Lesson 2, Volume 14
Corticosteroids in Acute Respiratory Failure

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Objectives

1. Outline which conditions causing acute respiratory failure benefit from corticosteroids.
2. Describe the studies providing data for efficacy of corticosteroids in these conditions.
3. Determine the biologic rationale for the use of corticosteroids in ARDS.
4. Discern the complications of corticosteroid therapy.
5. Provide recommendations for corticosteroid regimens in treating these conditions causing acute respiratory failure.

Key Words
adverse effects; alveolar hemorrhage; ARDS; corticosteroids; eosinophilic pneumonia; respiratory failure

Abbreviations
AEP = acute eosinophilic pneumonia; anti-GBM = anti-glomerular basement membrane; BMT = bone marrow transplantation; BOOP = bronchiolitis obliterans organizing pneumonia; CK = creatine kinase; \( \text{FEF}_{25-75\%} \) = forced midexpiratory flow rate; \( \text{FiO}_2 \) = fraction of inspired oxygen; IL = interleukin; LIS = lung injury score; MPA = microscopic polyangiitis; PCP = \textit{Pneumocystis carinii} pneumonia; PEFR = peak expiratory flow rate; SLE = systemic lupus erythematosus; \( \text{SpO}_2 \) = oxygen saturation measured by pulse oximetry; TNF = tumor necrosis factor; WG = Wegener's granulomatosis

The pulmonologist/intensivist may encounter a number of conditions that cause acute respiratory failure, and many of these conditions may potentially benefit from treatment with corticosteroids. In this lesson, we examine the data and rationale for corticosteroid use in conditions that are most likely to cause acute respiratory failure requiring admission to the ICU. We provide our recommendations for treatment based on the available data, recognizing that randomized, double-blind, placebo-controlled trials may be lacking. Our focus is primarily on human studies rather than \textit{in vitro} or experimental models. Given the space limitations, we will not discuss the mechanisms of action for corticosteroids; we refer the interested reader to the excellent discussion provided by Stellato and colleagues.\(^1\)
Status Asthmaticus

Although not all studies have reported a benefit, the majority support the efficacy of corticosteroids in treating acute, severe asthma or status asthmaticus. Fanta and coworkers conducted a randomized, double-blind, placebo-controlled trial in 20 patients who were refractory to 8 h of treatment with β-agonists and aminophylline. Eleven patients were randomized to a 2 mg/kg bolus followed by a 0.5 mg/kg/h infusion of hydrocortisone while 9 patients received placebo. At 24 h, the FEV₁ increased by 118% from baseline (p <0.025) in the corticosteroid group, whereas it increased by 36% from baseline (p = not significant) in the placebo group. All corticosteroid-treated patients had at least a 10% improvement in FEV₁, but only four placebo-treated patients had similar improvement (p <0.025). In a study by Younger and associates, after no improvement was observed with three bronchodilator treatments, 15 patients were randomized to an initial bolus of 2 mg/kg of methylprednisolone followed by 1 mg/kg every 6 h while 13 received placebo. By 24 h, the methylprednisolone-treated patients had a significant improvement in a clinical pulmonary index score (p <0.02) and FEF₂₅-₇₅% (p <0.05) improved more at 36 h compared to placebo-treated patients. Changes in PEFR, FEV₁, and FVC were similar between groups. Pierson and colleagues randomized patients to receive hydrocortisone, dexamethasone, betamethasone, or placebo. A significantly greater increase in PaO₂ was noted in the steroid-treated patients (58.5 to 78.1 mm Hg; all three steroid groups combined), compared to the patients who received placebo (57.9 to 64.4 mm Hg; p <0.005). No difference in changes in FEV₁ were seen. Seven of 15 patients in the placebo group, however, required reassignment to a steroid group. No differences were observed between the three steroid groups.

Other investigators have reported no benefit with corticosteroids in treating acute, severe asthma or status asthmaticus. The negative findings of some of these studies may reflect a period of observation that was too short, as the effects of corticosteroids may not be seen for at least 6 h. The actions of corticosteroids on the β₂-receptor, including synthesis of new β₂-receptors and reversal of β₂-receptor desensitization and down-regulation, take time and this likely accounts for some delay between administration of corticosteroids and effects on pulmonary function. Morrell and associates did not find a difference in pulmonary function between patients treated with 10 mg/kg of methylprednisolone or 2 mg/kg of methylprednisolone every 4 h for 48 h vs placebo. However, a number of patients in each of the three groups, who were on maintenance steroids before study entry, continued to receive oral steroids at undisclosed doses. An additional negative study was reported by Luksza, who compared 1200 mg/d and 400 mg/d of hydrocortisone to no steroid treatment. No difference in PEFR was observed; however, the study was not randomized or blinded, and more patients not receiving steroids required mechanical ventilation compared to those treated with hydrocortisone (20% vs 12%). In addition to brief observation times, other factors that may explain a lack of benefit for corticosteroids in acute asthma include: (1) airway remodeling with a component of fixed airway obstruction; (2) inclusion of patients with a component of COPD that would tend to negate the effect of steroid therapy; (3) inclusion of patients with a very severe and prolonged episode of status asthmaticus requiring a more extended course of corticosteroids; and (4) patients with corticosteroid-resistant asthma.

Various doses of corticosteroids have been evaluated in treating status asthmaticus. Haskell and coworkers randomized eight patients each to 15 mg (low), 40 mg (medium), and 125 mg (high) doses of methylprednisolone every 6 h for 3 days in a double-blind fashion. Compared with initial spirometry, the
high-dose group significantly improved (p <0.01) on the first day, the medium-dose group significantly
ingood (p <0.01) on the second day, and the low-dose group did not show a significant improvement.
In a randomized trial of 1 mg/kg/d vs 6 mg/kg/d of methylprednisolone in 45 patients, Marquette and
associates10 found no difference in improvement in FEV1. Ratto and colleagues11 conducted a trial in 70
patients comparing 80 mg or 160 mg of oral methylprednisolone twice a day to 125 mg or 250 mg of IV
methylprednisolone four times a day and found similar improvements in PEFR and FEV1. Studies
comparing different corticosteroid preparations have not shown any significant differences in efficacy.4

We think that corticosteroids should be used in all patients admitted to the ICU for status asthmaticus.
Although some studies have used hydrocortisone, we favor methylprednisolone given its fewer
mineralocorticoid effects. Given the available data, we recommend a dose of at least 40 mg every 6 h;
although some clinicians, including ourselves, prefer to use 60 mg every 6 h. Doses above that range
probably do not confer additional benefit. Given the lack of data, we do not recommend a specific
tapering protocol; dose reduction should be based on the individual clinical response.

