

A perspective on systemic corticosteroid therapy in severe bronchial asthma in adults

William B. Klaustermeyer, M.D. and Soo H. Choi, M.D.

ABSTRACT

Background: Systemic corticosteroids have been used in the treatment of asthma since 1950 and are still required for the treatment of acute severe asthma and corticosteroid dependent asthma.

Objective: To provide an updated overview of clinical considerations of systemic corticosteroids use in severe adult bronchial asthma.

Methods: PubMed searches were undertaken of studies published between 1950 and 2015.

Results: In this review the following concepts are discussed. 1) The onset of action of intravenous methylprednisone is 1–2 hours with a peak at 4–6 hours and duration of 12–30 hours. 2) Each patient should serve as their own control, using their best flow rates in the previous 6 months to 2 years. 3) The individual response to corticosteroid relates to the degree of obstruction at the time of onset of steroid treatment. 4) The pattern of response is variable but tends to be consistent for an individual patient. 5) In monitoring response to steroids frequent measures of peak expiratory flow rate and forced expiratory flow in 1 second are more useful than complete spirometric and lung mechanic tests measured less often. 6) In most cases oral steroids are as effective as parenteral regimens. 7) Patients usually respond in 3 days to 40 to 100 mg of methylprednisolone equivalent. 8) In corticosteroid resistant asthma consider compliance issues, allergen sensitivity, concomitant conditions, psychiatric factors and drug interactions. 9) Corticosteroid toxicity relates to the total lifetime dosage and serious side effects are usually not observed until a total dosage of 6.8 grams of prednisone equivalent.

Conclusion: Until we have a better understanding of the mechanisms of action of glucocorticoids, we will continue to rely on currently available systemic corticosteroids in severe asthma. The inpatient consistency as discussed in this review, should guide therapy.

(Allergy Asthma Proc 37:192–198, 2016; doi: 10.2500/aap.2016.37.3941)

Randhawa and Klaustermeyer¹ reviewed corticosteroid (CS) sparing treatment in CS-dependent asthma (CDA) over a 30-year period and concluded that systemic glucocorticoids remain the foremost therapy for severe asthma in both hospital and outpatient settings.¹ With the more recent increased use of monoclonal antibody therapy (omalizumab) and the U.S. Food and Drug Administration approval of the anti-interleukin-5 monoclonal antibody (mepolizumab), there may be further reduction in the use of systemic CS therapy in asthma.

In 1950, CS was first introduced for therapy in bronchial asthma.² Before 1950, a significant mortality was reported in a subset of adult asthma (refractory asthma onset >40 years of age). After the introduction of corticosteroid therapy (CST), the life expectancy in this

subgroup was doubled, from 3.5 years to 7.1 years.³ Since the early days of CST in asthma, multiple studies consistently demonstrated efficacy.^{4–7} There has been a reduction in relapse rate, admissions, symptoms, morbidity, and mortality.^{8,9} Kurohara *et al.*¹⁰ observed that underuse of CS and overreliance on other agents contributed to the majority of asthma admissions that required intubation and mechanical ventilation.

From 1960 to 1980, status asthmaticus was treated with aggressive therapy with high-dose parenteral CS, intravenous (IV) β -agonists, intubation, and mechanical ventilation.^{11–13} Since 1980, with the emphasis on prevention and control of asthma, under the guidelines outlined in the Global Initiative on Asthma and the National Institutes of Health National Asthma, Education and Prevention Program resulted in a marked reduction in the prevalence of CDA. These specific guidelines that have improved asthma management include the wide spread use of inhaled CS and combination inhaled CS and long-acting β -agonist therapy. In addition, allergen avoidance, immunotherapy, and omalizumab are effective in allergic asthma.

At the tertiary Veterans Affairs medical center in West Los Angeles, from 1972 to 1990, in our allergy/immunology center, we followed up, on average, 40 to

From the Veterans Affairs Greater Los Angeles Healthcare System/UCLA School of Medicine Division of Allergy and Immunology, Los Angeles, California
The author has no conflicts of interest to declare pertaining to this article
Address correspondence to William B. Klaustermeyer, M.D., VA Greater Los Angeles Healthcare System, 11301 Wilshire Blvd. (111R), Los Angeles, CA, 90073
E-mail address: william.klaustermeyer@va.gov
Copyright © 2016, OceanSide Publications, Inc., U.S.A.

80 patients with asthma and with CDA.¹⁴ In the past decade, this CDA number has been reduced to an average of five patients. Seven hundred patients with asthma are followed up in this allergy/immunology center, thus <1% of our patients with asthma currently have CDA. A similar marked reduction in patients with severe asthma admitted to our respiratory intensive care unit for asthma was observed.¹⁵ This was a reflection of improved methods of asthma prevention and control with a subsequent reduction in the severity of asthma.

