Approach to respiratory failure in emergency department

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Abstract. – Objectives and Background: The goal of this review is to provide update recommendations that can be used by emergency physicians who provide primary cares to patients with Acute Respiratory Failure (ARF), from the admission to an emergency department through the first 24 to 48 hours of hospitalization. This work wants to address the diagnosis and emergency medical care of ARF and the management of medical complications.

State of the Art: A lot of statement has been developed for the early management and treatment of ARF; moreover, over the last fifteen years, we have assisted to the rise of a new technique of ventilation, in the Emergency Department: Non Invasive Ventilation. This kind of ventilation was firstly applied in Intensive Care and in Respiratory Care Unit. Randomized controlled clinical trials have showed its usefulness in the early treatment of several forms of ARF, together with medical therapy.

Key Words: Respiratory failure, Pulmonary edema, Asthma, Pneumonia, Therapy in emergency department.

Introduction

Acute Respiratory Failure (ARF) was defined as the inability of the respiratory system to exchange gases and to oxygenate the blood adequately. We can distinguish two mechanisms at the basis of ARF:

1. Failure in pulmonary ventilation (pump failure);
2. Failure in gas exchanges (lung failure).

The first one is due to neuromuscular diseases, chest wall deformities, obstructive pulmonary diseases (Table I).

The second mechanism (mismatch in blood gas exchanges) is due to the following different pathologies:

- Adult acute respiratory distress syndrome;
- Neonatal respiratory distress syndrome;
- Acute cardiogenic pulmonary oedema;
- Severe status asthmaticus;
- Pneumonia;
- Airspace collapse (atelectasis);
- Pulmonary embolism.

The clinical signs and symptoms of patients with ARF, refer to the two main manifestations of pulmonary diseases: arterial hypercapnia and hypoxemia.

The pathophysiology of hypercapnia is based on four main mechanisms:

- Increase in CO₂ production (for instance, parenteral feeding with high doses of carbohydrates; high body temperature, etc.)
- Deterioration in gas exchanges as the increase in alveolar dead space ventilation (for instance in Chronic Obstructive Pulmonary Disease – COPD –, because of mismatch in ventilation/perfusion ratio, and in pulmonary embolism);
- Deterioration in respiratory mechanics that involves a huge effort, an increase in respiratory work and the development of a rapid shallow breathing ↑ CO₂;
- Alteration in the mechanism of control of the ventilation (for instance, in chronic hypercapnia, we observe a decrease in ventilatory drive with an increase in tolerance threshold to CO₂; it happens in metabolic alkalosis too).

The hypoxemia is due to different pathophysiological mechanisms:

- Hypoventilation;
- Alteration in gas diffusion;
Mismatch in ventilation/perfusion ratio;
• Pulmonary shunt.

Which are the clinical signs and symptoms of hypoxemia and hypercapnia? The first one shows with shortness of breath, tachycardia, mental confusion, changes of personality, restlessness, cyanosis, hyper/hypotension, arrhythmias and palpitations. Hypercapnia, instead, shows with sleepiness, mental confusion, cephalea, convulsions, miosis, papilledema, peripheral vasodilation, hypotension and coma.

The first goal of the initial diagnostic evaluation is to understand the underlying causes, and so to do differential diagnosis among all pathologic conditions that showed the most important clinical symptom of this illness: dyspnoea.

A – Approach to Patients with Dyspnoea

Clinical Evaluation

A patient with ARF usually presents with signs of respiratory distress: dyspnoea, cyanosis, tachypnea, accessory muscle use, paradoxical breathing and tachycardia. Primary care physician must apply the algorithm A-B-C-D, in order to exclude an Acute Upper Airway Obstruction (AUAO), first of all, and then he must operate as following:

1. He has to administer high flows of oxygen, to measure blood pressure, to take heart rate, respiratory rate, oxygen saturation, to make an electrocardiogram.

Moreover he has to take an arterial blood gas sample and a peripheral venous blood sample to evaluate CK, CKMB, T-troponine, LDH, AST, ALT and hemochrome.

2. At the same time he must evaluate the neurological state, in order to call for the resuscitator if Kelly score (Table II) is more than 3.

