

REVIEW

Glucocorticoid treatment in horses with asthma: A narrative review

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Abstract

Despite substantial research efforts to improve the treatment and outcome of horses with asthma, glucocorticoids (GC) remain the cornerstone of drug treatment of this prevalent disease. The high efficacy of GC to relieve airway obstruction explains their extensive use despite potential deleterious effects. However, much is yet to be uncovered concerning GC use in horses with asthma, including the comparative efficacy of the different drugs, the determination of minimal effective doses and the mechanisms underlying their variable modulation of airway inflammation. The objectives of this structured review were to report and compare the plethora of effects of the various GC used in asthmatic horses with a focus on impact on lung function, airway inflammation, and bronchial remodeling. Adverse effects are also briefly described, with an emphasis on those that have been specifically reported in horses with asthma. Ultimately, we aimed to highlight gaps in the literature and to identify future research areas.

KEYWORDS

corticosteroid, dexamethasone, heaves, horse, inhalation

1 | INTRODUCTION

Asthma is a frequent and debilitating pulmonary disease affecting horses worldwide. This chronic noninfectious inflammatory condition varies from mild and moderate, formerly known as “inflammatory airway disease,” to the more severe disease previously known as “recurrent airway obstruction” or “heaves.” Clinical exacerbations of severe asthma (SEA) occur when affected horses, mostly adults living in temperate climates, are exposed to antigenic triggers, such as molds and dust present in hay and bedding. In warmer regions, exacerbations of pasture asthma are more common during periods of high heat, humidity, and airborne

fungal spores and grass pollen concentrations.¹ Clinical signs include cough, nasal discharge, exercise intolerance, and increased respiratory effort at rest. Diagnosis involves exclusion of other respiratory diseases, characterization of airway inflammation (generally >25% neutrophils in bronchoalveolar lavage fluid [BALF] during exacerbations) and, ideally, an assessment of lung function.² The latter is mostly limited to research settings because of the complexity and portability of currently available equipment. Therefore, the evaluation of the lung function has been mostly used in research facilities to assess drug efficacy.

The milder forms of asthma affect horses of all ages and include heterogeneous phenotypes with variable BALF inflammatory subsets (elevated proportion of mast cells or neutrophils or eosinophils or a combination of these inflammatory cells). The presence of cough and nasal discharge suggest a respiratory condition in some cases, but the diagnosis is less straightforward in instances where poor performance is the only complaint. Even though the terminology “asthma” incorporates

Abbreviations: ASM, airway smooth muscle; BALF, bronchoalveolar lavage fluid; COPD, chronic obstructive pulmonary disease; CXCL-8, (interleukin-8); GC, glucocorticoids; GCR, glucocorticoid receptors; HPA, hypothalamic-pituitary-adrenal; IAD, inflammatory airway disease; IL, interleukin; LPS, lipopolysaccharides; NET, neutrophil extracellular traps; NF-κB, nuclear factor-kappa B; SEA, severe equine asthma.

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the spectrum of inflammatory respiratory conditions in horses, it does not reflect a continuum in the disease, nor a common pathogenesis.²

Antigen avoidance is the strategy of choice to manage SEA and it is achieved by modifying the diet, mainly by replacing dry hay by less dusty hay alternatives, and by reducing the environmental antigenic exposure. Yet, this approach is not always feasible or adequately implemented, and weeks to months can be required to normalize the lung function. Conversely, glucocorticoids (GC) have the advantage of relieving airway obstruction much faster than antigen avoidance,^{3,4} making these drugs the cornerstone of treatment of asthma. The impacts of GC on the lung function, pulmonary inflammation, bronchial remodeling, as well as their adverse effects in horses with asthma will be addressed here. The objectives of this review were to explore current knowledge on GC use in asthmatic horses and to identify gaps in the literature to guide future research. Although GC have been mainly studied in horses with SEA, their use is largely extrapolated to the treatment of milder forms of asthma² and they are generally considered effective to control pasture asthma.^{5,6} Even though asthma in horses and humans share many similarities,⁷ these are different and heterogeneous conditions for which treatment response, including to GC treatment, needs specific investigation.

2 | MATERIALS AND METHODS

Searches of PubMed, CAB Abstracts and Web of Sciences databases were performed until 19 October 2020 using the key words (horse* OR equine OR Equidae OR Equus) AND (glucocorticoid* OR corticosteroid* OR dexamethasone OR prednisolone OR prednisone OR triamcinolone OR isoflupredone OR methylprednisolone OR fluticasone OR beclomethasone OR betamethasone OR ciclesonide OR budesonide) AND (asthma* OR "recurrent airway obstruction" OR heaves OR COPD OR "chronic obstructive pulmonary disease*" OR "inflammatory airway disease*" OR "IAD" OR "broken wind" OR "small airway disease*"). A snowball selection was also applied to incorporate additional publications. Case reports, case series, retrospective studies, prospective clinical trials, systematic reviews, meta-analyses, and letters, but not narrative reviews, book chapters or meeting abstracts, were included in this manuscript. The literature search was restricted to studies available in English or French. After removal of duplicates using the reference manager ENDNOTE (version X9.3.3), the search yielded 210 resources from which titles and abstracts were screened for relevance to this manuscript (the papers had to concern GC, asthma and the equine species), leaving 85 articles eligible for full-text review. Then, 61 additional references were obtained from snowballing or to support the information presented.

3 | MECHANISMS OF ACTION OF GC

Endogenous corticosteroids include mineralocorticoids, androgenic steroids (androgens, estrogens, progestogens), and GC. The latter are synthesized enzymatically from cholesterol in the *zona fasciculata* of the

adrenal glands⁸ in response to stimulation by the ACTH. The pituitary gland produces ACTH after stimulation by the corticotropin-releasing hormone originating from the hypothalamus in response to stress.