RESPONSE RATE

The initial airway response to methylprednisolone (125 mg IV) occurs at 1 to 2 hours, peaks at 4 to 6 hours, and persists for 12 to 30 hours.^{5,6} Peak expiratory flow rates (PEFR) correlate with other lung mechanic measures. This airway response is identical to the hematologic effect of a single dose of glucocorticoid. The reduction in circulating monocytes and lymphocytes onset is 1 to 2 hours, peaks at 4 to 6 hours, and persists for 24 hours.¹⁶

The response rate of individual patients with asthma should guide the duration and course of SCT. Most patients with asthma respond to conventional CS treatment within 3 days, whereas a subgroup requires ≥ 7 days. The characteristics of the slow responders include (1) age > 40 years, (2) nonatopic asthma, (3) duration of attack of >7 days, (4) poor long-term asthma control, (5) hospitalizations in the previous year, and (6) maintenance oral CS. The response rate was not influenced by sex, concomitant respiratory tract infection, or the duration of the asthma diagnosis.^{17–20}

In one study of CDA, improvement was related to the initial degree of obstruction (by pulmonary function tests) more than the CS dosage received.²¹ The individual patient rate of recovery was constant and could be described by a single second-degree polynomial equation. The mean recovery rate was 10 days to reach 50% of the previous best forced expiratory volume in 1 second (FEV₁) (within 2 years of the study). This measure of previous best value to follow recovery in CDA uses each patient as his or her own control.

Krouse *et al.*¹¹ studied hospitalized patients with refractory asthma. Patients were randomized to two groups. Group A received methylprednisolone 125 mg IV every 6 hours for 3 days, then oral prednisone 25–30 mg daily for a total of 10 days, whereas group B received methylprednisolone 125 mg IV every 6 hours for 10 days. In group A, there were two patients whose condition deteriorated compared with the 10-day high-dose IV steroid group. This study concluded that each individual had an individual response pattern to CS and that most patients responded to a short duration of IV CS. A small subgroup

of patients required a longer duration of therapy. Although the 10-day high-dose CS was the most-effective dosage, this high dose is rarely recommended because of the potential serious CS toxicity.¹⁴

The recovery rate to CST is traditionally measured by PEFR and FEV₁, other spirometric measures, symptoms, and pulse oximetry. In patients with CDA, PEFR and FEV₁ vary considerably with time. We examined the variability of pulmonary tests in stable outpatients with CDA for 10 months. Due to weekly variability, it may take months to establish a good baseline in patients on long-term CST. We found a lack of correlation between patient assessment of clinical status, CS dosage, and spirometry.²²

A study of hospitalized adult patients with asthma was analyzed to determine the rate and degree of response to therapy.²³ PEFR was measured twice daily during hospitalization and weekly after discharge. The daily PEFR measurements demonstrated the response to therapy during hospitalization and at a follow-up visit at 1–2 weeks. The PEFR monitoring did not correlate with relapse or repeated hospitalization in the 5–17 month follow-up period.

Steroid Resistance

Patients who require higher doses of CS for control of asthma may have CS-resistant asthma (CRA). Severe asthma and CRA are not interchangeable terms. CRA as defined by Ito *et al.*²⁴ is a <15% increase in baseline FEV₁ after a 14-day course of 40 mg/day oral prednisone. CDA is defined as daily oral CS treatment required for control of asthma.¹

Noncompliance, misdiagnosis of asthma, allergen sensitivity, concomitant conditions (gastroesophageal reflux, severe rhinosinusitis), psychiatric issues, drug interactions, and substance abuse should be considered before diagnosing CRA. Glucocorticoid resistance can be more frequently seen in patients with asthma and with a current or past history of smoking,²⁵ reduced glucocorticoid receptor binding,²⁶ and African Americans.²⁷ Possible treatments available that may reduce glucocorticoid resistance include cessation of smoking, adding a low-dose theophylline,²⁸ macrolides,²⁹ treating infection, and anti-immunoglobulin E therapy.^{30,31}

The optimal strategy is to give the lowest effective dose of systemic CS. The most effective dosage regimen is a divided daily dosage; however, this is also the most toxic regimen. In terms of CS toxicity, a single A.M. dose is preferable to divided doses, and an alternate day dosing is better than daily dose. The optimal starting dose, duration of therapy, and route of administration remain controversial.

Although patients with CRA may appear refractory to CS, other routes of administration and different formulations of steroids may improve asthma control.