3. If neurological state is not compromised patient can be managed by emergency physician, entirely. Arterial blood gas (ABG) evaluation:

- Hypoxemia with hypercapnia → pump failure due to neuromuscular disease or chest wall deformities; Lung failure due to COPD or acute asthmatic status.

This last situation can be treated with pharmacological therapy and/or with non invasive ventilation, if indicated. Patient must undergo endotracheal intubation (ETI) if his clinical conditions deteriorate.

- Hypoxemia with no hypercapnia → lung failure due to ARDS or cardiogenic pulmonary oedema or pulmonary embolism or pulmonary infection. If oxygen saturation in more than 90% continue to administer O₂ with face mask and high flows. If oxygen saturation is less than 90% consider the use of Non Invasive Ventilation (NIV), together with medical therapy.

4. Clinical evaluation must be associated with radiological evaluation (Chest X-Rays) and with continuous ABG evaluations (after 1 hour and after each changing in clinical conditions). Patient must undergo endotracheal intubation if his clinical conditions deteriorate.

Evidence and Information Sources

A comprehensive literature search was performed in order to select the latest rec-

Table II. Kelly scale.

- Awoke patient, he executes 3 complex orders
- Awoke patient, he only executes simple orders
- Sleepy patient, he can be awaken under verbal orders
- Sleepy patient, he can be awaken under physical stimulus
- Coma with no brainsteam alteration
- Coma with brainsteam alteration
ommendations for the early diagnosis and the therapy of the pathologies below.

In developing of the present guidelines we considered the latest evidences in the management of dyspnoea, asthma, COPD, ARDS and we applied the ATS Consensus Conference indications and the BTS guidelines for the use of NIV in ARF.

B – Approach to Patients with Acute Upper Airway Obstruction (AUAO)

Etiology
The causes of AUAO can be summarized in Table III.

Clinical Evaluation
We distinguish two different types of upper airway obstruction: the extra thoracic presents inspiratory stridor, because of the collapse of upper extra thoracic airways, during the inspiration when tracheal pressure is minor than atmospheric one. The intra thoracic one that presents expiratory stridor, because the extrathoracic airways collapse during the expiration, when the intrapleural pressure is greater than atmospheric one.

The stridor is the main symptom of AUAO (Table IV), and it’s often associated with cyanosis, loss of consciousness, nape’s hyperextension (especially in the epiglottiditis), trismus (especially in the peritonsillar abscess), dysphagia (severe epiglottiditis or pharyngeal obstruction). We usually observe asymmetries in diaphragmatic ranges, in respiratory movements, in the intercostal and supraclavicular re-entrances.

If the physician suspects an epiglottiditis, he should be cautious in carrying out clinical examination: in fact he could provoke a complete obstruction stimulating with the tongue depressor. Moreover, if respiratory distress continues and the patient is stable (rapid shallow breathing, valid cough, conscious, lucid and alert patient but with no cardiovascular alterations) physician should take blood pressure and oxygen saturation, continuously, and often control ABG. If patient presents with respiratory arrest he should follow the Advanced Life Support Algorithm. In a second time physician should make differential diagnosis between epiglottiditis and viral croup.

Anaphylaxis: if patients present with glottis’ oedema should be immediately intubated before developing complete obstruction of upper airways. Then they should be submitted to infusion therapy with adrenaline (1 mg in bolus repeatable), corticosteroids (hydrocortisol – methylprednisolone) at high doses, fluids.

Table III. Modified by G. Garetto, La Nuova Medicina d’Urgenza, Ed. C.G. Torino.

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Neoplasms</th>
<th>Traumatic</th>
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<tbody>
<tr>
<td>Viral laryngotracheitis (croup)</td>
<td>Bacterial epiglottiditis</td>
<td>External bodies aspiration</td>
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<tr>
<td>Bacterial epiglottiditis</td>
<td>Bacterial tracheitis</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Bacterial tracheitis</td>
<td>Subglottic hemangioma</td>
<td>Obstructive Sleep Apnea Syndrome (OSAS)</td>
</tr>
<tr>
<td>Tracheal and endobronchial neoplasms</td>
<td>Thyroid and mediastinal tumors</td>
<td>Neurogenic diseases</td>
</tr>
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</table>

Bilatertal paralysis of recurrent nerve

Table IV. Infectious AUAO.