COPD

Although corticosteroids are used by many clinicians in treating acute respiratory failure from COPD,
2 few controlled studies support its use. The most frequently referenced trial is by Albert and colleagues.12
Forty-four patients with COPD and acute respiratory insufficiency were randomized to
methylprednisolone 0.5 mg/kg every 6 h for 72 h or placebo, in addition to treatment with IV
aminophylline, inhaled isoproterenol, and antibiotics. Bedside spirometry was done before and after
bronchodilator inhalation three times daily. At each time interval, the percent change in FEV1 was
greater in the methylprednisolone group (p <0.0001). Twelve of 22 (55%) patients in the
methylprednisolone arm had ≥40% improvement in prebronchodilator FEV1 compared to 3 of 21 (14%)
in the placebo arm (p <0.01). For the postbronchodilator FEV1, 9 of 22 (41%) patients receiving
methylprednisolone improved by at least 40%, compared to 3 of 21 patients (14%) receiving placebo (p
<0.05). In an editorial, Glenny13 challenged the statistical methods and analysis of the study on the basis
that the use of absolute spirometric volumes, rather than percent changes, should have been used to
assess differences between the groups. Using this method of analysis, Glenny concluded that there was
no effect of corticosteroid treatment. In addition, although not statistically significant, the mean admitting
FEV1 for the steroid group tended to be lower than the placebo group (602 ± 240 mL vs 675 ± 267 mL; p
<0.1), which may have affected the results because of the effect of regression to the mean.

Rubini and associates14 have evaluated the effects of corticosteroids on respiratory mechanics in eight
patients requiring mechanical ventilation for acute respiratory failure secondary to COPD. After
withholding bronchodilators for at least 12 h, respiratory mechanics were measured before and 90 min
after administration of 0.8 mg/kg of methylprednisolone. Decreases were observed in maximum
inspiratory resistance (20.3 to 15.3 cm H2O/L/s) and minimum airway resistance (16.2 to 11.9 cm
H2O/L/s) [both p <0.01]. Given the time course for effects of corticosteroids observed in status
asthmaticus, we are surprised at their results. A study often cited for showing no efficacy for
corticosteroids in treating acute exacerbations of COPD is that of Emerman and coworkers.15 In their
study, 96 patients with COPD who presented to the emergency department with acute respiratory distress
were randomized to receive either 100 mg of methylprednisolone or placebo in addition to hourly inhaled
isoetharine and IV aminophylline. No difference in improvement in FEV₁ or hospitalization rate was noted between groups. As the treatment effect was only assessed for an average of 4.5 h, the negative results may reflect insufficient time to observe a corticosteroid effect.

Given the available data, it is problematic to make a firm recommendation for the use and appropriate doses of corticosteroids in acute respiratory failure from COPD. In our practice, we tend to use corticosteroids for severely ill patients who require admission to the ICU, especially if they require mechanical ventilation. In the absence of controlled data, we use 40 to 60 mg of methylprednisolone every 6 to 12 h for 72 h.

Bronchiolitis Obliterans Organizing Pneumonia

The clinical syndrome of idiopathic bronchiolitis obliterans organizing pneumonia (BOOP), also known as cryptogenic organizing pneumonitis, was initially described in eight patients by Davison and associates¹⁶ in 1983 and in 50 patients by Epler and coworkers¹⁷ in 1985. BOOP has also been associated with a variety of conditions, including infections, drugs and toxins, irradiation, organ and bone marrow transplantation, collagen vascular diseases, malignancies, and inflammatory bowel disease.¹⁸ On chest radiograph, multiple patchy alveolar opacities, diffuse interstitial infiltrates, or a focal pulmonary opacity may be seen. Despite an overall good prognosis for patients with BOOP, progression to death occurs in 6 to 15% of cases,¹⁷,¹⁹ and patients with BOOP secondary to connective tissue diseases may have a worse outcome.¹⁷ Fulminant and life-threatening BOOP has been reported. Cohen and colleagues²⁰ described 10 patients with rapidly progressive BOOP with severe respiratory failure requiring mechanical ventilation in nine patients. Seven of these patients died despite aggressive therapy with corticosteroids and the additional use of cytotoxic therapy in four. Nizami and associates²¹ reported five patients with life-threatening BOOP causing hypoxemic respiratory failure; four patients required mechanical ventilation, and two subsequently died, although all patients were treated with corticosteroids.

Corticosteroids are considered the treatment of choice for BOOP, although the ideal dose and duration of treatment have not been clearly defined. Given the lack of data regarding the treatment of life-threatening BOOP, extrapolation from treatment of non-ICU patients is necessary. Two case series have reported successful treatment with corticosteroids.¹⁶,¹⁷ Doses ranged from 20 mg/d to 1 mg/kg/d of prednisone. Patients were treated for several months. Relapses were noted when therapy was discontinued or steroids were rapidly tapered during the first months of treatment. Cordier¹⁸ has recommended a regimen of 60 mg methylprednisolone every 12 h for 3 to 5 days, followed by daily prednisone at a dose of 1 mg/kg. After clinical and radiologic improvement is seen, the dose is decreased to 0.5 mg/kg/d for 1 to 2 months, followed by a gradual taper. King and Mortenson¹⁹ have recommended a dose of prednisone of 1.5 mg/kg/d (using ideal body weight) not to exceed 100 mg/d for 4 to 8 weeks followed by a dose of 0.5 to 1.0 mg/kg/d for 4 to 6 weeks or, for severe cases of BOOP, 250 mg of methylprednisolone IV every 6 h for 3 to 5 days followed by oral prednisone. The prednisone dose may be gradually tapered after 3 to 6 months if the patient's condition stabilizes or improves.