It may be useful to use different routes (IM or IV) of administration in CRA to determine if a particle route is more effective. For example, prednisolone may be preferable to prednisone in the treatment of patients with asthma and with impaired liver function. These patients may be unable to transform prednisone to prednisolone in the liver.³²

BIOMARKERS FOR STEROID RESPONSIVENESS

In addition to traditional spirometric measures to determine response to SCT, other tests are used to predict response to CS. Serum eosinophilia and sputum eosinophilia have been used indicators of response to SCT. The role of serum and sputum eosinophils as a marker of steroid response has not been well defined due to variability and limited data. The American Thoracic Society clinical practice guidelines recommends measuring exhaled nitric oxide (FeNO) to determine steroid responsiveness.³³ These promising biomarkers of asthma severity and steroid responsiveness were evaluated by a 2010 meta-analysis that addressed tailoring therapy based on sputum eosinophils and FeNO.³⁴ This analysis showed that tailoring asthma treatment based on sputum eosinophils is effective in decreasing asthma exacerbations; however, FeNO-guided therapy failed to show improvement. The studies analyzed in this meta-analysis revealed a heterogeneity in the definition of asthma control, asthma exacerbations, duration of the study, and cutoff levels for sputum eosinophils and FeNO. More research is needed to validate the role of these biomarkers.

Pathologic features of airway remodeling were found in one study of 68 patients with severe asthma who had a poor response to a short-term CST (<15% FEV₁ improvement after 10 days of 1 mg/kg per day of methylprednisolone).³⁵ Patients had bronchial biopsy before the administration of the steroid, and a reticular basement membrane of $\geq 7 \mu\text{m}$ was a good predictor of steroid resistance. Airway remodeling from prolonged and severe asthma increases the likelihood of steroid resistance. Analysis of the data indicated that, although inhaled CS therapy is effective in controlling asthma symptoms, inhaled CS therapy does not prevent subsequent airway function deficit.³⁶

ETIOLOGY OF ACUTE ASTHMA EXACERBATION

Noncompliance

Infection. There are no data that show how steroid dose effects recovery from infection. A study of five asthma deaths showed that three resulted from underuse of CS and two from infectious complications of SCT.³⁷ The signs of infection can be masked by the

anti-inflammatory effect of CS. It is essential to treat severe asthma exacerbations with effective dosages of CS but to monitor patients closely for infections. Results of one study indicated the infectious complication rate was not increased in patients given a daily dose of <10 mg daily or a cumulative dose of <700 mg of prednisone.³⁸ The infection rate was shown to decrease with the alternative day regimen in chronic steroid-dependent asthma.³⁹ IgG subclass deficiency has been noted in patients with CDA and seems to be secondary to long-term low-dose CS therapy.^{40,41} The association of low IgG subclasses, severe asthma, and recurrent infections has been reported, which indicates that IgG therapy may have a role in this asthma cohort.⁴² High-dose IV methylprednisolone therapy decreases immunoglobulin E in severe asthma.⁴³

Smoking Cigarettes. Patients with asthma who had a history of >10 pack-years had fewer eosinophils in their sputum. These patients were also shown to have an increased sputum neutrophil count, which may be partly responsible for CS resistance.⁴⁴ Noneosinophilic asthma seems to be a phenotype that increases steroid resistance.⁴⁵ Smoking cessation may restore CS sensitivity. Ex-smokers who had quit smoking for at least 1 year had a better response to oral prednisolone than did current smokers.²⁵

African American. In a 2005 cross-sectional study, African American patients with asthma had decreased steroid responsiveness compared with white counterparts.⁴⁶ In a retrospective study by Chan *et al.*,⁴⁷ more African American patients with asthma who were hospitalized were CS resistant. In a 2006 study,⁴⁸ patients with an admission diagnosis of asthma were reviewed for mortality, length of stay, and total hospital charges. The higher overall risk of death from asthma in black patients compared is attributed to factors that preceded hospitalization. Black patients with asthma are more likely to die of asthma exacerbations outside of the hospital than are white patients with asthma. The researchers indicate that inadequate access to health care, nonadherence to medical regimen, and delay in seeking medical attention are potential explanations.

Stress and Psychiatric Issues. Chronic psychosocial stress increases the severity of asthma and a number of exacerbations. Patients with asthma respond with increased bronchial tone to stressful situations. Mice studies showed that exposure to stress (psychological stress and allergens) decreased the inhibitory action of endogenous CS by diminishing function and expression of the glucocorticoid receptor (GR).⁴⁹ Analysis of human data demonstrated that reduced CS binding to GR may result in an impaired response to CS. De-

creased GR binding affinity and steroid responsiveness were observed in patients with atopic asthma exposed to allergens.⁵⁰

