in pulmonary function between the asthma and control groups • Significant decrease in pulmonary function in the asthma group after 30 days compared to the control group • Significant increase in neutrophil percentage of BALF in asthma group after 1 and 30 days • Mean airway smooth muscle mass was significantly increased in asthma horses compared to controls at all time points
Limitations:	• Assessors were not blinded • Small sample size

Leclere et al. (2012)	
Population:	Adult horses with chronic heaves (asthma) Selection criteria: • History of heaves for >4 years • Signs of airway obstruction and inflammation on hay exposure • No other health concerns based on clinical exam, CBC and biochemistry
Sample size:	11 horses
Intervention details:	All horses housed indoors and exposed to hay until clinical signs of heaves induced at beginning of study Treatment groups: Antigen avoidance group (n=5): • 24 hour turnout, no access to hay Inhaled corticosteroids group (n=6): • Fed hay indoors and treated with inhaled corticosteroids for 6 months • Then turned out with no hay access and treated with inhaled corticosteroids • 2,000 µg q12 hours for 1 month, then 2,000–3,000 µg q12–24 hours as required to control clinical signs for the duration of the study Each horse was examined at: • Baseline (after clinical signs of heaves induced) • 6 months of treatment • 12 months of treatment • Additional data collected after 1 and 7 months
Study design:	Prospective clinical trial
Outcome studied:	Objective assessments: • Pulmonary function

	• Endobronchial and peripheral lung biopsy histology and morphometric analysis/airway smooth muscle mass measurements • BALF cytology and polymerase chain reaction (PCR)
Main findings: (relevant to PICO question):	• Pulmonary function improved in both treatment groups with no significant difference between them • Airway smooth muscle mass significantly decreased with both treatments • Corticosteroids resulted in a quicker improvement in both pulmonary function and muscle mass • Neutrophil percentage of BALF returned to normal after exposure to antigen had ceased in both treatment groups • IL-8 was significantly decreased in both treatment groups
Limitations:	• No control group • Small sample size • Assessors were not blinded to treatment groups

Jackson et al. (2010)	
Population:	Adult horses with asthma (inducible airway obstruction) Case selection: • Asthma induced by straw and moldy hay • Atropine was administered (0.02 mg/kg IV), lung function was remeasured to test reversibility of airway obstruction • Horses were rested for at least 30 days prior to the study
Sample size:	12 horses
Intervention details:	Treatment groups: • Environmental: pine shavings and complete pelleted feed • Environmental + prednisone: pine shavings and complete pelleted feed and oral prednisone once a day (2.2 mg/kg) Horses were assessed for both treatments at: • Day 0 • Day 3, 7 and 14 • Day 44 (after 30 day wash-out) Timeline of study: • Horses randomly allocated to first treatment group • Heaves induced with management until airway obstruction resulted in maximal change in pleural pressure (>25 cmH_2O) • Lung function and BAL test at day 0, 3, 7, 14 • Treatment maintained for 14 days followed by a 30 day wash-out period • Crossover of treatment groups after washout period
Study design:	Prospective, crossover clinical trial

Outcome studied:	Objective assessments: • Lung function tests • BAL cytology
Main findings: **(relevant to PICO question):**	Environment modification only: • Improvement of lung function by day 3 • No effect on BALF cytology by day 14 Environment + prednisone: • Improvement of lung function by day 3 • Improved BALF neutrophil percentage by day 3, no further improvement at day 14 Wash-out period: • Best improvement in pulmonary resistance, interpleural pressure, total cell numbers and percentage neutrophils were seen in both groups at day 44 (after 30 day wash-out)
Limitations:	• Assessors were not blinded to the treatment group • Small sample size • Long-term effect not assessed

Miskovic et al. (2008)	
Population:	Adult horses with asthma (RAO) Age-matched healthy control horses Case selection of asthma horses (n=24): • Maximum transpulmonary pressure >15 cm H_2O • >25% neutrophils in BALF cytology • Reversible airway obstruction after modifying environment • Maximum of 5–6 years since diagnosis • No treatment except in times of acute asthma crisis • Turned out for 24 hours a day with no access to hay • No medications in the 6 months prior to the study Selection of controls (n=24): • Age-matched clinically normal horses • Normal clinical exam • No history of respiratory clinical signs • No signs of respiratory disease when housed and fed hay
Sample size:	48 horses
Intervention details:	Asthma horses were grouped based on number of years of environmental management since diagnosis: • Group I: 1 year (n=9) • Group II: 2–3 years (n=7) • Group III: 5–6 years (n=8) Management of asthma horses during study: • 24 hour turnout, no access to hay