Although spontaneous improvement has been noted in some patients, we recommend treatment with corticosteroids for patients with moderate to severe BOOP. Based on the current case series, we suggest an initial dose of 1 mg/kg/d of prednisone or equivalent, not to exceed 100 mg/d.
If clinical response is seen after 4 to 8 weeks, the dose should be decreased to 0.5 mg/kg/d for 4 to 8 weeks, followed by a gradual taper. Patients should probably be treated for at least 6 months, although some patients may require 12 months of therapy. In patients with life-threatening BOOP, an initial pulse of 1,000 mg/d of methylprednisolone for 3 to 5 days may be appropriate.

**Acute Lupus Pneumonitis**

The syndrome of acute lupus pneumonitis occurs in 1 to 4% of patients with systemic lupus erythematosus (SLE). The typical presentation is the abrupt onset of dyspnea, fever, cough, and pleuritic chest pain, which may be the presenting manifestation in some patients. Matthy and colleagues described 12 patients with acute lupus pneumonitis, representing 12% of their SLE patients who were hospitalized during a 6-year period. Mortality was 50% in their series, despite treatment with corticosteroids and the addition of azathioprine in some patients. Other fulminant cases of acute lupus pneumonitis have been reported.

Only anecdotal information is available to guide treatment of patients with acute lupus pneumonitis. Matthy and colleagues reported the dose of corticosteroids in 3 of 12 patients, which was 100 mg/d of prednisone in two patients and 400 mg/d of hydrocortisone in one patient; azathioprine at a dose of 2 mg/kg/d was used in seven patients. Successful treatment of a patient requiring mechanical ventilation with 1,000 mg/d of methylprednisolone for 5 days followed by 60 mg/d of prednisone was reported by Domingo-Pedrol and associates. Pulse methylprednisolone at a dose of 750 mg/d for 3 days, followed by prednisone 60 mg/d, was used by Freter and coworkers to successfully treat a patient with fulminant lupus pneumonitis. Inoue and colleagues also successfully treated two patients with 80 mg/d of prednisone and 200 mg/d of prednisone.

Based on the case series and data available for alveolar hemorrhage due to SLE, we recommend initial treatment with 1 mg/kg/d of prednisone or equivalent. In patients with life-threatening lupus pneumonitis, pulse methylprednisolone of 1,000 mg/d for 3 days, followed by 1 mg/kg/d of prednisone, may be of benefit. Although some authors have advocated the adjunctive use of cytotoxic agents and plasmapheresis, the role of these therapies remains undefined.

**Alveolar Hemorrhage Syndromes**

Alveolar hemorrhage is associated with a wide variety of disorders, including connective tissue diseases, vasculitides, coagulopathies, cardiac disease, and drug or toxin exposure. The alveolar hemorrhage syndromes are often misdiagnosed initially as pulmonary edema or pneumonia. To discuss all of these entities is beyond the scope of this lesson; therefore, we will focus on those conditions most likely to be encountered and in which benefit from corticosteroid therapy has been reported.

**SLE**

Alveolar hemorrhage, a well-recognized complication of SLE, may present with acute respiratory failure. Diffuse alveolar hemorrhage may be the presenting manifestation of SLE or may occur at any time during its course. Mortality >50% has been reported. No prospective or controlled trials assessing therapy have been performed, although high-dose corticosteroids have been advocated by many investigators. In a series of eight patients, Schwab and coworkers administered methylprednisolone...
1,000 mg/d for 3 days, with the addition of cyclophosphamide in five patients; 2 of the 8 patients died. Zamora and associates\textsuperscript{27} treated 18 of 19 episodes with 500 to 2,000 mg/d of methylprednisolone for 2 to 6 days followed by a taper. Cyclophosphamide was used in 10 episodes and plasmapheresis in 12 episodes, in addition to corticosteroids. Mortality was 42%.

Given this data and observations with treatment for other causes of alveolar hemorrhage, we recommend a course of pulse methylprednisolone, 1,000 mg/d, followed by a taper based on clinical course. It is beyond the scope of this lesson to discuss the merits of treatment with cyclophosphamide and plasmapheresis.

**Anti-Glomerular Basement Membrane Disease (Goodpasture's Syndrome)**

Pulmonary involvement in anti-glomerular basement membrane (anti-GBM) disease occurs in 60 to 80% of patients. Although virtually all patients have glomerulonephritis as evidenced by microscopic hematuria or proteinuria, frank renal failure may be present in only 50%. Alveolar hemorrhage may manifest clinically as blood-streaked sputum or submassive or massive hemoptysis; however, hemoptysis may be absent. Mechanical ventilation may be required in a small percentage of patients for severe alveolar hemorrhage. Pulse methylprednisolone at a dose of 1,000 mg/d for 1 to 3 days has been reported to be effective in controlling alveolar hemorrhage in patients with anti-GBM disease.\textsuperscript{28,29} However, corticosteroid monotherapy has not changed overall mortality due to the inability to prevent progression to end-stage renal disease.\textsuperscript{30} Combination therapy with cytotoxic agents and corticosteroids (prednisone 1 to 2 mg/kg/d) along with plasmapheresis has been reported to achieve the best outcome.\textsuperscript{30} We concur that pulse methylprednisolone should be used for patients with life-threatening alveolar hemorrhage due to anti-GBM disease.

**Wegener's Granulomatosis**

Although the lung is the most common organ system involved in Wegener's granulomatosis (WG), diffuse alveolar hemorrhage is uncommon. Between 5 and 15% of patients presenting with diffuse alveolar hemorrhage will have WG. In patients with WG, alveolar hemorrhage is often the initial presentation. A more fulminant course and a higher mortality is observed in patients with WG presenting with alveolar hemorrhage compared to those with a more typical presentation. Acute renal failure is often associated with alveolar hemorrhage in these patients.

Corticosteroids alone are not sufficient therapy for WG.\textsuperscript{31} The current standard treatment of WG, developed at the National Institutes of Health, consists of 1 mg/kg/d prednisone and 2 mg/kg/d cyclophosphamide based on ideal body weight.\textsuperscript{31} After 4 weeks, the prednisone is tapered over 1 to 2 months to 60 mg every other day. In patients with fulminant disease, 2 mg/kg/d of prednisone and 3-5 mg/kg/d of cyclophosphamide have been used. Some have suggested the use of pulse methylprednisolone at a dose of 1,000 mg/d for 3 days for life-threatening alveolar hemorrhage due to WG.\textsuperscript{32,33} We concur with these recommendations. Other immunosuppressives have been used, but the discussion of these therapies is beyond the scope of this lesson.