Obesity. In 2008, in a cross-sectional study of patients who were obese, a positive relationship between obesity and airway hyperresponsiveness was observed.⁵¹ Obesity is a risk factor for asthma in all demographic groups. Asthma in patients who are obese may represent a unique phenotype of asthma with more severe disease.⁵² Weight gain is a common complication of SCT, and treatment of the patient who is obese and with asthma leads to worsening obesity.⁵³

Vitamin D Deficiency

Vitamin D deficiency and asthma are two common conditions that share risk factors such as African American ethnicity, inner-city residence, and obesity. An association has been identified in these two disorders, and results of recent studies indicate a beneficial effect of vitamin D on asthma by preventing the morbidity of viral infections and enhancing steroid responsiveness.⁵⁴ In a cross-sectional study⁵⁵ of adult patients from the National Jewish Health Center, nonsmoking patients with asthma improved lung functions with higher vitamin D levels. Patients with vitamin D deficiency showed increased airway responsiveness.

Age. Elderly patients with asthma have immunoglobulin E-dependent mechanisms.⁵⁶ Aging is correlated with an increased neutrophil count and decreased eosinophilia in sputum, which may lead to more severe asthma. In a 2004 study, sputum samples were taken from healthy nonsmoking subjects in the age range of 18–74 years. Sputum neutrophil counts correlated significantly with age.⁵⁷ From the U.S. Centers for Disease Control and Prevention statistical data, patients with asthma and who were >65 years old had the highest mortality rate.

Hormonal Factors. Exacerbations of asthma increase in frequency during the premenstrual period. A 1997 study compared airway hyperactivity in 18 female subjects with asthma and with natural menstrual cycles versus 9 female subjects on an oral contraceptive pill.⁵⁸ The study showed that patients with asthma and on oral contraceptive pills have a cyclical change in airway reactivity that showed an association between hormonal cycling and increased airway hyperactivity.⁵⁹ One study showed an increased risk of developing adult onset asthma in postmenopausal women who used hormone replacement therapy.⁶⁰ The relationship between CS steroid resistance relating to vitamin D and hormonal factors is variable and poorly understood.

DOSE, ROUTE, AND WHICH SCS TO USE

Dose

In a Cochrane Review of nine randomized controlled trials of hospitalized patients with acute asthma, three different doses, low-dose prednisone (≤ 80 mg), medium dose (>80 and ≤ 360 mg), and high-dose (>360 mg) were compared.⁶¹ There appeared to be no difference among the different doses of CS. In a study by Britton *et al.*⁶², 26 hospitalized patients with asthma were divided to three different doses of CS. After PEF, there was no advantage of the higher doses.

Adult patients in status asthmaticus were randomized to a controlled, double-blind prospective trial of 20 mg versus 125 mg IV methylprednisolone every 6 hours for 7 days.⁶³ Individual responses were variable, but magnitude and spirometric improvement were not significantly different. The study revealed no advantage in using the higher dose.⁶³ In conclusion, 80 to 100 mg/day equivalent dose of prednisone worked for the majority of patients with acute asthma, and higher dosages are of no advantage and may increase toxicity.¹⁴

Route

Rodrigo and Rodrigo⁶⁴ reviewed four studies that compared IV and oral CS in the emergency department for patients with acute asthma. They concluded that IV and oral CS appeared to have equivalent effects on pulmonary function improvement at 24 hours. A study by Ratto *et al.*⁶⁵ compared IV methylprednisolone and an equivalent dose of oral methylprednisolone. There was no significant difference in FEV₁, days of hospitalization, or adverse effects. Rowe *et al.*⁶⁶ reviewed seven randomized controlled trials, two studies used IM CS and five studies used oral CS. Both oral and IM steroid decreased the 7–10 day relapse rate, with no difference between the two treatments.

Which SCS To Use

Sue *et al.*⁶⁷ randomized patients with acute asthma to a low equivalent dose of IV hydrocortisone (100 mg IV every 6 hours), methylprednisolone (20 mg IV every 6 hours), dexamethasone (3.75 mg IV every 6 hours) for 72 hours and then the steroid was tapered over 3 days. All the patients had significant improvement in FEV₁ after 9 hours. There was no significant difference in FEV₁ among the three groups at 72 hours. Aggarwal *et al.*⁶⁸ randomized 94 patients to two groups. Group A was given hydrocortisone 200 mg IV every 6 hours until discharge from the emergency department, followed by oral prednisolone 0.75 mg/kg daily for 2 weeks. Group B was given methylprednisolone 125 mg IV bolus, then 40 mg IV every 6 hours until discharge, followed by oral methylprednisolone 0.6 mg/kg daily for 2 weeks. Group

B had significant improvement over group A in PEFR, FEV₁, and asthma score at a 2-week follow-up.