The numerous GC targets result in a multifaceted reduction of inflammation.⁹ Glucocorticoid receptors (GCR) are found in all tissues, with the isoform GCR- α being the most widely expressed and the main effector of GC functions. Glucocorticoid receptor β does not bind GC, but it can modulate steroid response by its interactions with DNA of GC responsive genes, a mechanism possibly contributing to resistance to treatment.^{10,11} The potent anti-inflammatory actions of GC are mediated primarily by effects on gene transcription (genomic effects). The lipophilic GC can penetrate the cell membrane freely to bind the cytoplasmic GCR- α . This binding causes the release of chaperone molecules and subsequent translocation of the GC-GCR complex to the nucleus. There, the interactions with GC responsive elements lead to transactivation (increase in gene expression)⁸ of anti-inflammatory genes, such as interleukin (IL)-10, or transrepression (decrease in gene expression) of pro-inflammatory genes. Transrepression mostly occurs through the modulation of DNA-bound transcription factors, notably nuclear factor-kappa B (NF- κ B) and activator protein-1.⁸ Of note, the NF- κ B pathway is responsible for the production of several pro-inflammatory cytokines, chemokines, and adhesion molecules in response to various stimuli⁹ and it is overexpressed in many inflammatory diseases, including SEA in which its expression in bronchial cells correlates with lung dysfunction.¹²

Because modification of gene expression and subsequent protein translation take hours, these genomic effects have a delayed onset of action. On the contrary, nongenomic mechanisms can occur within minutes and are caused by interactions with the cellular membrane or with the cytosolic or membrane-bound GCR. The consequences of nongenomic actions of GC are being increasingly recognized in the treatment of asthma in humans¹³ and their effects, including alteration of calcium intracellular levels, reduced smooth muscle contraction and modulation of reactive oxygen species production, are summarized elsewhere.¹⁴ Although seldom studied in horses, the nongenomic actions of GC on neutrophils are mediated in part by the GCR.¹⁵

The pharmacokinetics and pharmacodynamics of different GC used in horses have been reviewed recently.¹⁶

4 | EFFECTS OF GC ON THE LUNG FUNCTION

The effects of GC on the lung function have been mainly studied in horses with SEA in research settings. In these conditions, the improvement is evident within a few days of treatment, but inhaled and systemic corticosteroids have limited residual effect after cessation of the treatment.¹⁷⁻²⁰ For this reason, when GC use is required, it should be combined with modifications of dietary and environmental conditions.

Meta-analysis evaluating the effects of GC on clinical score²¹ and lung function²² in asthma did not detect a difference in the magnitude

of improvement between systemic and inhaled use. However, when inhaled GC are directly compared to appropriate systemic administration, the latter is never inferior, but often superior.^{17,18,23-25} Instances where inhaled administration is more effective involve comparison with either prednisone,²⁶ which is not bioavailable in horses²⁷ or the long-acting formulation of dexamethasone 21-isonicotinate, which was possibly used at too low a dose according to the authors.²⁸ Furthermore, it is expected that systemic administration should result in a faster and greater improvement in horses suffering from severe airway obstruction in which mucus accumulation, bronchospasm, and cough might impair lower airways deposition of inhaled medication. A brief review supported that systemic administration has a faster onset of action than by inhalation.²⁹

The effects of GC on arterial blood gas are conflicting.³⁰⁻³⁴ The lack of a control group^{33,34} or the combination of GC administration with environmental modifications and bronchodilators,^{30,31} complicated the interpretation of the results.

4.1 | Systemic use of GC

Dexamethasone is a highly potent GC and the most studied in the treatment of asthma. Consequently, it was used as a positive control in several studies assessing the effects of novel drugs on airway inflammation and lung function in SEA. When compared to a phosphodiesterase-4 inhibitor (theophylline),³⁵ a new generation phosphodiesterase-4 inhibitor (L-826141),³⁶ a MAPK p38 inhibitor,³⁷ a leukotriene D4 receptor antagonist,²⁰ and a selective estrogen receptor modulator (tamoxifen),³⁸ the effects of dexamethasone (0.04-0.06 mg/kg q24h, IV or PO, 7-14 days) on the lung function were never equaled.

Intravenous (0.04-0.1 mg/kg q24h)^{23,35,39,40} and oral (0.05 mg/kg q24h)⁴¹ treatment with dexamethasone improves the lung function of horses with SEA within 3 days. Faster relief of airway obstruction occurs with transient changes noted 6 hours after oral administration (at dosage of 0.164 and 0.082 mg/kg) and as early as 2 hours after IV administration (0.1 mg/kg) in horses with SEA.¹⁹ Dexamethasone (0.1 mg/kg, IV, q24 h, 7 days) improves the clinical score, the lung function, the mucus score, and the cough frequency during exacerbation of SEA.⁴²

The oral administration of a low dose (5 mg) of injectable dexamethasone for a week improves the lung function and the clinical score of horses with SEA, although to a magnitude insufficient for clinical use.²⁵ Given the poor improvement observed with the oral administration of the injectable dexamethasone,^{25,35} it is advisable to administer products intended for oral use. Interestingly, the bioavailability of dexamethasone powder is better than that of the injectable forms in fasting horses, whereas it is similar when they are fed.⁴³

Because treatment adherence is sometimes not achieved in clinical settings,⁴⁴ and objective lung function measurements are lacking, GC efficacy is more challenging to discern in such conditions. Dexamethasone administered in the home environment by the usual caregiver (0.08 mg/kg q24h 4 days, 0.04 mg/kg q24h 4 days, then 0.04 mg/kg q48h 8 days, PO) to SEA horses does not improve the

clinical scores despite concurrent environmental modifications and bronchodilator administration.⁴⁵ As suggested by the authors, these results could have been biased by the low number of animals included, the various housing conditions, and the presence of an outlier. In contrast, owners and trainers were able to identify an improvement in performance, coughing, nasal discharge, and breathing difficulty in horses with varying degree of asthma treated with dexamethasone (0.1 mg/kg, PO, q24, 3 weeks) in their usual environment.³² In that study, a single assessment by a veterinarian did not differentiate between the horses receiving the placebo or the GC, although the respiratory frequency and the hypoxemia significantly improved.³²

The efficacy of the dexamethasone-21-isonicotinate formulation and its ideal dose for the treatment of asthma are unclear. Although a single intramuscular administration (0.06 mg/kg) with a 10-day follow-up does not improve the lung function,²⁸ others observed a reduction of airway obstruction with another posology (0.04 mg/kg IM every 3 days for 10 days).³⁹

The effects of GC in the milder forms of asthma have been little investigated. The clinical usefulness of dexamethasone (0.05 mg/kg IM q24h, 15 days) is supported by the decrease of airway hyper-responsiveness in mild-moderate asthmatic horses.⁴⁶ However, in smoke-induced mild asthma, administration of dexamethasone (20 mg IM q24h, 16 days) does not potentiate the enhanced performance and VO₂ peak obtained with the improvement of air quality.⁴⁷