<table>
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<tr>
<th>Supraglottic</th>
<th>Subglottic</th>
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<tbody>
<tr>
<td>Severe tonsillitis (&gt; 10 years)</td>
<td>Viral croup (3 months-3 years)</td>
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<tr>
<td>Peritonsillar abscess (&gt; 10 years)</td>
<td>Bacterial tracheitis</td>
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<tr>
<td>Retropharyngeal abscess (&gt; 3 years)</td>
<td></td>
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<tr>
<td>Epiglottiditis (3-7 years)</td>
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</table>
Foreign bodies obstruction: do not introduce fingers into the oral cavity in order to take it out; it could slip down. If patient can speak the physician could remove it with a powerful blow in the interscapular zone (from one to four powerful blows). Moreover he can try with Heimlich’s manoeuvring. This one can be performed with supine patient, in case of loss of consciousness. If foreign body cannot be still removed, patient should be submitted to endoscopic removal, or to cricothyroidotomy, or to tracheostomy.

C – Approach to Patients with ARF Due to Neuromuscular Diseases or Chest Wall Deformities

Classification
See Table V for the classification

Signs and Symptoms of Hypoventilation
• Rapid shallow breathing
• Paradoxical breathing
• Alternating breathing
• Inability in carrying out a valid cough
• Shortness of breathing (at the end).

In patients with chest wall diseases, ARF is due to hypoventilation with an increase in respiratory work and rapid shallow breathing. Hypercapnia and hypoxemia associated with hypoventilation due to neuromuscular diseases are due to different mechanisms:
• Muscular weakness;
• Decrease of pulmonary and thoracic compliance;
• Increase in respiratory work;
• Decrease in central sensibility.

The clinical approach to these patients could be differentiated on the base of their conditions at the admission to the first aid.

Preserved and stable vital functions: if upper airways are pervious, if there are no cardio-vascular troubles and Kelly score is “1” and patient presents only dyspnoea, deliver oxygen with facial mask and control arterial saturation and blood pressure continuously. If arterial blood sample shows an oxygen saturation more than 90% and a PaCO₂ less than 45 mmHg, evaluate ABG after 1 hour and control clinical conditions. Chest radiography should be done as soon as possible, to help the physician in differential diagnosis among neuromuscular diseases, chest wall deformities and brainstem pathologies.

Preserved But Instable Vital Functions
Cardio-circulatory arrest: ask for emergency team and follow the algorithm ALS for the cardiac arrest. Patient will be admitted to the Intensive Care Unit (ICU).

D – Approach to Patients with ARF Due to COPD

The term COPD encompasses two well defined entities: emphysema and chronic bronchitis. Emphysema is characterized by permanent and abnormal enlargement of airspace, distal to the bronchiole, associated to a destruction of alveolar wall, without evident fibrosis, and to an obstruction of distal lower airway. Bronchitis is defined only by a clinical definition as presence of cough and expectoration for more than three months per year for more than two consecutive years. The key feature that unites these diseases (bronchitis and emphysema) and the asthma (that we’re going to treat below) under the definition of COPD is the physiologic phenomenon of obstruction to forced expiratory airflow.

COPD is a slowly progressive disease characterized by punctuated exacerbations two or three times a year in patients with significant obstruction. It is identified by the presence of airflow limitation that is not fully reversible and does not change markedly over several months. The disease is predominantly caused by smoking. The exacerbation, in most cases its due to infections, especially bacterial in-
The pathogens most often involved in COPD exacerbations are *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*; less often, gram negative bacteria, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. Among viruses have been identified: Rhinovirus, Influenza virus, Parainfluenza virus, Coronavirus, Respiratory Syncytial Virus, Adenovirus. The cause of exacerbation may be unidentifiable up to 30% of exacerbation.