Discharge after Emergency Department Visit or Hospitalization, Outpatient-Duration, Tapering

O'Driscoll *et al.*⁶⁹ in a double-blind study after 10 days of 40 mg prednisolone daily compared active versus placebo taper. There was no significant difference or need for tapering. In a study of 35 patients admitted with acute asthma and treated with oral prednisolone 40 mg daily until full recovery (stable PEF within 15% of their previous best PEF or predicted PEF over 48 hours).⁷⁰ The patients were randomized to a 14-day taper dose of prednisolone (5 mg every other day) or placebo on discharge.⁷⁰ The pulmonary function obtained at 14 and 28 days (the mean over 7–14 days and 21–28 days in the case of PEF) were compared with baseline value on discharge.⁷⁰ The values were compared between the two groups. There was no further change in PEF, FEV₁, FVC, or total lung capacity at 14 or 28 days after discharge, and there was no difference between the two groups.⁷⁰ Recovery of adrenal function after a short course of SCT of up to 3 weeks seems to be rapid, and tapering is unnecessary.⁷¹

Avoidance of Glucocorticoid Adverse Effects

The wide range and severity of adverse effects from systemic CS therapy are well known in the medical literature.⁷² Psychiatric complications of systemic CS include anxiety, mood disorders, psychoses, delirium, and dementia.⁷³ Kwong *et al.*¹⁴ observed complications in 51 patients who received SCT for >1 year. Serious ocular and skeletal complications (avascular necrosis in >10% of patients) were directly proportional to the total lifetime dosage of CS. The frequency of complications was very high (92%). The lowest lifetime dosage associated with serious complications was 6.8 g of prednisone equivalent. The number of complications was inversely related to the time (in terms of years) over which the CS was given, which is for a given total steroid dose. There were fewer complications if the administration time was longer. Avascular necrosis has been observed after 6 weeks of high-dose CS therapy.⁷⁴ Adverse effects have been observed in doses of prednisone as low as 5 mg/day.⁷⁵ In patients on SCT, it is important for clinicians to monitor complications continuously and to track the lifetime total SCT dosage.

A single dose of short-acting steroid compared with an identical agent given in divided doses or an equivalent anti-inflammatory dose of a long-acting agent decreases adverse effects. A 6:00 to 8:00 A.M. dose more closely resembles the innate diurnal cortisol cycle,⁷⁶ which preserves the innate adrenocorticotrophic hormone cortisol cycle.⁷⁷

Duration of Action and Cost of Corticosteroids

The duration of action and average wholesale cost of CS (provided by West Los Angeles VA Medical Center Hospital Pharmacy, January 4, 2016) are as follows:

- Oral prednisone: duration of action, 18 to 36 hours. Cost: 5-mg tablets, \$0.20/tablet; 10-mg tablets, \$0.22/tablet; 20-mg tablets, \$0.26/tablet.
- Oral dexamethasone: Duration of action, 36 to 72 hours. Cost: 0.5-mg tablets, \$0.21/tablet; 1-mg tablets, \$0.39/tablet; 4-mg tablets, \$0.64/tablet.
- Methylprednisolone injection. Cost: 40-mg vial, \$5.38/vial; 125-mg vial, \$8.68/vial.
- Inhaled Beclomethasone HFA (QVAR). Cost: 40-mcg inhaler, 120 doses/inhaler, \$167.40; 80-mcg inhaler, 120 doses/inhaler, \$224.14.
- Mometasone Twisthaler. Cost: 220-mcg, 30-dose inhaler, \$200.46 (for 1 puff daily dosing); 110-mcg, 30-dose inhaler, \$185.68 (for 1 puff daily dosing); 220-mcg, 60-dose inhaler, \$235.56 (for 1 puff twice a day dosing); 220-mcg, 120-dose inhaler, \$337.58 (for 2 puff twice a day dosing).
- Mometasone HFA Inhaler. Cost: 220-mcg, 120-dose inhaler, \$235.56; 100-mcg, 120-dose inhaler, \$200.46.

CONCLUSION

In this review, we considered various aspects of CST in severe asthma. Asthma is a disease characterized by variability both in etiology and response to therapy. This review focused on the consistent pattern of response observed in individual patients, which allowed tailoring of treatment based on individual characteristics in these patients with severe disease. Until the basic mechanisms that underlie the actions of glucocorticoids are better understood, clinicians await effective new CS drugs or new effective CS sparing agents with fewer adverse effects. In the interim, physicians are dependent on the currently available systemic glucocorticoids for treatment of this important subgroup of patients with severe asthma.

ACKNOWLEDGMENTS

The authors thank Sabrina Lee and David Smith for their excellent administrative support in preparation of this manuscript.