Another potential benefit of GC in the clinical management of airway obstruction is the prevention of tachyphylaxis to β 2-adrenergic agonists. Dexamethasone (0.1 mg/kg IV q24h, 5 days) prevents the clenbuterol-induced β 2-adrenergic receptor density downregulation on equine lymphocytes.⁴⁸ Thus, it is commonly recommended to use β 2-adrenergic agonists and GC concomitantly to prevent reduced efficacy of the bronchodilator. However, this effect might be cell-dependent as dexamethasone (100 μ M) does not prevent the agonist-induced downregulation in equine bronchial fibroblasts.⁴⁹

Prednisolone administration (2 mg/kg PO q24h, 7 days) ameliorates the airway obstruction in SEA, but less so than dexamethasone (0.05 mg/kg PO q24h) despite a similar suppression of cortisol production.⁴¹ In contrast, treatment with prednisolone (1 mg/kg 4 days, 0.75 mg/kg 4 days and then 0.5 mg/kg 4 days, PO) improved the clinical score in SEA similarly to dexamethasone (0.1 mg/kg 4 days, 0.075 mg/kg 4 days and 0.05 mg/kg 4 days, IM) in another study. However, the environmental modifications performed concurrently made assessment of the GC response equivocal in this latter study.⁵⁰

The poor efficacy of prednisone in SEA is expected because of its low gastrointestinal absorption.²⁷ Furthermore, prednisone is an inactive prodrug and the hepatic metabolism required to obtain active metabolites is suspected to be inadequate in horses. Accordingly, prednisone (2.2 mg/kg q24 PO, 10 days⁵¹ and a 1-month decreasing regimen starting at 500 mg q12h PO²⁶) does not improve the lung function when used concurrently with environmental changes in SEA. When the antigenic exposure of the asthmatic subjects is unchanged, a 10-day prednisone administration (1 mg/kg q24h PO) does not modify lung function.³⁹ In 2 SEA horses used to assess the sensitivity of forced expiration technique to detect response to treatment, the

lung function improved with prednisone administration (1 mg/kg q12h PO, 14 days), however environmental changes were implemented simultaneously.⁵²

Triamcinolone acetonide, a potent long-acting GC, is typically administered intramuscularly or intra-articularly. A single dose (0.08-0.09 mg/kg IM) improves the lung function for approximately 4 weeks in SEA.^{53,54} Notably, this dose administered once intra-articularly has a similar potency to relieve airway obstruction, which suggests that enhanced performance perceived after such use might be related to a pulmonary condition rather than a locomotor disease in some cases.⁵⁴

Similarly, the intra-articular administration of methylprednisolone acetate (200 mg once) ameliorates the lung function in SEA, but the effect is mild, transient, and likely without clinical relevance. Indeed, the pulmonary resistance decreased within 24 hours, but returned to baseline 3 days after administration.⁵⁵ The same dose administered intramuscularly does not relieve airway obstruction.⁵⁵

Isoflupredone acetate (0.03 mg/kg IM q24h, 2 weeks) improves the lung function similarly to dexamethasone (0.04 mg/kg IV q24h, 2 weeks) in SEA.⁴⁰ However, the hypokalemia resulting from the high mineralocorticoid activity of isoflupredone is a concern in horses.⁴⁰

4.2 | Inhaled administration of GC

Beclomethasone dipropionate is a prodrug requiring cleavage by esterase enzymes within the lung to become pharmacologically active, limiting its systemic bioavailability.⁵⁶ Several regimens of beclomethasone have been investigated for the treatment of SEA. Doses as low as 500 µg improve the lung function within 24 hours,⁵⁷ although the same dose (500 µg q12h) administered for 10 days in horses kept in an antigenic environment ameliorated but did not normalize lung function.²⁸ Inhalation of beclomethasone (1320 µg q12h, 7 days) relieves airway obstruction, but possibly less so than dexamethasone (0.1 mg/kg IV q24h).²³ When given at a higher dose for a longer duration (3750 µg q12h, 15 days) in horses kept in stable environmental conditions, beclomethasone improves the lung function starting a week after initiation of treatment with some animals having normal lung function at the end of treatment.³³ However, these results need to be interpreted with caution as there was no control group.³³ The PaO₂ and PaCO₂ were not significantly altered by the treatment in that study. Conversely, the administration of beclomethasone (1600 µg q24h, 10 days) to horses with SEA kept in their natural environment improved the PaO₂ after treatment and also 8 weeks later. However, this study lacked a placebo control group and the unusual persistence of beneficial effects suggests that the antigenic exposure was not stable, despite effort to do so.³⁴ The reduction of airway obstruction by beclomethasone is supported by *in vitro* experiments in which precision-cut lung slices from horses without respiratory disease were studied. The bronchoconstriction induced by leukotriene C₄ is attenuated by beclomethasone and the rapid onset of action (<30 minutes) suggests a nongenomic mechanism of action.⁵⁸

Fluticasone is an inhaled GC for which systemic adverse effects are less likely considering its low oral bioavailability (<1%)⁵⁶ and its efficacy attributable to local lung absorption.⁵⁹ Despite these

favorable properties, it is detectable in plasma after inhalation in horses.⁶⁰

Fluticasone (2000 µg q12h) administered to horses with SEA kept in an antigenic environment markedly improves the lung function after a month.³ The degree of airway obstruction then remains stable for the next 5 months of treatment, but further improves when the horses are moved to a low antigenic environment. However, even after 11 months of fluticasone treatment (including antigen avoidance for the last 5 months), some residual bronchospasm can persist.³ In contrast, the combination of fluticasone (2500 µg q12h) and salmeterol (250 µg q12h; a long-acting β₂-agonist) normalizes respiratory mechanics within a week and no residual bronchospasm is present after 12 weeks of treatment,⁴ indicating that GC and β₂-adrenergic agonists might act synergistically. Of note, fluticasone improved lung function faster than environmental management in these 2 trials.^{3,4} Interestingly, fluticasone (1980 µg q12h) hastens the improvement in lung function only in SEA horses with the most severe airway obstruction when used in combination with antigen avoidance strategies.²⁶ Fluticasone (2000 µg q12h, 5 days) used with bronchodilators and antigen avoidance did not improve respiratory signs in 2 horses with an unusual presentation of SEA (>80% eosinophils in BALF).⁶¹