**Microscopic Polyangiitis**

Microscopic polyangiitis (MPA) is a systemic necrotizing vasculitis that clinically and histologically
affects small vessels (capillaries, venules, or arterioles) without formation of granulomas, as is seen with WG. Like WG, MPA is an antineutrophil cytoplasmic autoantibody-associated vasculitis. MPA and WG have similar clinical features. MPA is the most common cause of the pulmonary-renal syndrome.\(^{34}\) Pulmonary capillaritis is thought to be common with MPA. Savage and associates\(^{35}\) observed that 10 of 34 patients (29\%) with MPA had pulmonary hemorrhage. Gaudin and coworkers\(^{36}\) reported that, of their series of 18 patients with MPA, capillaritis was present in 11 (61\%) and 12 (67\%) had acute alveolar hemorrhage.

For treatment of MPA, Savage and coworkers\(^{34}\) used a regimen of prednisolone 60 mg/d, and cyclophosphamide 3 mg/kg/d as initial therapy. Azathioprine at a dose of 1 mg/kg/d was used as additional therapy in 17 patients and plasma exchange was also performed in 18 patients. They reported an overall response rate of 79\%. Prednisolone was reduced at weekly intervals to 20 mg/d by 4 weeks and then to a maintenance dose of 5 to 10 mg/d for 1 year or longer. Cyclophosphamide was given for 8 weeks, and azathioprine, at a dose of 3 mg/kg/d after the initial 8 weeks, was continued for 1 year or longer. Relapses were observed in 12 of 34 patients (35\%). Treatment similar to that for fulminant WG with pulse methylprednisolone and cyclophosphamide has been advocated.\(^{34}\) With the clinical similarities between MPA and WG and the lack of controlled studies, we agree that such recommendations seem appropriate.

**Bone Marrow Transplantation**

Diffuse alveolar hemorrhage has been reported in patients undergoing autologous and allogenic bone marrow transplantation (BMT). In 141 consecutive patients undergoing autologous BMT, Robbins and colleagues\(^{37}\) found that 29 patients (21\%) developed alveolar hemorrhage between 7 and 40 days after transplantation. Mortality in patients developing alveolar hemorrhage was 79\% in their series. Jules-Elysee and associates\(^{38}\) reported that 10 of 77 patients (13\%) treated with autologous BMT developed acute respiratory failure from alveolar hemorrhage, with a mortality rate of 100\%. Agusti and colleagues\(^{39}\) noted that 11 of 47 patients (23\%) who had received allogenic BMT and died of pulmonary complications had evidence of diffuse alveolar hemorrhage at post-mortem examination.

Administration of corticosteroids to patients with diffuse alveolar hemorrhage following BMT may improve outcome. Successful treatment of four patients with alveolar hemorrhage following autologous BMT, two of whom required mechanical ventilation, was reported by Chao and coworkers.\(^{40}\) Their treatment regimen consisted of methylprednisolone 1,000 mg/d for 3 days, followed by a 50\% reduction in dose every 3 days to 60 mg/d. At that point, the patients were changed to an equivalent prednisone dose, which was gradually tapered over 2 months. In a retrospective analysis, Metcalf and associates\(^{41}\) studied 65 episodes of alveolar hemorrhage in 63 of 603 consecutive patients who had undergone BMT. The need for endotracheal intubation was 100\% in the group who did not receive steroids, 80\% in the low-dose steroid group (≤30 mg/d methylprednisolone or equivalent), and 45\% in the high-dose steroid group (>30 mg/d of methylprednisolone or equivalent). The mortality rate was 92\% in the nonsteroid group, 90\% in the low-dose steroid group, and 67\% in the high-dose steroid group. Most patients in the high-dose steroid group received 125 to 250 mg of methylprednisolone every 6 h for 4 or 5 days, followed by a taper over 2 to 4 weeks based on clinical improvement. No increased risk of infection was noted between the steroid and nonsteroid groups. In the absence of other data, and if the presence of infection has been sufficiently excluded, we recommend treatment for BMT-associated alveolar hemorrhage with methylprednisolone at a dose of 125 to 250 mg every 6 h for 4 or 5 days followed by a
taper over 2 to 4 weeks.

**Pneumocystis carinii Pneumonia**

This section will focus specifically on the use of corticosteroids for *Pneumocystis carinii* pneumonia (PCP)-induced respiratory failure. Although the incidence of PCP has decreased with the use of chemoprophylaxis, this pneumonia remains the most common opportunistic infection associated with HIV infection and the most common diagnosis among HIV-infected patients requiring ICU admission. Before the use of corticosteroids, the survival for patients with AIDS-related PCP who required admission to the ICU for mechanical ventilation was <15%. The first suggestion that corticosteroids might be beneficial in PCP-induced acute respiratory failure was noted in case reports in 1985 and 1987, followed by a number of case series published between 1987 and 1990. We will not discuss these reports but will focus on the randomized trials conducted to evaluate the role of corticosteroid treatment in respiratory failure due to PCP.

Montaner and coworkers\(^4\) randomized 37 patients who had an oxygen saturation on pulse oximetry (SpO\(_2\)) >85% and <90% on room air, or a decrease in SpO\(_2\) of 5% with exercise, to receive prednisone or placebo. Patients randomized to prednisone received 80 mg/d for 7 days, 40 mg/d for 2 days, 30 mg/d for 2 days, 20 mg/d for 2 days, 15 mg/d for 2 days, and 10 mg/d for 2 days. The end point of the study was a 10% decrease in baseline SpO\(_2\) on day 3 or thereafter. The study was terminated early after deterioration was noted in 5.6% of the subjects treated with prednisone (N=18) compared to 42.1% in the placebo group (N=19) \(p = 0.0136\). Gagnon and associates\(^4\) randomized 23 patients with PaO\(_2\) <75 mm Hg on a fraction of inspired oxygen (FiO\(_2\)) of 0.35 and PaO\(_2\) >60 mm Hg on an FiO\(_2\) of 1.0 via face mask to treatment with methylprednisolone 40 mg IV every 6 h for 7 days or placebo. The study was also terminated early after interim analysis revealed the development of respiratory failure in 25% of the methylprednisolone group (N=12) and 82% of the placebo group (N=11) \(p <0.008\), while the mortality rate was 25% in the methylprednisolone group and 82% in the placebo group \(p <0.008\). In the largest study to date by Bozzette and colleagues\(^4\), 251 patients were randomized to prednisone (or equivalent IV methylprednisolone) or placebo. Patients were excluded if they had a PaO\(_2\)/FiO\(_2\) ratio <75 or required mechanical ventilation. The treatment regimen was prednisone 40 mg bid for 5 days, 40 mg/d for 5 days, and 20 mg/d for the duration of anti-Pneumocystis therapy. Respiratory failure developed in 14% of the steroid group (N=123) compared to 30% in the placebo group (N=128) \(p <0.001\), while the mortality rate was 11% in the steroid group and 22% in the placebo group \(p <0.01\).