REFERENCES

1. Randhawa I, and Klaustermeyer WB. Oral corticosteroid-dependent asthma: A 30-year review. *Ann Allergy Asthma Immunol* 99:291–302; quiz 302–303, 370, 2007.
2. Carryer HM, Koelsche GA, Prickman LE, et al. The effect of cortisone of bronchial asthma and hay fever occurring in subjects sensitive to ragweed pollen. *J Allergy* 21:282–287, 1950.
3. Keeney EL, and Palmer LA. The pathology of corticosteroid-treated asthma. *J Allergy* 36:97–108, 1965.

4. CONTROLLED trial of effects of cortisone acetate in status asthmaticus; report to the Medical Research Council by the subcommittee on clinical trials in asthma. *Lancet* 20:803–806, 1956.
5. Klaustermeyer WB, and Hale FC. The physiologic effect of an intravenous glucocorticoid in bronchial asthma. *Ann Allergy* 37:80–86, 1976.
6. Klaustermeyer WB, and Hale FC. Respiratory mechanics during daily and alternative day corticosteroid therapy in asthma. *Ann Allergy* 37:87–90, 1976.
7. Fanta CH, Rossing TH, and McFadden ER. Glucocorticoids in acute asthma: A critical controlled trial. *Am J Med* 74:845–851, 1983.
8. Fiel SB, Swartz MA, Glanz K, and Francis ME. Efficacy of short-term corticosteroid therapy in outpatient treatment of acute bronchial asthma. *Am J Med* 75:259–262, 1983.
9. Rowe BH, and Keller JL. Effectiveness of steroid therapy in acute exacerbations of asthma: A meta-analysis. *Am J Emerg Med* 10:301–310, 1992.
10. Kurohara ML, Placik IM, and Klaustermeyer WB. Asthma: Analysis of intubated patients over a one-year period. *Mil Med* 161:567–570, 1996.
11. Krouse HA, Santiago SM, and Klaustermeyer WB. Intravenously given methylprednisolone in refractory asthma. *West J Med* 132:106–110, 1980.
12. Klaustermeyer WB, Di Bernardo RL, and Hale FC. Intravenous isoproterenol: Rationale for bronchial asthma. *J Allergy Clin Immunol* 55:325–333, 1975.
13. Klaustermeyer WB, Winn WR, and Olsen CR. Use of cuffed endotracheal tubes for severe exacerbations of chronic obstructive lung disease. *Am Rev Respir Dis* 105:268–275, 1972.
14. Kwong FK, Sue MA, and Klaustermeyer WB. Corticosteroid complications in respiratory disease. *Ann Allergy* 58:326–330, 1987.
15. Santiago SM Jr, and Klaustermeyer WB. Mortality in status asthmaticus: A nine-year experience in a respiratory intensive care unit. *J Asthma Res* 17:75–79, 1980.
16. Fauci AS. Mechanisms of corticosteroid action on lymphocyte subpopulations II. Differential effects of in vivo hydrocortisone, prednisone and dexamethasone on in vitro expression of lymphocyte function. *Clin Exp Immunol* 24:54–62, 1976.
17. Jenkins PF, Benfield GF, and Smith AP. Predicting recovery from acute severe asthma. *Thorax* 36:835–841, 1981.
18. Benfield GF, and Smith AP. Predicting rapid and slow response to treatment in acute severe asthma. *Br J Dis Chest* 77:249–254, 1983.
19. Klaustermeyer WB. Slow response to treatment of acute bronchial asthma. *Chest* 90:310–311, 1986.
20. Klaustermeyer WB, Fang M, and Kinney JL. The slow response to therapy in a patient with multiple admissions for bronchial asthma. *Ann Allergy* 58:103–104, 129–130, 1987.
21. Klaustermeyer WB, and Kinney JL. Nomograms to follow recovery rate in status asthmaticus in a veteran population. *Mil Med* 163:177–179, 1998.
22. Klaustermeyer WB, Garb MD, Santiago SM, and Kinney JL. Variability of pulmonary function tests in stable corticosteroid dependent asthma patients. *Allergy Proc* 12:255–259, 1991.
23. Klaustermeyer WB, Kurohara M, and Guerra GA. Predictive value of monitoring expiratory peak flow rates in hospitalized adult asthma patients. *Ann Allergy* 64:281–284, 1990.