In the prevention of exacerbations, a high dose of inhaled fluticasone (6 mg BID, 7 days) is as effective as dexamethasone (0.1 mg/kg IV q24h, 7 days). However, the latter is more potent in the treatment of exacerbation.²⁴

In mild asthmatic horses, inhaled fluticasone (3000 µg q12h, 15 days) decreases airway hyperresponsiveness similarly to dexamethasone (0.05 mg/kg IM q24h).⁴⁶

Ciclesonide is a prodrug activated by esterase within the lungs to confer pharmacological activity.⁵⁶ Its high protein-binding in circulation likely limits its systemic effects as GC linked to proteins do not activate their receptors.⁵⁶ Ciclesonide aerosolized using the Soft Mist technology, and a novel administration system, improves lung function during exacerbation of SEA, with the regimen of 2700 µg q12h being maximally effective¹⁸ with results comparable to those obtained with dexamethasone (0.066 mg/kg PO q24h, 2 weeks).

Inhaled budesonide has dose-dependent effect on the lung function of horses with SEA and the dosage of 1800 µg q12h for 2 weeks is as potent as dexamethasone (0.04 mg/kg IV q24h).¹⁷ Nebulized budesonide (1500 µg q12h, 10 days) improves the respiratory clinical score during exacerbation of SEA, but not during remission.⁶² The interpretation of these latter results needs caution as a low-dust environment was also implemented and the study lacked a control group.⁶²

The nebulization of the injectable form of dexamethasone (5 mg q24h, 7 days) does not improve lung function in SEA, whereas it significantly suppresses the endogenous cortisol production.²⁵ These results contrast from findings in healthy horses, where nebulized dexamethasone at the same dose does not suppress the hypothalamic-pituitary-adrenal (HPA) axis and has a low systemic bioavailability.⁶³ The suppression of the HPA axis in asthmatic horses and not in controls is consistent with another study where the plasma concentration of inhaled budesonide was significantly greater in SEA

than in healthy horses.⁶⁴ The authors suggested that this might be caused by an increased pulmonary absorption of drugs by the diseased epithelium. Alternatively, it could be explained by a higher delivery to the gastrointestinal tract in asthmatic animals because of greater airway obstruction, cough, or mucus accumulation impairing penetration in lower airways. The plasma and urinary clearance of nebulized dexamethasone has been described.⁶⁵

5 | EFFECTS OF GC ON INFLAMMATION

5.1 | Effects of GC on BALF cell populations

Despite the potent anti-inflammatory effects of GC, these drugs generally fail to normalize airway neutrophilia unless antigen avoidance is implemented concurrently.

In horses in chronic exacerbation kept in a constant antigenic environment, parenteral dexamethasone (0.04 mg/kg IV q24h, 14 days) does not modify airway neutrophilia despite normalization of the lung function.^{20,36,37} Similarly, oral administration (0.1 mg/kg q24h, 3 weeks³² or 0.06 mg/kg q24h, 14 days⁶⁶) does not reduce airway neutrophilia when the environment is unchanged. A shorter treatment with a higher dose (0.1 mg/kg IV, 3 days) also fails to improve pulmonary inflammation in SEA.²⁴ In another study, the administration of dexamethasone (0.04 mg/kg IV q24h, 2 weeks) significantly decreased airway neutrophilia even when antigen avoidance was not implemented, but the percentage of neutrophils failed to normalize in most horses.¹⁷ The limited information available in milder forms of asthma is similar: treatment with dexamethasone administered intramuscularly (0.05 mg/kg q24h, 15 days⁴⁶ and 20 mg q24h, 10 days⁶⁷) does not decrease BALF neutrophils, eosinophils, or mast cells.

The studies in which GC are combined to environmental modifications are harder to interpret and conflicting.^{42,50,68-70} For instance, airway neutrophilia decreases with dexamethasone (0.1 mg/kg 4 days, 0.075 mg/kg 4 days and 0.05 mg/kg 4 days, IM), but not with prednisolone (1 mg/kg 4 days, 0.75 mg/kg 4 days and 0.5 mg/kg 4 days, PO) when it is combined with environmental management.⁵⁰ When administration of dexamethasone (0.165 mg/kg q24h 7 days, 0.083 mg/kg q24h 7 days and 0.04 mg/kg q24h 7 days, PO) is started when the antigenic exposure used to induce exacerbation is stopped, a decrease in airway neutrophilia is unsurprisingly obtained.⁷⁰ Dexamethasone (decreasing regimen starting at 0.165 mg/kg q24h, 3 weeks PO) combined with feeding modification improves airway neutrophilia to a greater extent than dietary alterations alone in SEA.⁶⁸

The duration of antigenic exposure before administration might modulate the treatment response. When the exacerbation time is short before treatment, dexamethasone (0.1 mg/kg IV q24 h, 1 week) decreases but does not normalize airway neutrophilia.⁴² However, these results need to be interpreted with caution as no control group was included. Similarly, when the treatment is started as soon as significant airway obstruction occurs, dexamethasone (0.1 mg/kg IV q24h, 10 days) decreases airway neutrophilia in SEA compared to horses receiving no treatment.³⁹

The administration of prednisone (2.2 mg/kg q24h PO, 14 days), concurrently with environmental changes, decreases airway neutrophilia to a greater extent than environmental changes alone in SEA.⁵¹ These results are surprising considering the poor bioavailability of this drug²⁷ and the fact that oral prednisone (400 mg/horse q24h, 10 days⁷¹ or 1 mg/kg q24h, 10 days³⁹) did not improve airway neutrophilia in 2 other trials.^{39,71}

