Use of Systemic Steroids in Pulmonary Diseases

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Steroids are in use for respiratory treatment since decades yet the practice remains under question for several reasons; from indications and prescribed dosages to the recorded benefits and the feared of adverse effects.[1,2]Systemic steroids are main stay of therapy in several diseases and should be used where clearly indicated. Below are major indications of systemic steroids use in pulmonary diseases.

1) Asthma

Asthma is characterized by chronic airway inflammation. Inhaled corticosteroids are the main stay of treatment in asthma, however systemic steroids is indicated in certain situations ,mainly exacerbations.

Chronic severe cases

As per GINA (Global Initiative for Asthma) 2017 recommendations,[3] despite good inhaler/inhalation techniques and adherence to step 4 medicines (high dose ICS*/LABA**),if symptoms persists, addition of low dose corticosteroids (<7.5 mg/day of prednisone or equivalent) can be considered in patients with severe asthma.

*ICS: Inhaled corticosteroids
** LABA: Long Acting Beta-2 Agonist

Asthma Exacerbation

Assessment of severity is recommended before starting the treatment. In patients with severe or life threatening asthma, Systemic corticosteroids should be administrated within one hour of presentation, particularly:

- If patient has no improvement on inhaled/nebulized short acting beta 2 agonist (SABA).
- Exacerbation developed while taking systemic corticosteroids.
- Patient had previous exacerbation requiring systemic steroids.
- Have FEV_1(Forced expiratory volume in one second)of <60% predicted value.

Dosage and type of steroids

The optimal dose for systemic steroids in asthma exacerbation remains unclear. [4]

- GINA 2017 recommends prednisolone at a dose of1 mg/kg/day with max dose of 50 mg/day.[3]This can be given as a single or divided doses, and are as effective as intravenous steroids provided that the patient is able to swallow it properly(British Guidelines on the management of Asthma 2016)
- Intravenous glucocorticoids should be given to patients who present with severe asthma exacerbation, or are unable to take oral glucocorticoids. The exact dose of glucocorticoids to use for patients with life-threatening asthma is largely based on expert opinion.
    - For severe cases admitted to the ICU, a higher initial dose of Methylprednisolone 60 to 80 mg every 6 to 8 hours is often required.
    - A lower initial dose of 40 to 60 mg every 12 to 24 hours is likely adequate for less severe cases.[5]
- Oral dexamethasone for 2 days can be used in place of prednisolonebut there is concern of metabolic side effects if continued for longer periods.

Table 1: Corticosteroid dose equivalent [6,7]

Equivalent Dose	Steroid
1.2 mg	Betamethasone (long-acting)
1.5 mg	Dexamethasone (long-acting)
8 mg	Methylprednisolone (intermediate-acting)
8 mg	Triamcinolone (intermediate-acting)
10 mg	Prednisone (intermediate-acting)
10 mg	Prednisolone (intermediate-acting)
40 mg	Hydrocortisone (short-acting)
50 mg	Cortisone (short-acting)

- Methylprednisolone has good anti-inflammatory properties. Oral prednisone and methylprednisolone are rapidly absorbed with complete bioavailability, and their efficacy is comparable to intravenous methylprednisolone.Prednisolone has high glucocorticoid activity with less mineralocorticoid effect and it is used for long term

treatment. Hydrocortisone has more mineralocorticoid activity therefore it is not suitable for long-term use, but useful intravenously (IV) in emergency situations. Dexamethasone and betamethasone have longer duration of action and are associated with significant side effects~~so it use is discourage in asthma~~.

Duration:

The duration of therapy can be tailored to individual responses. It should be continued for approximately 5-7 days after discharge.[3] Tapering is not required if oral steroids are prescribed for less than 2 weeks.[3]

2) Allergic Broncho Pulmonary Aspergillosis (ABPA)

ABPA is a hypersensitivity reaction (IgG and IgE) against *Aspergillus fumigatus* (or other species) in patients with underlying cystic fibrosis or asthma. Patients who have poorly controlled asthma or asthma with recurrent exacerbations should be evaluated for ABPA.Diagnosis of ABPA includes serum Ig-E levels above 1000 IU/ml; peripheral eosinophilia; fleeting radiographic opacities; central bronchiectasis on HRCT scan chest; positive skin prick test to aspergillus; precipitating antibody IgG to aspergillus.[8]

Dose and duration:

Systemic corticosteroid is the main stay of therapy and usually starts with oral prednisolone 0.5 mg/kg (or equivalent)[9]for first 2-4 weeks followed by gradual tapering, with aim to stop therapy in 4-6 months.

Other standard therapy of asthma including inhaled corticosteroid along with inhaled beta 2 agonists should be continued.

3) Chronic obstructive pulmonary disease (COPD)

Acute Exacerbations of COPD

There is huge burden of chronic obstructive pulmonary disease (COPD) worldwide. According to GOLD (Global initiative for chronic Obstructive Lung Diseases) 2017 guidelines [10], systemic steroids can be used during exacerbations. Steroid improve oxygenation, lung function, shorten recovery time, and reduce hospital stay.