24. Ito K, Chung KF, and Adcock IM. Update on glucocorticoid action and resistance. *J Allergy Clin Immunol* 117:522–543, 2006.
25. Chaudhuri R, Livingston E, McMahon AD, et al. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med* 168:1308–1311, 2003.
26. Adcock IM, and Barnes PJ. Molecular mechanisms of corticosteroid resistance. *Chest* 134:394–401, 2008.
27. Federico MJ, Covar RA, Brown EE, et al. Racial differences in T-lymphocyte response to glucocorticoids. *Chest* 127:571–578, 2005.
28. Kidney J, Dominguez M, Taylor PM, et al. Immunomodulation by theophylline in asthma. Demonstration by withdrawal of therapy. *Am J Respir Crit Care Med* 151:1907–1914, 1995.
29. Simpson JL, Powell H, Boyle MJ, et al. Clarithromycin targets neutrophilic airway inflammation in refractory asthma. *Am J Respir Crit Care Med* 177:148–155, 2008.
30. Holgate ST, Chuchalin AG, Hebert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 34:632–638, 2004.
31. Verma P, Randhawa I, and Klaustermeyer WB. Clinical efficacy of omalizumab in an elderly veteran population with severe asthma. *Allergy Asthma Proc* 32:346–350, 2011.
32. Madsbad S, Bjerregaard B, Henriksen JH, et al. Impaired conversion of prednisone to prednisolone in patients with liver cirrhosis. *Gut* 21:52–56, 1980.
33. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: Interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 184:602–615, 2011.
34. Petsky HL, Cates CJ, Lasserson TJ, et al. A systematic review and meta-analysis: Tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). *Thorax* 67:199–208, 2012.
35. Bourdin A, Kleis S, Chakra M, et al. Limited short-term steroid responsiveness is associated with thickening of bronchial basement membrane in severe asthma. *Chest* 141:1504–1511, 2012.
36. Martinez FD. Asthma treatment and asthma prevention a tale of 2 parallel pathways. *J Allergy Clin Immunol* 119:30–33, 2007.
37. Leung FW, Santiago SM, and Klaustermeyer WB. Corticosteroid therapy and death in cases of adult bronchial asthma. *West J Med* 138:565–569, 1983.
38. Stuck AE, Minder CE, and Frey FJ. Risk of infections complications in patients taking glucocorticoids. *Rev Infect Dis* 11:954–963, 1989.
39. Portner MM, Thayer KH, Harter JG, et al. Successful initiation of alternate-day prednisone in chronic steroid-dependent-asthmatic patients. *J Allergy Clin Immunol* 49:16–26, 1972.
40. Klaustermeyer WB, Wong SC, Schoettler JJ, et al. Quantitative immunoglobulins and IgG subclasses in patients with corticosteroid-dependent reversible airway obstruction. *Ann Allergy* 63:327–330, 1989.
41. Klaustermeyer WB, Gianos ME, Kurohara ML, et al. IgG subclass deficiency associated with corticosteroids in obstructive lung disease. *Chest* 102:1137–1142, 1992.
42. Ayres JG, and Thompson RA. Low IgG subclass levels in brittle asthma and in patients with exacerbations of asthma associated with respiratory infection. *Respir Med* 91:464–469, 1997.
43. Gordon EH, Kinney JL, and Klaustermeyer WB. The effect of high dose glucocorticoid therapy on immunoglobulin E in asthma. *Ann Allergy* 53:476–479, 1984.
44. Chalmers GW, Macleod KJ, Thompson L, et al. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax* 57:226–230, 2002.
45. Thomson NC, Shepherd M, Spears M, and Chaudhuri R. Corticosteroid insensitivity in smokers with asthma: Clinical evidence, mechanisms, and management. *Treat Respir Med* 5:467–481, 2006.
46. Federico MJ, Covar RA, Brown EE, et al. Racial differences in T-lymphocyte response to glucocorticoids. *Chest* 127:571–578, 2005.