As reported for systemic administration, inhaled GC generally does not alter airway inflammation. Yet, differences in drugs, doses, lengths of treatment, duration of exacerbation, and concomitant environmental changes all contribute to conflicting results. Fluticasone (either 3000 µg or 6000 µg q12h, 3 days) does not modify airway neutrophilia in severe²⁴ and in mild-moderate asthma (3000 µg q12h, 15 days).⁴⁶ Even prolonged administration (6 months, 2000 µg q12h for the first month, then adjusted to control clinical signs), does not improve airway neutrophilia in contrast to the horses managed with antigen avoidance.³ Expectedly, the administration of fluticasone (2000 µg q12h, 21 days) in horses with SEA decreases airway neutrophilia when it is accompanied by improvement of hay quality.⁷² Conversely, in another cohort of SEA, the administration of fluticasone (1980 µg q12h 2 weeks; then 1100 µg q24h 1 week and 1100 µg q48h 1 week), along with environmental management, did not improve airway neutrophilia.²⁶ Interestingly, half of these horses were treated by their owners, suggesting that efficacy of environmental and treatment recommendations might be poorer in field conditions. In SEA, the combination of fluticasone (2500 µg q12h) and salmeterol (250 µg, q12h) improves airway neutrophilia after 8 weeks of treatment while environmental modifications results in a significant improvement after 1 week of treatment.⁴

Similar to fluticasone, inhaled budesonide (1800 µg q12h, 14 days)¹⁷ and beclomethasone (500 µg q12h, 10 days)²⁸ do not modify BALF cytology in horses kept in an antigenic environment. In contrast, a 7-day treatment with aerosolized beclomethasone (1320 µg q12h) reduces BALF neutrophilia during antigenic exposure, but without normalizing it. In that study, corticosteroid treatment also decreased pro-inflammatory lymphocyte populations (CD4+ and B lymphocytes).⁷³ Likewise, beclomethasone (1600 µg q24h, 10 days) reduced airway neutrophilia in horses kept in their natural environment, however a control group was not included.³⁴ Inhalation of budesonide (1500 g q12h, 10 days) decreased airway neutrophilia in horses with SEA, but the treatment was accompanied by a low-dust environment and there was no control group.⁶² The nebulization of dexamethasone (15 mg q24h, 13 days) does not modify BALF cytology in mild asthma.⁷⁴

Combined, these results suggest that the environment, rather than GC, is mainly responsible for the improvement of airway neutrophilic inflammation in many studies.

5.2 | Effects of GC on pulmonary gene expression and markers of inflammation

Several studies have explored the effects of GC on pulmonary gene expression in asthmatic horses. The results are disparate as different treatment regimens, environmental management, and horses with

different disease severity were investigated. Furthermore, variation in PCR methodology possibly influenced the results and it should be specifically designed to limit bias in each experimental trial. A normalization technique was proposed for the study of BALF gene expression in horses with milder forms of asthma treated with GC.⁷⁵

Consistent with the anti-inflammatory properties of GC, downregulation of several pro-inflammatory genes in BALF of asthmatic horses have been reported. Fluticasone administered for 6 months decreases the messenger ribonucleic acid expression of interleukin-8 (CXCL-8) in BALF cells of SEA horses kept in an antigenic environment. However, this reduction is smaller than that obtained with antigenic avoidance.³ The alveolar macrophages gene expression of CXCL-8 and IL-1 β is reduced by a single administration of fluticasone (2000 μ g) after an experimental challenge (aerosolization of *Aspergillus fumigatus*).⁷⁶ In milder forms of asthma, dexamethasone (20 mg IM q24h, 10 days) downregulates the gene expression of IL-5 and TNF- α in BALF cells, whereas the expression of several other genes is unchanged (IL-1 β , IL-4, IL-6, CXCL-8, IL-10, IL-12, IL-17, IL-23, IFN- γ , and eotaxin-2).⁷⁷ Neither dexamethasone-21-isonicotinate (0.06 mg/kg IM once) nor beclomethasone (500 μ g q12h, 10 days) modify the gene expression of NF- κ B and activator-protein 1 from epithelial cells of SEA horses kept in an antigenic environment.²⁸

Variable results are obtained when environmental modifications are performed. Adding dexamethasone (decreasing regimen starting at 0.165 mg/kg q24h PO) to dietary modification results in a greater decrease in the BALF cells gene expression of CXCL-8, CXCL-2, and IL-1 β than feeding modifications solely in SEA.⁶⁸ The administration of dexamethasone (0.05 mg/kg IM q24h, 2 days) does not modify the gene expression of CXCL-8, TNF- α , IL-1 β , INF- γ , and IL-6 of SEA horses in remission at pasture.⁷⁸ In that study, the treatment decreased the gene expression of IL-6 and TNF- α during exacerbation, but it was combined with environmental improvement.⁷⁸ In contrast, a 3-week treatment with fluticasone (2000 μ g q12h), along with enhanced hay quality, fails to modify the gene expression of pro-inflammatory cytokines despite an improvement of airway neutrophilia, lung function, and clinical signs in horses with SEA.⁷²

Several other variables of lung inflammation have been assessed. In SEA, dexamethasone (0.06 mg/kg q24h PO, 2 weeks) reduces the neutrophil extracellular traps (NETs) formation and neutrophilic apoptosis without modifying neutrophilic activation (evaluated through the marker of activation CD11b) or the gene expression of IL-17 from BALF cells.⁶⁶ Inhaled budesonide decreases BALF metalloproteinases in horses with SEA, but interpretation of these results is complicated by concomitant environmental modification and the lack of a control group.⁷⁹ Finally, dexamethasone (0.06 mg/kg q24h PO, 2 weeks) increases the BALF regulatory T cells in SEA, but not in controls.⁸⁰

5.3 | Effects of GC on peripheral leukocytes, systemic markers of inflammation, and in vitro studies

The inflammation in SEA,⁸¹ and in milder forms of asthma,⁸² is not merely localized to the lung as several pro-inflammatory markers are

increased in circulation. Nonetheless, most studies evaluating the effects of GC on systemic inflammation have been performed in healthy horses.

Dexamethasone reduces the lipopolysaccharides (LPS) induced expression of CXCL-8,^{15,83} IL-1 β ,⁸³ TNF- α ,^{15,83} and TLR-4¹⁵ from peripheral neutrophils of healthy horses. Furthermore, dexamethasone inhibits phorbol myristate acetate induced NETs formation⁶⁶ and respiratory burst of peripheral neutrophils.¹⁵ However, the IL-17-induced CXCL-8 production by equine neutrophils is not downregulated by dexamethasone.⁸⁴ This finding could contribute to the persistence of airway neutrophilia during GC treatment as CXCL-8 is a potent neutrophilic chemoattractant. However, these results need confirmation in asthmatic horses as it was performed in healthy animals. Enhanced neutrophilic viability induced by GC⁸³ could also participate to the persistence of neutrophils in the airways.