In addition to causing infection in the HIV-positive patient, PCP may occur in solid organ transplant recipients, bone marrow transplant recipients, patients undergoing chemotherapy for hematologic and solid organ malignancies, and patients with chronic inflammatory diseases requiring prolonged use of corticosteroids or other immunosuppressives (eg, methotrexate). The mortality rate of PCP in these patient populations is higher than the HIV population, ranging from 34 to 58%. A retrospective review evaluating the effects of adjunctive corticosteroids in non-HIV patients with severe PCP was done by Pareja and coworkers.\(^5\) Of 30 patients with a PaO\(_2\) <65 mm Hg or oxygen saturation <90% on room air, 16 patients received increased steroids (>60 mg prednisone or equivalent daily), while 14 patients were maintained on a low dose of steroids (<30 mg prednisone or equivalent daily) or had steroid therapy tapered. The high-dose steroid group demonstrated a shorter duration of mechanical ventilation (6.3 vs 18.0 days, \(p = 0.047\)), a shorter duration of ICU stay (8.5 vs 15.8 days, \(p = 0.025\)), and a shorter duration...
of supplemental oxygen requirement (10.0 vs 32.2 days, p = 0.05). No difference in mortality was noted (44% vs 36%, p = not significant).

Based upon the available literature, we concur with the recommendations for adjunctive corticosteroid therapy, as stated by the National Institutes of Health-University of California Expert Panel consensus statement, with the regimen of 40 mg of prednisolone twice a day on days 1 through 5, 40 mg/d on days 6 through 10, and 20 mg/d on days 11 through 21. IV methylprednisolone can be given at 75% of these doses in patients unable to take oral therapy. Most patients requiring ICU care will meet the definition of moderate or severe pulmonary dysfunction for which corticosteroids are recommended (PaO₂ < 70 mm Hg or alveolar-arterial oxygen gradient > 35 mm Hg). To obtain maximum benefit, corticosteroids should be initiated within 24 to 72 h of the diagnosis. Based on the limited data, we recommend corticosteroid treatment for non-HIV patients with PCP-induced respiratory failure. To limit the possibility of an adverse outcome, we recommend obtaining appropriate studies to evaluate for co-existing bacterial or opportunistic pathogens.

**Acute Eosinophilic Pneumonia**

Idiopathic acute eosinophilic pneumonia (AEP) was described by Allen and colleagues in 1989. AEP is a clinical entity distinct from other eosinophilic lung diseases. Based on their observations, Allen et al proposed the following clinical criteria for the diagnosis of AEP: (1) acute febrile illness of <5 days' duration; (2) hypoxemic respiratory failure; (3) diffuse alveolar or mixed alveolar-interstitial infiltrates on chest radiograph; (4) BAL sample containing eosinophils >25%; (5) absence of parasitic, fungal, or other infection; (6) prompt and complete response to corticosteroids; and (7) failure of relapse after discontinuation of corticosteroids. The duration of symptoms has been reported to be between 3 and 22 days, although symptoms may progress in a rapid fashion with development of respiratory failure requiring mechanical ventilation in <24 h from time of symptom onset. Cough, fever, and dyspnea are the prominent symptoms with pleuritic chest pain and myalgias also are reported.

PaO₂ measuring < 60 mm Hg on room air is found in the majority of patients, with the remainder having an increased alveolar-arterial gradient. Peripheral WBC counts are usually elevated with a neutrophilic predominance. Patients with AEP usually do not have peripheral blood eosinophilia, in contrast to patients with chronic eosinophilic pneumonia, although some patients have been reported with peripheral eosinophilia either initially or during the course of their illness. Most patients demonstrate bilateral infiltrates on chest radiograph, although rarely patients will present with unilateral findings. In a review of 15 patients, Pope-Harman and colleagues found that 27% had interstitial infiltrates, 27% had alveolar infiltrates, and 46% had mixed alveolar and interstitial infiltrates. An increase in the percentage of eosinophils in the BAL fluid is typically found in patients with AEP. The average percentage of eosinophils in the BAL sample has been reported as 40.3 ± 27.5%. Transbronchial biopsies or open lung biopsies reveal infiltration of the alveoli and interstitium by eosinophils, as well as acute and organizing diffuse alveolar damage in some patients. The diagnosis of AEP should be considered in all patients with acute respiratory failure accompanied by unexplained diffuse pulmonary infiltrates, and BAL should performed immediately since it is the only method of establishing the diagnosis.

Corticosteroids are the cornerstone of treatment for AEP. Case series and reports have demonstrated the
efficacy of corticosteroids. In nine patients reported by Tazelaar and associates, all patients were treated successfully with unspecified high-dose corticosteroids. In their original report and subsequent series of 15 patients, Allen et al used 60 to 125 mg methylprednisolone every 6 h. Most patients demonstrated rapid improvement within 1 to 2 days, with some patients showing improvement within hours. By 6 to 7 days, a response was seen in all patients. Following the resolution of hypoxemia and requirement for mechanical ventilation, corticosteroid therapy was changed to 40 to 60 mg of prednisone each day, which was tapered over 4 to 12 weeks. Although some authors have reported spontaneous improvement without the use of corticosteroids, these patients likely had less severe disease.