47. Chan MT, Leung DY, Szeffler SJ, and Spahn JD. Difficult-to-control asthma: Clinical characteristics of steroid-insensitive asthma. *J Allergy Clin Immunol* 101:594–601, 1998.
48. Krishnan V, Diette GB, Rand CS, et al. Mortality in patients hospitalized for asthma exacerbations in the United States. *Am J Respir Crit Care Med* 174:633–638, 2006.
49. Bailey MT, Kierstein S, Sharma S, et al. Social stress enhances allergen-induced airway inflammation in mice and inhibits corticosteroid responsiveness of cytokine production. *J Immunol* 182:7888–7895, 2009.
50. Nimmagadda SR, Szeffler SJ, Spahn JD, et al. Allergen exposure decreases glucocorticoid receptor binding affinity and steroid responsiveness in atopic asthmatics. *Am J Respir Crit Care Med* 155:87–93, 1997.
51. Sharma S, Tailor A, Warrington R, and Cheang M. Is obesity associated with an increased for airway hyperresponsiveness and the development of asthma? *Allergy Asthma Clin Immunol* 4:51–58, 2008.
52. Dixon AE, Holguin F, Sood A, et al. An official American Thoracic Society Workshop report: Obesity and asthma. *Proc Am Thorac Soc* 7:325–335, 2010.
53. Gibson PG. Obesity and asthma. *Ann Am Thorac Soc* 10(suppl.):S138–S142, 2013.
54. Earthman CP, Beckman LM, Masodkar K, et al. The link between obesity and low circulating 25-hydroxyvitamin D concentrations: Considerations and implications. *Int J Obes (Lond)* 36:387–396, 2012.
55. Sutherland ER, Goleva E, Jackson LP, et al. Vitamin D levels, lung function, and steroid response in adult asthma. *Am J Respir Crit Care Med* 181:699–704, 2010.
56. Crawford WW, Gowda VC, and Klaustermeyer WB. Age effects on objective measures of atopy in adult asthma and rhinitis. *Asthma Allergy Proc* 25:175–179, 2004.
57. Thomas RA, Green RH, Brightling CE, et al. The influence of age on induced sputum differential cell counts in normal subjects. *Chest* 126:1811–1814, 2004.
58. Tan KS, McFarlane LC, and Lipworth BJ. Modulation of airway reactivity and peak flow variability in asthmatics receiving the oral contraceptive pill. *Am J Respir Crit Care Med* 155:1273–1277, 1997.
59. Troisi RJ, Speizer FE, Willett WC, et al. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study. *Am J Respir Dis Crit Care Med* 152(pt. 1):1183–1188, 1995.
60. Barr RG, Wentowski CC, Grodstein F, et al. Prospective study of postmenopausal hormone use and newly diagnosed asthma and chronic obstructive pulmonary disease. *Arch Intern Med* 164:379–386, 2004.
61. Manser R, Reid D, and Abramson M. Corticosteroids for acute severe asthma in hospitalised patients. *Cochrane Database Syst Rev* (1):CD001740, 2001.
62. Britton MG, Collins JV, Brown D, et al. High-dose corticosteroids in severe acute asthma. *Br Med J* 2:73–74, 1976.
63. Tanaka RM, Santiago SM, Kuhn GJ, et al. Intravenous methylprednisolone in adults in status asthmaticus. Comparison of two dosages. *Chest* 82:438–440, 1982.
64. Rodrigo G, and Rodrigo C. Corticosteroids in the emergency department therapy of acute asthma: An evidence based evaluation. *Chest* 116:285–295, 1999.
65. Ratto D, Alfaro C, and Sipsey J. Are intravenous corticosteroids required in status asthmaticus? *JAMA* 260:527–529, 1988.
66. Rowe BH, Spooner CH, Ducharme FM, et al. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev* (3):CD000195, 2007.
67. Sue MA, Kwong FK, and Klaustermeyer WB. A comparison of intravenous hydrocortisone, methylprednisolone, and dexamethasone in acute bronchial asthma. *Ann Allergy* 56:406–409, 1986.
68. Aggarwal P, and Bhoi S. Comparing the efficacy and safety of two regimens of sequential systemic corticosteroids in the treatment of acute exacerbation of bronchial asthma. *J Emerg Trauma Shock* 3:231–237, 2010.
69. O'Driscoll BR, Kalra S, and Wilson M. Double-blind trial of steroid tapering in acute asthma. *Lancet* 341:324–327, 1993.
70. Hatton MQ, Vathenen AS, Allen MJ, et al. A comparison of 'abruptly stopping' with 'tailing off' oral corticosteroids in acute asthma. *Respir Med* 89:101–104, 1995.
71. Webb J, and Clark TJ. Recovery of plasma corticotropin and cortisol levels after three-week course of prednisolone. *Thorax* 36:22–34, 1981.
72. David DS, Grieco MH, and Cushman P. Adrenal glucocorticoids after twenty years. A review of their clinically relevant consequences. *J Chronic Dis* 22:637–711, 1970.
73. Kenna HA, Poon AW, de los Angeles CP, and Koran LM. Psychiatric complications of treatment with corticosteroids: Review with case report. *Psychiatry Clin Neurosci* 65:549–560, 2011.
74. Richards JM, Santiago SM, and Klaustermeyer WB. Aseptic necrosis of the femoral head in corticosteroid-treated pulmonary disease. *Arch Intern Med* 140:1473–1475, 1980.
75. Mash B, Bheekie A, and Jones PW. Inhaled vs oral steroids for adults with chronic asthma. *Cochrane Database Syst Rev* (1):CD002160, 2001.
76. Thorn GW. Clinical considerations in the use of corticosteroids. *N Engl J Med* 274:775–781, 1966.
77. Harter JG, Reddy WJ, and Thorn GW. Studies on an intermittent corticosteroid dosage regimen. *N Engl J Med* 269:591–596, 1963. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.