	Management of controls: • 24 hour turnout with access to a three sided stable shelter and hay Each horse was examined once during the study
Study design:	Cross-sectional study
Outcome studied:	Objective assessments: • Lung function • Forced expiratory manoeuvres • BALF cytology Subjective assessments: • Clinical examination score
Main findings: (relevant to PICO question):	• Asthma Group II had higher clinical exam scores than the control group • There was no difference in the standard lung function tests between the asthma and control groups • Forced expiratory flow (FEF, mean between 75–95% of the exhaled vital capacity) was lower in the asthma groups than control group • No difference in BALF total nucleated cell count between the asthma and control groups
Limitations:	• Clinical examination assessors were not blinded • Small sample number in each group

Auger & Moore-Colyer (2017)	
Population:	Stable design (n= 8 barns/blocks with 32 stables): • American Barns: open windows, roof ventilation, main doors open • Single stable complexes: half doors, windows, vents
Sample size:	128 air samples
Intervention details:	Management regimes (two barns and two stable blocks/regime): • Steamed hay and shavings (Regime 1) • Dry hay and shavings (Regime 2) • Haylage and straw (Regime 3) • Dry hay and straw (Regime 4) Stables sampled once a day when the yard was quiet, horses were present in the stables and free to move around Two samples per stable (breathing zone (BZ) as horses ate and stable zone (SZ))
Study design:	Split-plot design study
Outcome studied:	Objective assessments: • Airborne respirable dust concentration (ARD, particles <5 µm)

Main findings: (relevant to PICO question):	• Steamed hay and shavings – lowest ARD (SZ and BZ) • Dry hay and straw – highest ARD
Limitations:	• Factors including wind, temperature and humidity varied • Feeding system varied – mangers/hay nets/from the ground • Horses movements in stables may have affected samples • Samples were only collected at quiet times; sampling at busiest times would have shown peak variability in regimes • Only four regimes were used

Appraisal, application and reflection

There are currently no studies directly comparing inhaled immunotherapy with environmental modification for the management of equine asthma, and only limited studies exploring the use of inhaled immunotherapy. Papers that directly investigated the effect of inhaled immunotherapy on clinical signs of asthma in horses were included. Five papers were found that investigated the use of inhaled CpG. Comparators used included placebos, inhaled corticosteroid or varying doses of CpG. There are no reports of adverse effects to CpG inhalation.

Due to the incomplete understanding of the pathophysiology of equine asthma (Couëtil et al., 2016) it is difficult to assess the effect of specific interventions on disease modification. The different studies measured a variety of outcomes. Bronchoscopy and BAL fluid analysis, clinical exam scoring, and arterial blood gas analysis were used in all 5 studies. Other outcomes investigated included pulmonary function tests, immunologic analysis of tracheal washes and serum, and owner questionnaires.

The length of these studies ranged; the longest being Klier et al. (2019) which assessed the horses 8 weeks after the treatment period. Therefore, none of these studies is able to determine the long-term effect of inhaled immunotherapy on disease modification.

Four studies found inhaled CpG to improve the clinical signs associated with equine asthma (Klier et al., 2019; Klier et al., 2017; Klier et al., 2015; and Klier et al., 2012). A significant improvement in clinical score was found following treatment with CpG compared to beclomethasone inhalation in the one study that assessed this (Klier et al., 2019). Allergen-specific inhaled immunotherapy was found to be of no significant benefit over inhaled CpG (Klier et al., 2017).

Two studies investigated the effects of CpG inhalation on immunomodulation. CpG inhalation was found to significantly increase IL-10 and IFN- γ (Klier et al., 2012) although the clinical benefits of this are yet to be assessed. CpG inhalation significantly reduced the expression of MMP-2, MMP-9, TIMP-1 and TIMP-2 and IL-4 in tracheal wash fluid (Barton et al., 2019). The authors suggest this indicates CpG may be able to prevent the formation of pulmonary fibrosis and be effective in modifying the disease course of equine asthma.

The five studies investigating the effects of immunotherapy together provide mild evidence supporting the use of inhaled immunotherapy as a treatment for equine asthma.

Due to the lack of papers with a direct comparison relevant to the PICO, papers comparing environmental modification with an alternative treatment for equine asthma were included in this Knowledge Summary. Seven papers were identified that investigated the effect of environmental management on horses with asthma.

Three papers found that environmental modification by outdoor turnout with no access to hay improved lung function and the clinical signs associated with equine asthma (Jackson et al., 2010; Couëtil et al., 2005; and

Leclere et al., 2012). There was no significant improvement in clinical scores of asthmatics or pulmonary function when inhaled fluticasone or oral prednisone were used alongside environmental modification (Couëtil et al., 2005). Leclere et al. (2012) found that inhaled corticosteroids improved pulmonary function of asthmatics more quickly than environmental modification alone, but after 6 months of either treatment there was no significant difference in pulmonary function between groups.

Leclere et al. (2010) found a significant negative impact of poor environmental management (stabled with access to hay for 30 days) on pulmonary function of asthmatic horses when compared to healthy horses.