We recommend the use of corticosteroids for any patient with AEP requiring admission to an ICU and for any patient requiring mechanical ventilation. Based on the available literature, we suggest IV methylprednisolone at an initial dose of 60 to 125 mg every 6 h, followed by oral prednisone at a daily dose of 40 to 60 mg after the patient has stabilized. The dose may be tapered over a 2- to 6-week period based on the clinical course.

Bleomycin Pneumonitis

Bleomycin is an antibiotic with activity against a variety of tumors, including squamous cell carcinoma of the head and neck, cervix, and esophagus, as well as germ cell tumors, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. Interstitial pneumonitis, producing respiratory compromise and death in some patients, is the most serious adverse effect of bleomycin. The incidence of bleomycin interstitial pneumonitis ranges from 3 to 11%, with an overall mortality estimated to be between 1 and 2%. In patients with severe bleomycin toxicity, the mortality rate may be as high as 60%.

At doses above 400 U of bleomycin, the incidence of pulmonary toxicity increases. A number of cases with fatal pneumonitis have been reported in patients receiving lower doses, and doses as low as 60 U have been reported to cause toxicity. While the onset of bleomycin interstitial pneumonitis is usually insidious with progression to interstitial fibrosis, acute presentations and fulminant courses with rapid development of symptoms and acute respiratory failure can occur. High inspired oxygen concentrations (as low as 0.35) have been suggested in clinical and experimental studies to increase the risk of developing pneumonitis from bleomycin. In addition to causing an interstitial pneumonitis, bleomycin has also been reported to cause an acute hypersensitivity pneumonitis, with eosinophilic infiltrates noted on biopsies and peripheral eosinophilia.

As opposed to patients with slowly progressive interstitial fibrosis, corticosteroids may be of benefit in patients with acute pneumonitis. Yagoda and associates noted reversal of pulmonary toxicity in some patients with prednisone 100 mg/d, but the numbers of patients treated and responders were not provided. Successful treatment of a patient exhibiting hypoxemia with prednisone 80 mg/d was reported by McCusker and colleagues. Gilson and Sahn reported a patient who responded to prednisone 60 mg/d for mild toxicity and later to methylprednisolone 125 mg every 6 h after developing severe hypoxemia requiring mechanical ventilation following surgery. White and Stover reported improvement in all seven patients treated with prednisone 60 to 100 mg/d. Steroid therapy was required for many months to maintain improvement, and premature tapering of steroids led to recurrence of symptoms in five patients. In three patients with the hypersensitivity pneumonitis form of bleomycin toxicity, Holoye and colleagues found that all improved with steroid therapy. Some patients, however, have had a fulminant course and died despite treatment with corticosteroids.
Although controlled trials have not been performed to evaluate the efficacy of corticosteroids in treating bleomycin-induced pneumonitis, given the published case reports and series and the lack of alternative therapies, we recommend treating patients with moderate to severe pneumonitis with corticosteroids at a dose of 60 to 100 mg/d of prednisone or its equivalent.

**ARDS**

A number of trials have demonstrated that patients with ARDS do not benefit from a short course of high-dose corticosteroids administered early in the disease. Bone and coworkers\(^56\) conducted a prospective, double-blind, randomized study to determine if early treatment with corticosteroids would decrease the incidence of ARDS in patients at risk from sepsis. Patients treated with methylprednisolone 30 mg/kg every 6 h for 24 h showed a trend toward an increased incidence of ARDS, 50 of 152 (32\%) compared to 38 of 152 (25\%) in the placebo-treated group (p = 0.10). In patients who developed ARDS, the 14-day mortality rate was 52\% (26 of 50) in the steroid group compared with 21\% (8 of 38) in the placebo group (p = 0.004). In addition, reversal of ARDS was noted in 31\% of the steroid-treated patients vs 61\% in the placebo group (p = 0.005). Luce and colleagues\(^57\) evaluated the efficacy of methylprednisolone in preventing ARDS in patients with septic shock. Patients were randomized in double-blind fashion to four doses of methylprednisolone 30 mg/kg every 6 h or placebo. Thirteen of 38 patients (34\%) in the methylprednisolone group developed ARDS compared to 14 of 37 (38\%) in the placebo group (p = not significant), while mortality was 58\% in the steroid group vs 54\% in the placebo group (p = not significant). Bernard and associates\(^58\) also conducted a double-blind, randomized trial of methylprednisolone 30 mg/kg every 6 h for a total of four doses vs placebo in patients with early ARDS. The mortality rate at 45 days was 60\% (30 of 50) in the steroid group and 63\% (31 of 49) in the placebo group (p = 0.74); reversal of ARDS was similar in the steroid and placebo groups, 36\% (18 of 50) vs 39\% (19 of 49) (p = 0.77).

Although not effective in early ARDS, there is evidence that corticosteroids may be beneficial in the fibroproliferative or late phase of ARDS. Ashbaugh and Maier\(^59\) treated 10 patients with methylprednisolone 125 mg every 6 h beginning 6 to 22 days after the onset of ARDS. Open-lung biopsies in those patients demonstrated cellular proliferation, obliteration of alveoli, and fibrosis. Following a clinical response, the dose of steroids was then tapered over 3 to 6 weeks. Eight of the 10 patients recovered, with two patients dying of sepsis. Hooper and Kearl\(^60,61\) initially reported 10 patients, followed by an additional 16 patients, who were treated with corticosteroids for "established" ARDS. ARDS was present 3 to 40 (mean, 9.2) days before steroid therapy. Patients were thought not to be infected, and patients with positive blood or wound cultures were excluded from the study. BAL or lung biopsy was not performed. The initial dose of methylprednisolone was 125 to 250 mg every 6 h based on the severity of respiratory compromise for 72 to 96 h before tapering the dosage approximately 50\% every 2 to 3 days. All patients showed improvement in respiratory parameters with an overall survival of 81\% (21 of 26).