In equine whole blood cultures, dexamethasone, and to a lesser extent hydrocortisone, inhibits the stimulated release of TNF- α , IL-1Ra, and IFN- γ .⁸⁵ Triamcinolone (0.04 mg/kg IV once) administered to healthy horse decreases the production of several eicosanoids (thromboxane B₂, prostaglandin E₂ and prostaglandin F_{2 α}) in whole blood stimulated by LPS.⁸⁶ Finally, dexamethasone (10⁻⁵ M) decreases the gene expression of CXCL-8 induced by IL-4, LPS, and TNF- α from pulmonary artery endothelial cells of normal adult horses.⁸⁷

6 | EFFECTS ON AIRWAY REMODELING

Characteristics of airway remodeling in asthma have been reviewed⁸⁸ and include increased airway smooth muscle (ASM) mass, abnormal extracellular matrix deposition, mucus gland hypertrophy, and epithelial fragility. Few studies have investigated the modulation of bronchial structural changes by GC.

A 6-month fluticasone administration (2000 μ g q12h 1 month, then at doses required to control lung function) decreases the ASM mass in peripheral airways by approximately 30% in horses with SEA kept in an offending environment.³ A shorter fluticasone treatment (2500 μ g q12h, 3 months) results in a similar improvement (about 30% decrease in ASM mass) after 3, but not 1 month of treatment.⁴ The same improvement is obtained after 2 months of fluticasone treatment (2500 μ g q12h) in SEA horses (unpublished results from the authors). The combination of fluticasone and salmeterol might be synergistic as it normalizes the thickness of the extracellular matrix of central airways, whereas fluticasone and salmeterol used in monotherapies have no such effect.⁴

Interestingly, the peripheral ASM maximal velocity of shortening correlates with the time elapsed since the last GC treatment in horses with SEA.⁸⁹ The authors proposed that the apparent decrease in hypercontractility might be related to direct interaction between ASM and GC or through modification of the inflammatory microenvironment.

The smooth muscle myosin heavy chain (+) insert provides a faster rate of muscle contraction and possibly contributes to airway hyperresponsiveness in asthma.⁹⁰ Its gene expression, which is increased in ASM from central airways of horses with asthma,⁹¹ is reduced 2-fold after 3 months of fluticasone treatment in SEA

(2000 µg q12h 1 month, then at doses required to control lung function).⁹¹ Similar results are obtained after 2 months of fluticasone administration (2500 µg q12h; unpublished results from the authors).

In vitro, dexamethasone decreases serum-induced collagen production of equine bronchial fibroblasts and has a biphasic effect on cellular proliferation (anti-proliferative at high concentration [10^{-6} and 10^{-4} M] and pro-proliferative in lower ranges [<1 µM]).⁴⁹ Dexamethasone, alone or synergistically with β 2-adrenoreceptor agonists, also limits the TGF- β 1-induced transition of fibroblasts to myofibroblast. All these effects could contribute to the anti-remodeling properties of GC in asthma.

During clinical remission of SEA, the degree of bronchiolar inflammation is higher in horses stabled and pharmacologically treated (corticosteroid \pm bronchodilators) compared to the subjects kept at pasture.⁹² These results are consistent with data obtained from BALF cytologies.³

7 | ADVERSE EFFECTS

Most studies evaluating short-term use of systemic or inhaled GC do not report any clinical adverse effects.^{40,46} However, their long-term administration is usually limited by fear of adverse events including laminitis, immunosuppression, and interactions with endocrine metabolism.

7.1 | Laminitis

Reports of GC-induced laminitis are anecdotal.^{93,94} Several mechanisms such as interaction with digital vascularization, abnormal keratinocytes growth, and induction of peripheral insulin resistance have been proposed to explain a possible laminitis risk with GC and are reviewed elsewhere.⁹⁵⁻⁹⁷ However, clinical signs related to laminitis have rarely been reported when it was specifically monitored in asthma.^{17,24,40} Furthermore, a retrospective case-control study did not support an increased risk of laminitis in a large number of horses treated with prednisolone.⁹⁸

Triamcinolone is thought to be associated with greater risk of laminitis based on cases where doses which markedly exceed the recommended dosing rate were administered⁹⁹⁻¹⁰¹ and on a pharmacokinetic study that described the apparition of hoof rings in 4/5 horses 2 to 14 months after the use of triamcinolone (0.2 mg/kg IV).¹⁰² However, the incidence of laminitis appears rare when large numbers of horses are examined (development of laminitis in 3/2000 horses treated with GC intra-articularly, mainly triamcinolone,¹⁰³ and in 1/205 horses receiving 10-80 mg of triamcinolone via various routes of administration, with the affected horse having a history of laminitis¹⁰⁴).

Although the association of corticosteroids with laminitis is controversial, cautious use is recommended especially in horses with an endocrine or systemic inflammatory disease, or a local foot condition. Indeed, GC do not affect the basal tone of digital veins and arteries in vitro, but they potentiate the vasoconstrictor effects of biogenic

amines.¹⁰⁵ Furthermore, the administration of dexamethasone (0.1 mg/kg IV q24h, 6 days) reduces skin temperature and amplifies the temperature drop induced by phenylephrine, indicating a possible potentiation of the vasoconstrictor effects of catecholamines.¹⁰⁶ These studies suggest that GC might prompt laminitis development when given during a stressful or an inflammatory condition. However, it is unclear if asthma represents a predisposing factor. Indeed, SEA has been positively associated with the onset of laminitis, but negatively associated with its recurrence in a retrospective study.¹⁰⁷ Prednisolone administration is associated with the development of subsequent episodes of laminitis in horses, but not of the first onset.¹⁰⁷ In summary, GC-induced laminitis is uncommonly reported when asthmatic horses are treated systemically at recommended doses although it remains a potential complication to consider in predisposed animals. To our knowledge, episodes of laminitis have never been reported with inhaled GC.