Two papers investigated the effect of environmental management on airway smooth muscle mass (ASM). It was found that horses with heaves had a significantly increased ASM compared to healthy horses, both prior to antigen exposure and after 30 days of antigen exposure (Leclere et al., 2011). Leclere et al. (2012) found a significant decrease in ASM of horses with heaves after 12 months of environmental management or inhalation of corticosteroids. There was no significant difference in ASM between the groups, but inhaled corticosteroids resulted in a faster reduction of ASM.

Auger and Moore-Coyler (2017) identified that dry hay and straw result in a higher concentration of airborne respirable dust (ARD) and showed that by modifying the stable environment, concentrations of ARD can be significantly reduced.

Miskovic et al. (2008) found that after 6 years of outdoor environmental management with no access to hay, horses with RAO had a significantly lower forced expiratory flow than age-matched healthy horses. Vandeput et al. (1998) found that contact with dry hay can bring horses with COPD out of remission and result in development of clinical signs. These studies provide moderate evidence that environmental management alone is insufficient to permanently cure RAO.

The papers reviewed in this Knowledge Summary all had major limitations. Firstly, the management of horses was heterogenous within studies, horses were kept in their normal environments, with different types and quality of bedding and forage material used, as well as different stable designs and levels of ventilation. This makes it difficult to assess the effect of treatment as the environments of individual horses will also have affected the clinical study results. All of the studies had low study populations and no details were given about power calculations, decreasing the statistical power of results. Other major limitations are the lack of controls in some studies which is likely to affect the clinical significance of each study. The immunotherapy papers share many of the same authors, and there are no publications available from a separate research group, which may create author bias.

Alternative treatments for asthma, that can be used alongside environmental management, are needed. There is the potential for poor owner compliance in maintaining appropriate environmental modifications (Simoes et al., 2020) and in horses with underlying or a history of endocrinopathy, systemic corticosteroid use may be unsuitable (Cornelisse & Robinson, 2011). Recent research has identified inhaled ciclesonide as an effective treatment for equine asthma without affecting serum cortisol (Lavoie et al., 2019), however further research is needed to compare the effect of inhaled ciclesonide with environmental management for equine asthma.

In conclusion, there is low level evidence to support the use of inhaled immunotherapy, alongside environmental modification, as a treatment for equine asthma. The long-term effect of immunotherapy is yet to be assessed, but these papers find it to be effective for up to 8 weeks following a treatment period. There is also the need for further research into the effect of immunotherapy when environmental factors including housing, bedding and forage are controlled, in order to determine if immunotherapy can be recommended as a sole treatment for equine asthma.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts on OVID Platform [1973–week 26 2020] PubMed via NCBI website [1910–week 26 2020]
Search terms:	CAB Abstracts: 1. (equine* or horse* or pony or ponies or equid or exp Equidae/ or exp horses/) 2. ("allergic asthma" or COPD or "chronic obstructive pulmonary disease" or RAO or "recurrent airway obstruction" or "allergic airway disease" or "equine asthma syndrome" or EAS or asthma or heaves or hypersensitivity or "summer pasture-associated obstructive pulmonary disease" or SPAOPD) 3. (Immunotherapy or "allergen specific immunotherapy" or ASIT or "intra-dermal testing" or CpG or immunomodulation) 4. ((stable or stables or hous* or exp stables/) and (manage* or design or ventilat*)) 5. (environment* and (modi* or manage*)) 6. (1 and 2 and (3 or 4 or 5)) PubMed: (equine OR horse OR pony OR ponies OR equid) AND (allergic asthma OR COPD OR chronic obstructive pulmonary disease OR RAO OR recurrent airway obstruction OR allergic airway disease OR equine asthma syndrome OR EAS OR asthma OR heaves OR hypersensitivity OR summer pasture associated obstructive pulmonary disease OR SPAOPD) AND ((immune modulation OR immune therapy OR immunotherapy OR immunomodulatory OR immunomodulation OR allergen specific immunotherapy OR ASIT OR intra dermal testing OR CpG) OR (((stable OR stables OR house OR housing) AND (manage OR management OR design OR ventilated OR ventilation)) OR ((environment OR environmental) AND (modify OR modification OR manage OR management)))) Filter: Veterinary Science
Dates searches performed:	22 Jun 2020

Exclusion / Inclusion Criteria	
Exclusion:	Articles not relevant to the PICO question: • species other than equine • diseases other than equine asthma (and terms formerly known as) • articles not including one of the treatment methods in the PICO Unpublished papers Papers unavailable in English Literature reviews, Knowledge Summaries, discussions and reviews
Inclusion:	All research papers relevant to the PICO: • equine asthma • immunotherapy or environmental management

Search Outcome							
Database	**Number of results**	**Excluded – Irrelevant to PICO**	**Excluded – Relevant but not in English**	**Excluded – Irrelevant, not in English**	**Excluded – Not clinical trials**	**Excluded – Wrong species**	**Total relevant papers**
CAB Abstracts	110	59	5	9	29	1	7
PubMed	249	112	0	26	26	74	11
Total relevant papers when duplicates removed							**12**

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

If you would like to make any acknowledgements, please state them in this section.

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