Dose:

Oral prednisolone:40 mg/day.[11,12]

If patient is unable to take medicine orally,I/V methylprednisolone 40 mg every 8 hours

Duration:

A 5-7days course of oral steroids is recommended, though optimal duration can be variable. [10]

Stable COPD

In Stable COPD prolonged use of systemic steroids is associated with undesirable effects and mainstay of treatment is bronchodilators, coupled with inhaled steroids. Systemic steroids in stable COPD is not recommended.[10]

4) Tuberculosis

a) In patients with tuberculous meningitis and pericarditis, an initial adjuvant corticosteroid therapy is recommended for 6-8 weeks in tapering doses.[13]

b) Scientific data does not support use of steroids in pleural effusion, genito-urinary TB and pulmonary TB.

c) Clinically manifest adrenal insufficiency as a result of TB is an absolute indication for corticosteroids. On the other hand, corticosteroid replacement may not be necessary for subclinical adrenal insufficiency which is common among patients with pulmonary as well as extrapulmonary TB.[14]

5) Community Acquired Pneumonia

Community Acquired Pneumonia (CAP) is the leading cause of infectious morbidity and mortality worldwide.In last few years corticosteroids have been evaluated in different studies with CAP. The indication is in *severe* CAP only whose criteria include:

- *major* criteria of severe CAP, or direct admission to the ICU, includes either the need for mechanical ventilation or the presence of septic shock requiring vasopressors. The 9 *minor* criteria are: respiratory rate 30 breaths per min; ratio of arterial oxygen tension to inspired

oxygen fraction ≥250; multi lobar infiltrates;confusion and/or disorientation; uremia (blood urea nitrogen level ≥20 mg/dL); leukopenia (WBC count <4000 cells/$mm^{>3}$); thrombocytopenia (platelet count <100,000 platelets/$mm^{>3}$); hypothermia (core temperature <36°C); and hypotension requiring aggressive fluid resuscitation.

- The presence of any of the major or≥3 minor criteria are sufficient evidence for admission to an ICU or high-level monitoring unit.[15]

- The other score to assess disease severity in CAP is CURB 65.It includes presence of Confusion;Urea(BUN > 19 mg/dL or 7 mmol/L); Respiratory Rate >30 per minute; Blood Pressure: diastolic < 60 or systolic < 90 mmHg; and Age > 65 years. Every component has one point, patient 2-5 score are high risk group and required admission.

In a multicenter, double-blind, randomized, placebo-controlled trial, Methylprednisolone treatment for 7 days in hospitalized patients with CAP was found to shorten~~ed~~ time to clinical stability.[16] In another study of severe CAP, it was found that a short steroid course decreases risk of treatment failure and reduces radiographic progression of pulmonary infiltrations within 3 to 5 days.[17]A meta-analysis confirmed that ~~the~~ adjunct steroid therapy in severe CAP reduces the overall length of hospital stay without affecting the in-hospital mortality and ICU stay.[18]

Dose: [19]

- For patients who can take oral medications: prednisone 40-50 mg daily.
- Patients who are unable to take oral medications:methylprednisolone 0.5 mg/kg IV every 12 hours.

Duration: Total of 5-7 days.[19]

6) **Interstitial lung diseases (ILD)**

This term encompasses variety of diseases, some of which respond to steroids. One of the commonest variety, Idiopathic Pulmonary Fibrosis (IPF) has an unfavorable outcome with steroid use. Others where steroids benefit include Sarcoidosis and NSIP:

I. Sarcoidosis

Sarcoidosis is a granulomatous disorder of unknown etiology. It is characterized pathologically by the presence of non-caseating granulomas. Sarcoidosis can involve multiple organs mainly Lungs. Most patients with mild disease can be managed on symptomatic treatment only; when therapy is required, steroids are the first line treatment.

- In patients with mild disease, such as skin lesions, eye inflammation, or cough, topical glucocorticoid therapy with creams, eye-drops, or inhalers may be sufficient
- In pulmonary sarcoidosis,systemicsteroids are started when there is dyspnea, hypoxia, and progressive deterioration in pulmonary function and radiological evidence of progression of disease.

Dose

The optimal dose and duration of glucocorticoid therapy is not known.[20] The treatment is individualized on the basis of patient symptoms and response rate.Usually starting dose isoral prednisolone at a daily dose of 0.3 to 0.6 mg/kg ideal body weight (20-40 mg /day)depending on disease severity[21]with gradual tapering of 5 mg every 2 weeks reducing to maintenance dose of 10 to 15 mg/day.

Duration

Usual duration of steroids of 12 to 18 months**.**Longer therapy may be requiredif the patient has recurrence of symptoms and progression of radiographic infiltrates.[22]

Treatment response is monitored with PFTs along with patient's clinical responseevery 1-3 months.Patient who fail to respond to an initial 3 months therapy are unlikely to respond to more prolonged therapy.