7.2 | Effects on blood leukocytes and immunosuppression

As expected with systemic GC administration in adult horses¹⁰⁸⁻¹¹³ and foals,¹⁰⁸ increased neutrophils and decreased lymphocytes and eosinophils blood counts have been described in horses with SEA administered dexamethasone and isoflupredone.⁴⁰ As in other species, a higher vascular neutrophil count is attributed to the release from the marginalized pool.¹¹⁴ This effect is not observed when fluticasone is administered to horses with SEA.¹¹⁵

Short-term GC treatments are usually not associated with clinical immunosuppression, but cases of pneumonia after long-term systemic use have been described in horses.¹¹⁶ Immunosuppression induced by GC could be multifactorial. For example, the administration of dexamethasone to horses (0.88 mg/kg IM q24h, 3 days) and ponies (5 mg IV once) increases serum iron concentration which could facilitate bacterial proliferation.¹¹⁷ Furthermore, dexamethasone (0.2 mg/kg IM twice weekly during 8 weeks) significantly suppresses the production of immunoglobins G α and G β after vaccination in healthy horses.¹¹⁸ The administration of injectable hydrocortisone (1 mg/kg) to healthy horses increases the migration capacity of stimulated neutrophils, whereas the bacterial phagocytosis and killing capacity against *Staphylococcus aureus* are unchanged.¹¹⁹ Generally, the use of inhaled corticosteroids is considered safer because of the local delivery. In agreement with this, the administration of fluticasone for almost a year to horses with SEA does not alter their innate and acquired immune function, including lymphocyte function and the amnestic and novel responses to vaccination after 6 months of treatment.¹¹⁵

7.3 | Impact on the HPA axis

The HPA axis is controlled by negative feedback signals resulting in the reduction of corticotropin-releasing hormone secretion when

endogenous or exogenous GC stimulate the hypothalamic GCR. This in turn decreases ACTH production by the pituitary gland, and ultimately the production of cortisol by the adrenal glands.⁵⁶ Horses with SEA have similar cortisol levels at rest and at exercise compared to healthy animals.¹²⁰ Multiple equine studies have described adrenal suppression with systemic and inhaled GC, but typically without clinical signs. Furthermore, the responsiveness to ACTH administration usually remains unchanged.^{53,121,122} Dexamethasone administered at different dosages ([0.1 mg/kg IV q24h, 7 days]¹²²; [0.088 mg/kg or less, IM, every 5 days for 30 days]¹²¹; [0.044 mg/kg IM once]¹²³; [0.04 mg/kg q24h, IV, 2 weeks],¹⁷ [20 mg, IM, once]¹¹²) causes adrenal suppression as early as 2 hours after the administration. A single dose of triamcinolone (0.09 mg/kg IM) suppresses endogenous cortisol production for approximately 4 weeks in horses with SEA.⁵³ The administration of a smaller dose of triamcinolone (0.044 mg/kg IM) results in maximal adrenal suppression by 12 hours and lasts 14 days.¹²³ Isoflupredone acetate (0.03 mg/kg IM q24h, 14 days) also seems to cause a longer suppression than dexamethasone.⁴⁰ Methylprednisolone administered intra-articularly (200 mg once) briefly suppresses cortisol production, from 6 to 24 hours after the injection.⁵⁵

Although a month-long administration of inhaled fluticasone at a decreasing dosage does not modify the adrenocortical function,²⁶ longer administration (11 months) suppresses the endogenous cortisol production in SEA horses.¹²⁴ Inhaled beclomethasone (1320 µg q12h, 7 days) suppresses cortisol, which normalizes 2 days after discontinuation of treatment.¹²² Even lower doses of beclomethasone ([from 500 to 1500 µg q12h, 1 week]⁵⁷ and [528 µg q12h, 5 days]¹²⁵) causes adrenal suppression. The administration of inhaled budesonide (1800 µg q12h, 2 weeks) induces HPA axis suppression in horses with SEA to a similar extent to dexamethasone (0.04 mg/kg IV q24h, 2 weeks).¹⁷ Conversely, ciclesonide administered at different dosages (up to 2700 µg q12h, 14 days) does not alter serum cortisol measurements, which is consistent with the low oral bioavailability of this drug.¹⁸

Theoretically, HPA axis suppression could lead to hypo-adrenocorticism after drug withdrawal, but this has not been reported in horses with asthma. Nevertheless, and to minimize the disturbance of the endogenous GC circadian rhythm of horses,¹²⁶ it is commonly recommended to administer GC in the morning.

7.4 | Metabolic effects

Glucocorticoids interfere with glucose and lipid metabolism. These effects have not been assessed specifically in asthmatic horses, therefore it is unknown if their disease status could affect the metabolic alterations. Increased blood glucose^{102,123,127} and triglycerides¹⁰² and insulin resistance¹²⁸ are expected with GC administration. Use of dexamethasone (0.05 mg/kg IM q24h, 7 days) also results in a clinically irrelevant increase in blood lactate.¹²⁷

Glucocorticoids alter calcium metabolism by increasing urinary excretion and decreasing gastrointestinal absorption¹²⁹ along with an inhibition of calcium release from bones.¹³⁰ Because administration of

GC to human patients is associated with osteoporosis, this effect was investigated in pony foals where prolonged treatment (>3 months) with dexamethasone (0.005-0.05 mg/kg q24h IM) led to osteonecrosis.¹³⁰ In healthy and severe asthmatic horses administered triamcinolone (0.09 mg/kg IM once), serum osteocalcin, an indicator of bone turnover, is significantly reduced and it takes up to 150 days for some horses to reach their baseline levels.¹³¹ In a horse with SEA and histologic alteration of the parathyroid gland, the use of dexamethasone (0.06 mg/kg PO q24h, 8 days) was believed to have precipitated clinical signs related to refractory hypocalcaemia and hypomagnesaemia.³⁸

Glucocorticoids have variable mineralocorticoid properties and can therefore influence electrolyte balance, even with selective GC such as dexamethasone and triamcinolone.¹²³ The higher mineralocorticoid potency of isoflupredone might explain the hypokalemia induced by this drug in horses with SEA (0.03 mg/kg IM 24 h, 14 days).⁴⁰

Rarely, and not specifically in asthmatic horses, large overdoses of GC have been associated with hyperadrenocorticism with signs such as muscle wasting, polydipsia/polyuria, and hepatopathy.^{99,101}