Meduri and colleagues\(^62-64\) have published a number of studies reporting the efficacy of corticosteroids for the fibroproliferative phase of ARDS. They initially described eight patients, followed by an additional 17 patients, who were given an initial bolus of 200 mg followed by 2 to 3 mg/kg/d in divided doses every 6 h of methylprednisolone. The patients had undergone mechanical ventilation for 5 to 23 (mean, 15) days before initiation of steroid therapy. Bronchoscopy with bilateral BAL and protected
brush sampling was performed before initiation of steroid treatment to exclude infection, and weekly bronchoscopy with BAL was done for early detection of nosocomial pneumonia. By day 7 of treatment, the PaO₂/FIO₂ ratio increased from 164 to 234 (p = 0.0004) and lung injury score (LIS) decreased from 3.0 to 2.1 (p = 0.001). Overall survival rate was 72% (18 of 25) while ICU survival was 87% (13 of 15) in the rapid responders (improvement by day 7), 83% (5 of 6) in the delayed responders (improvement by day 14), and 25% (1 of 4) in the nonresponders. The average duration of corticosteroid treatment was 36 days. Pneumonia developed in 38% of responders and 75% of nonresponders.

Meduri and colleagues recently published the results of a randomized, double-blind, placebo-controlled trial of corticosteroids for non-resolving ARDS. Patients were eligible for the study if they had required mechanical ventilation for 7 days with a LIS of >2.5 and had <1 point reduction in the LIS from day 1 of their ARDS, as well as no evidence of untreated infection. The treatment protocol for methylprednisolone was a loading dose of 2 mg/kg, followed by 2 mg/kg/d from day 1 to day 14, 1 mg/kg/d from day 15 to day 21, 0.5 mg/kg/d from day 22 to day 28, 0.25 mg/kg/d on days 29 and 30, and 0.125 mg/kg/d on days 31 and 32, with one-fourth of the total daily methylprednisolone dose given every 6 h. If the patient was extubated before day 14, treatment was advanced to day 15 of drug therapy. Bronchoscopy with bilateral BAL was performed before initiation of steroid therapy as well as weekly to exclude ventilator-associated pneumonia. Enrollment was stopped after 24 patients, 16 in the methylprednisolone arm and 8 in the placebo arm, based on interim statistical analysis. Significant changes were observed for PaO₂/FIO₂ ratio (262 vs 148, p <0.001), LIS (1.7 vs 3.0, p <0.001), mean pulmonary artery pressure (22.5 vs 30.0 mm Hg, p = 0.01), and multiple-organ dysfunction syndrome score (0.7 vs 1.8, p <0.001) in the corticosteroid-treated group vs the placebo group, respectively. According to the study protocol, four patients in the placebo arm were blindly crossed over to the methylprednisolone arm when no improvement was observed 10 days after treatment; only 1 of the 4 patients survived. ICU survival was 100% (16 of 16) in the steroid group vs 37% (3 of 8) in the placebo group (p = 0.002), while overall survival was 87% (14 of 16) vs 37% (3 of 8), respectively (p = 0.03). The two deaths in the methylprednisolone arm occurred after ICU discharge and were related to a cardiac arrhythmia in one patient and recurrent aspiration in the other patient with neurologic dysfunction. An increased incidence of infections was noted in the steroid group with a risk ratio of 1.80 compared to placebo, although the 95% confidence interval was 0.86 to 3.76. Four of 16 surveillance bronchoscopies in patients without fever identified a significant growth of pathogens.

Meduri has written an excellent review of the host defense response in the progression of ARDS and how that response may be affected by corticosteroid therapy. Fibroproliferation is a stereotypical reparative reaction to tissue injury and is characterized by the replacement of damaged epithelial cells with an accumulation of mesenchymal cells and their connective tissue products in the airspaces and walls of the intra-acinar microvessels. This process occurs within 7 days of the onset of ARDS, with a rapid increase in the second and third week of respiratory failure. Unchecked fibroproliferation results in extensive fibrotic remodeling of the lung parenchyma. A number of cytokines mediate the host defense response to injury. Higher initial plasma and BAL levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-2, IL-4, IL-6, and IL-8 have been reported in nonsurvivors of ARDS compared to survivors, with persistent elevation of plasma and BAL TNF-α, IL-1β, IL-6, and IL-8 levels also noted in nonsurvivors of ARDS. In the absence of inhibitory signals, these mediators of the host defense response sustain ongoing inflammation with tissue injury and stimulate proliferation of mesenchymal cells with deposition of extracellular matrix products and collagen, resulting in fibrosis. Thus, an
overaggressive and protracted host defense response, rather than the inciting condition, is likely the major factor influencing outcome in ARDS. It has been hypothesized that activity of glucocorticoids produced by the hypothalamic-pituitary-adrenal axis as well as anti-inflammatory cytokines, such as IL-4, IL-10, IL-1 receptor antagonist, and soluble TNF receptors, are necessary to regulate termination of the host defense response. Corticosteroids inhibit the host defense response at many levels and inhibit the transcription of TNF, IL-1, IL-2, and IL-6, as well as suppress the synthesis of phospholipase A2, cyclo-oxygenase-2, and nitric oxide synthase-1 genes, decreasing the production of prostanoids, platelet-activating factor, and nitric oxide, three additional key molecules in the inflammatory pathway. In addition, corticosteroids have an inhibitory effect on fibrogenesis and the expression of adhesion molecules.

Meduri and colleagues were able to demonstrate that patients with ARDS who responded to corticosteroids and responded had significant reductions in plasma and BAL TNF-α, IL-1β, IL-6, and IL-8 levels compared to nonsurvivors not treated with corticosteroids. In a separate study, Meduri and colleagues also reported that in patients treated with methylprednisolone, significant decreases in plasma and BAL procollagen propeptide types I and III, which are secreted by fibroblasts and reflect collagen synthesis, were seen, whereas no changes in these levels were observed in the placebo group. Decreases in plasma and BAL procollagen propeptide levels correlated with improvements in lung injury scores and PaO2/FIO2 ratios. Thus, there appears to be some rationale for use of corticosteroids in the fibroproliferative phase in ARDS. It appears a therapeutic window exists for treating fibroproliferative ARDS, and treatment will be ineffective once end-stage fibrosis has developed. In an earlier study by Meduri and associates, open lung biopsies were obtained in 12 patients before treatment with methylprednisolone for late ARDS. Histology from the responders demonstrated myxoid cellular fibrosis, preserved alveolar architecture, and absence of arteriolar subintimal fibroproliferation; whereas nonresponders had dense acellular fibrosis, distorted alveolar architecture, and arteriolar subintimal proliferation.