II. Non-specific interstitial pneumonia (NSIP)

NSIP is the second most common form of pathological pattern of Interstitial Lung Diseases(ILD). NSIP has fibrotic (poorer outcome)and cellular subtypes. It may be idiopathic or associated with number of conditions like connective tissue diseases (CTD), autoimmune diseases, drug induced and hypersensitivity lung disease.

Dose and duration

The optimal dose and duration of glucocorticoid therapy is not known asmost studies of patients with idiopathic NSIP consist of a small number of patients and a variety of regimens.

- Start prednisolone with 1 mg/kg ideal body weight per day up to a maximum of 60 mg/day for one month, followed by 40 mg/day for an additional two months.[23]

- For patients with severe disease requiring hospitalization, some specialists have used pulse intravenous methylprednisolone.[24]The usual regimen is 500-1000 mg/day for three days followed by oral prednisolone as mentioned above.

- In patients who respond or stabilize with treatment, the prednisolone dose is gradually tapered, aiming to reach 5 to 10 mg daily or on alternate days, by the end of 12 months, with attempted cessation after at least one year of therapy.

- Some patients relapse when prednisolone is tapered or discontinued. Such patients can be maintained for a longer period on low-dose prednisolone.If relapse occurs with a higher prednisolone dose, alternative is to add another immunosuppressive agent.

III. Cryptogenic Organizing Pneumonia ~~(COP)~~

COP is classified as an interstitial lung disease (ILD). It could be idiopathic or secondary,to connective tissue diseases (CTD), organ transplant, drugs, radiation and infection. Diagnosis includes bilateral patchy consolidations on chest imaging, after exclusion of common causes such as pneumonia.Steroids are mainstay of therapy

Dosesand duration:

The optimal initial dose of systemic glucocorticoid therapy is not known.

- Typically use an initial dose of prednisolone of 0.75 to 1 mg/kg (using ideal body weight)per day, to a maximum of 100 mg/day.[25]

- Maintain the initial oral dose for four to eight weeks.

- If the patient improves, the dose is gradually tapered to 0.5 to 0.75 mg/kg per day every four to six weeks.
- Oral steroids can be stopped after approximately six months if the patient remains stable.
- In case of worsening or recurrence, the dose should be increased to the prior dose.

The patient should be routinely followed with a conventional chest radiograph and pulmonary function testing every two to three months as long as systemic glucocorticoid therapy is required. After cessation of glucocorticoids, the patient should be followed clinically for the next year and repeat the chest radiograph approximately every three months.

IV. Hypersensitivity pneumonitis (HP)

HP, also known as extrinsic allergic alveolitis, is a clinical syndrome characterized by variable presentations (acute, subacute, and chronic/fibrotic) secondary to exposure to organic dust and chemicals.Management of HP includes avoidance of environmental allergens and use of systemic steroids in severe cases.

Dose

- Initial dose of prednisone is 0.5-1 mg/kg of ideal body weight/day (upto maximum dose of 60 mg/day)[26]for 1-2 weeks in acute HP and 4-8 weeks for sub-acute/chronic HP, followed by a gradual taper to a maintenance dose of approximately 10 mg/day.

Duration [27]

- Total duration of therapy in acute HP is 4-6 weeks
- For sub-acute HP the duration is 12 weeks. Therapy should be guided by clinical response, pulmonary function, and radiographic improvement.
- Chronic fibrotic HP is usually poorly responsive to steroids therapy. Non responders may benefit from lung transplantation.

Steroids side effects and monitoring

Unnecessary use of steroids should be avoided. It is imperative for a physician to have knowledge about its side effects so that these can be monitored appropriately.Moreover, the steroid dosages and duration has to be kept to the minimum required for the particular indication.

1. Glucocorticoid use can cause sleep disturbance and psychiatric side effects like mood disorders, delirium, and panic disorder.

2. Prolonged use of systemic steroids causes osteoporosis or osteopenia. In order to prevent glucocorticoid-induced osteopenia calcium with vitamin D is recommended if glucocorticoid is used in doses ≥5 mg/day.Patients requiring 5 mg per day or more of systemic steroids intended for more than 3 months should receive prophylactic bisphosphonates to prevent osteoporosis including fractures. In elderly patients, postmenopausal females, or those with increased fracture risk, prophylactic bisphosphonates should be considered when using steroids even for a lesser duration.[3,28,29]

3. Prolong use of steroids can lead to drug-induced diabetes mellitus ~~(Type 2 Diabetes)~~.

4. Prolong steroids cause adrenal suppression by effecting hypothalamo-pituitary-adrenal axis. If steroids are suddenly withdrawn after prolonged usage, there is a potential risk of circulatory shock.

5. Steroids cause impaired immunity and predispose patients to certain infections, especially tuberculosis, fungal and certain viral infections; physician should have a high index of suspicion in such patients.[30,31]

6. It is recommended that patient should be on *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis if steroids dose of > 20 mg is continued for > 1 month.[32]

7. Systemic steroids especially along with non-steroidal anti-inflammatory drugs, can exacerbate gastritis or peptic ulcers.

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