7.5 | Impacts of GC on airways microorganism populations

The interactions between the inflammatory pulmonary microenvironment and microorganisms in asthma are poorly understood, but a role for virus, bacteria, altered microbiome, and fungus in the pathogenesis of the disease is suspected^{67,74,132-135} and was recently reviewed.¹³⁶ The study of airway microbiome in equine asthma is at its onset and follows the growing interest in understanding the crosstalk between the lung and gut microbiota and immune functions in humans.¹³⁷ Of note, the airway microbiome is associated with alteration of the GC response in humans.^{138,139}

In horses, few data are available concerning the impacts of GC on the airway microbiome and the effect of the latter on treatment response is unknown. The use of dexamethasone (20 mg q24h IM, 10 days) alters the abundance of some operational taxonomic units (roughly bacterial species) from the lower respiratory tract of healthy and mild asthmatic horses.⁶⁷ The nebulization of dexamethasone (15 mg q24h, 13 days) decreases the microbiota diversity in mild asthma in upper, but not in lower airways, and it does not modify the upper airway mycobacteria nor the nasal equine herpesvirus-2 DNA expression from nasal swabs.⁷⁴ Oral and pharyngeal fungal infections are a possible complication of inhaled GC in humans. This has not been observed to our knowledge in the equine species and no fungal growth occurred from pharyngeal swabs of horses with SEA treated with beclomethasone.³³

7.6 | Miscellaneous effects

Coughing during inhalation of GC is frequently reported in human asthmatics⁵⁶ and it has been noted in SEA after inhalation of

beclomethasone,^{6,57,122} budesonide,¹⁷ and nebulized dexamethasone.²⁵ However, it is uncertain if the induction of cough is related to the GC, the vehicle, the inhalation device, or simply to the disease itself.

The administration of GC has deleterious effects on the tegument with skin thinning, fragility, and delayed healing observed even with inhaled use in humans.⁵⁶ The chronic use of inhaled fluticasone (2500 µg q12h, 5 months) resulted in local alopecia around the nostrils in 1 study and the histopathology results were consistent with locally GC-induced epidermal and follicular atrophy (unpublished results from the authors).

Alterations of coagulation can occur with GC in other species; however, it has not been reported in the horse so far. Indeed, the administration of dexamethasone (0.05 mg/kg IM q24h, 7 days) does not affect thromboelastographic variables.¹⁴⁰

Behavioral changes, occasionally described in humans¹⁴¹ after GC administration, have not been described in the equine species to our knowledge.

7.7 | Corticosteroid resistance

Corticosteroid insensitivity is a well-recognized phenomenon in asthma in humans although there is no consensual definition. The cellular mechanisms leading to GC resistance in asthma are only partially understood but include the overexpression of pro-inflammatory transcription factors and of the GCR-β.^{10,142} The GC sensitivity is also modulated by several clinical factors,¹⁴² such as genetics, neutrophilic inflammation,¹⁴³ and comorbidities, including obesity.¹⁴⁴ Corticosteroid resistance is not objectively defined in horses and the severity of the disease, the presence of comorbidities, the antigenic exposure, the compliance, and the administration techniques by the caregivers could all influence treatment response.

8 | CONCLUSIONS AND FUTURE DIRECTIONS

This review highlights the potency of GC for relieving airway obstruction in asthma, but also underlines the varying clinical response. These heterogeneous results undoubtedly reflect disparity in research protocols including differences in the severity of asthma, the GC used, and the dose administered. Of note, several studies investigated the effects of GC treatment concurrently to modification of diet or stabling conditions. Although this is likely more representative of clinical management in the field, it further complicates the evaluation of the specific impacts of GC administration. However, even in controlled research settings, the environmental conditions cannot be completely standardized (including variation in humidity, temperature and pollen concentration) and can influence the respiratory condition,¹⁴⁵ emphasizing the necessity to include a control group. Most available GC successfully relieve airway obstruction, but no normalization of neutrophilic

inflammation is expected when antigen avoidance is not implemented, even though indicators of neutrophilic activation (such as NETs) can be attenuated. From this review, several questions are raised for future investigations.

- Few studies have assessed GC treatment in horses with mild and moderate asthma, including their impact on performance in sport or racehorses. The usefulness of adding GC to environmental management in this condition remains to be determined.
- Airway luminal neutrophilia, and possibly mastocytic and eosinophilic inflammation, are not controlled by potent anti-inflammatory drugs such as GC. Therefore, a better understanding of the role of neutrophils in the disease would be helpful to specifically determine if GC attenuate the deleterious activities of these leukocytes. The impacts of GC on markers of inflammation in BALF, in bronchial tissue, and in circulation are also poorly understood.
- Understanding the specific contributions of genomic and nongenomic actions of GC, as well as the signaling pathways implicated in the beneficial effects on bronchoconstriction and remodeling would be useful for the development of alternative therapies. Particularly, the characterization of the mechanisms involved in the reduction of ASM mass by GC is an area of research applicable to translational medicine. Indeed, treatments targeting ASM are relevant as it is the main contributor to airway hyper-responsiveness, and it is associated with long-term persistent-fixed airway obstruction in humans.¹⁴⁶
- Only partial reversibility of bronchial remodeling was achieved with long-term inhaled GC in SEA. Consequently, determining if further improvement can be obtained with systemic administration or with combination treatment (β2-adrenoreceptor agonists, anticholinergics, etc.) would be valuable for the long-term management of this incurable disease. The possible synergy between β2-adrenoreceptor agonists and GC to control airway inflammation and remodeling merits further investigation.
- Comparative studies of the available inhaled and systemic GC would be useful to establish the value of each drug and the minimal effective dose of systemic GC. Furthermore, many pharmacodynamic and pharmacokinetic information is extrapolated from human data. Obtaining equine-specific knowledge in this area (such as oral bioavailability, protein-binding, or affinity with the GCR) would be useful to guide clinical recommendations and to reduce the risks of adverse effects.
- Investigations specifically monitoring adverse events could allow the practitioners to weigh the pros and cons more clearly when using GC but would require the study of large cohorts of horses. The possible association between laminitis and a diagnosis of SEA needs to be examined further.
- The impacts of comorbidities, environmental factors, microbiome, and physiological states, such as aging, sex, and estrus variation, on disease severity and treatment response to GC require investigation. A definition of GC resistance is needed to characterize uncontrolled asthma and to guide clinicians and researchers toward precision medicine.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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