Given the data of case series and one, albeit small, double-blind randomized controlled trial, it appears that there is a role for corticosteroids in the fibroproliferative phase of ARDS, as opposed to preventative therapy, early in the course, or late in the fibrotic stage of ARDS. In patients who have not exhibited clinical improvement after 7 to 14 days of conventional therapy, we think it is reasonable to initiate a trial of corticosteroids after excluding infection with bronchoscopy and BAL, recognizing that ARDS and systemic inflammatory response syndrome may clinically simulate infection. In the absence of any trials evaluating dosage or duration of steroid treatment, we recommend the protocol used by Meduri and colleagues, including weekly surveillance bronchoscopy to detect potentially occult pneumonia. A low threshold in evaluating patients for development of a new infection while they are undergoing corticosteroid therapy should be maintained. An National Institutes of Health-sponsored multicenter randomized, controlled trial is planned to further assess the efficacy of corticosteroid therapy for fibroproliferative ARDS.

**Acute Complications of Corticosteroid Therapy**

There are few acute adverse effects associated with the use of corticosteroids. For the purposes of this discussion, we will consider acute adverse effects as those occurring within several days of initiation of steroid therapy. Perhaps the most concerning acute side-effect associated with corticosteroid therapy is...
myopathy. A number of single reports and case series have documented prolonged muscle weakness in critically ill patients. Many of these patients also received neuromuscular blocking agents in addition to corticosteroids. Lacomis and associates\(^6\) described 14 patients with acute myopathy in the ICU who were treated with 43 to 644 mg/d of methylprednisolone. Nine of the 14 patients received vecuronium and/or pancuronium for 1 to 10 days. Eleven patients were severely weak while 12 patients were slow to wean from mechanical ventilation. Distal and proximal muscles were affected equally in nine patients with the remaining five having weaker proximal musculature. Elevations in creatine kinase (CK) were noted in three patients. All patients had electromyographic studies consistent with a myopathy. Muscle histopathology demonstrated myofiber necrosis with selective thick (myosin) filament loss in the most patients. Douglass and colleagues\(^7\) conducted a prospective study to assess the incidence of acute myopathy in patients requiring mechanical ventilation for status asthmaticus. Twenty-five patients were treated with 10 mg of dexamethasone every 8 h or 250 mg of hydrocortisone every 6 h in addition to bronchodilators, with 22 patients also receiving a vecuronium infusion. In 19 of 25 patients (76%), elevations in CK levels were observed, and 9 of 25 (36%) developed a clinically detectable myopathy. Patients who developed a myopathy received vecuronium for a mean of 5.4 days compared to 1.3 days for those patients with no myopathy. In patients who developed a myopathy, the need for mechanical ventilation was significantly longer, 12.9 days compared with 3.1 days (p <0.02).

Initially it was thought that the risk of acute myopathy was increased with the use of vecuronium or pancuronium because these compounds possess a steroidal structure and because other neuromuscular blocking agents may be safer. Leatherman and coworkers,\(^7\) however, demonstrated that this assumption was incorrect. In their study, 107 patients requiring mechanical ventilation for status asthmaticus were treated with 125 mg of methylprednisolone every 6 h in conjunction with bronchodilators. Pancuronium, vecuronium, and atracurium (a nonsteroidal neuromuscular blocker) were also administered to 69 of the patients. Twenty of 107 patients (19%) developed a clinically significant myopathy, 35% of the atracurium group, 31% of the vecuronium group, and 10% of the pancuronium group. Elevations of CK levels were noted in all patients tested. Electromyographic testing and muscle biopsies were consistent with acute myopathy. None of the 38 patients treated with corticosteroids alone developed a myopathy. In the 20 patients who developed a myopathy, the duration of paralysis was significantly longer compared to the 49 who did not, 3.4 vs 0.6 days, respectively (p <0.001). Complete recovery required a minimum of 2 to 3 weeks, with some patients requiring several months.

Although most reported cases of acute myopathy have been in patients who have received a combination of corticosteroids and neuromuscular blocking agents, corticosteroid therapy alone has been reported to cause acute myopathy. Williams and associates\(^7\) described two patients with status asthmaticus requiring mechanical ventilation who developed acute myopathy as demonstrated by elevated CK levels and muscle biopsy following treatment with 30 mg/d of dexamethasone for 10 days and 48 mg/d of betamethasone for 6 days. Four patients who developed acute myopathy after treatment with 60 to 125 mg/d of methylprednisolone for 5 to 10 days for acute respiratory failure were reported by Hanson and coworkers.\(^7\) Additional cases of acute myopathy with corticosteroid therapy alone have also been reported by others.\(^7\)

In summary, acute myopathy may occur in critically ill patients receiving corticosteroids with or without neuromuscular blocking agents. Electrodiagnostic testing and muscle and nerve biopsies demonstrate this entity to be distinct from polyneuropathy of critical illness and chronic steroid myopathy. The use of neuromuscular blocking agents should be limited to the shortest duration necessary, as the risk of
myopathy increases with duration of neuromuscular blockade. Although the need for prolonged mechanical ventilation has been reported in some patients, it is unclear if the diaphragm is directly affected by acute corticosteroid myopathy. A respiratory muscle myopathy has been reported with chronic steroid therapy, and some animal models have demonstrated effects of corticosteroid treatment on the diaphragm after 10 to 14 days.

Anaphylactic reactions have been described in a number of patients after receiving oral, intramuscular, intra-articular, and intravenous hydrocortisone, prednisone, prednisolone, methylprednisolone, and dexamethasone. Neuropsychiatric complications may occur with corticosteroid therapy, including acute mania, psychosis, depression with suicidal ideation, and delirium. Neuropsychiatric symptoms are typically seen with doses of >60 to 80 mg/d of prednisone or equivalent, and most patients develop symptoms within 1 or 2 weeks of initiating therapy. For treating steroid-induced psychosis, phenothiazines are considered the drugs of choice. Hypokalemia may be observed with corticosteroid treatment, particularly with hydrocortisone. Hyperglycemia is frequently seen and should be treated to avoid osmotically induced diuresis and loss of calories. Although controversial, we and others do not believe that evidence supports an association between acute use of corticosteroids and the development of peptic ulcer disease. A low threshold should be maintained in evaluating patients for the development of concurrent infections while receiving corticosteroids.

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