Clinical Evaluation

The diagnosis of the exacerbations is clinical and is based on three parameters: increasing in sputum production, purulent expectoration, worsening dyspnoea. There is a severity scale for exacerbations based on these findings: type 1 (severe exacerbations) have all of the above symptoms; type 2 (moderate exacerbations) present only two of the three symptoms; type 3 (mild exacerbations) present only one of the symptoms but associated with one of the following at least: an upper respiratory tract infection in the past five days, fever, increasing in cough or wheezing, increasing in respiratory rate or in the heart rate by 20% above the baseline. Each patient ranks the importance of different symptoms individually, however breathlessness is the most significant symptom. Individual symptoms are not useful in making or excluding the diagnosis of COPD.

Additional Diagnostic Tests

Chest radiography: some observational studies showed substantial rate of chest radiograph abnormalities. However, chest radiography is not routinely necessary during exacerbations, neither for the diagnosis (level of hierarchy IV). It could be useful if there is the suspect of pneumonia, or pneumothorax or aspiration (such as in neuromuscular diseases), or if patient is non-responsive to the therapy. As chest radiography can sometime reveal a parenchymatous pulmonary lesion such as tuberculosis or bronchial carcinoma, patients who have not had a radiography prior to the exacerbation should obtain one.

Spirometry: spirometric assessment, at the time of presentation, or during the course of treatment, is not useful in judging severity or guiding management of patients with acute exacerbation of COPD (level of hierarchy IV).

Serological Assays Are Only of Epidemiological Value

Sputum samples for microbiological tests (using Gram stain and culture) is indicated in seriously ill patients, if sputum is persistently present and purulent, or if there is a history of prior treatment failure (level of hierarchy IV).

Arterial blood gas sample is necessary to assess the severity of exacerbation and for the initial management of the patient. Moreover, patients who have low *PaO₂*, high *PaCO₂*, low pH are more likely to relapse within 14 days of initial presentation.

ECG and/or Echocardiogram is useful to assess cardiac status if there are features of cor pulmonale (level of hierarchy IV).

CT scan of the thorax is necessary in suspect of pulmonary embolism. It is useful (level of hierarchy IV) to investigate symptoms that seem disproportionate to the spirometric impairment, to investigate some suspect abnormalities in chest radiograph.

Reversibility testing: there is a considerable variability in change in FEV₁ in response to the same stimulus from day to day, so it is virtually impossible to interpret the response to an individual reversibility test unless the response is very large (an increase in FEV₁ more than 400 ml). Reversibility testing is not recommended in the latest guideline produced jointly by the American Thoracic Society and the European Respiratory Society.

Referral for specialist advice: these are made when clinically indicated, at all stages of disease, not only in the most severely disabled patients (level of hierarchy IV).

Need of Hospital Management

Most patients with acute exacerbation of COPD can be managed at home, but some of
them need hospital treatment. This may be because of the following reasons:

- Need for therapies that are not available at home (such as non invasive ventilation);
- Severe breathlessness;
- Poor/deteriorating general conditions;
- Cyanosis;
- Worsening peripheral oedemas;
- Impaired neurological conditions, mental confusion;
-Acute onset;
- Significant comorbidity particularly for heart diseases;
- Changes in chest radiograph;
- Significant alteration in arterial blood gas analysis (PaO₂ < 60 mmHg; pH < 7.35).

Management

The following assessment about the management in acute setting of COPD are based on the analysis of the most recent guidelines from 2001 to 2004.

**BRONCHODILATORS**

Bronchodilators are central in management of symptoms of acute exacerbation of COPD. However they do not modify the decline of lung function or, by inference, the prognosis of the disease (grade B). Anticholinergic drugs inhibit vagal stimulation of the bronchial tree and are associated with a reduction of the smooth muscle tone and an impairment of bronchial gland secretion. The bronchodilating effects of short acting inhaled anticholinergics last up to 8 hours after the administration (grade A). If administered with metered-dose inhaler (MDI), the recommended dose of ipratropium bromide is 2-4 puff (40-80 microg) four times daily. For more severe exacerbations, 0.5 mg each 8 hours (0.5 mg corresponds to 40 gtt of 0.25% solution). The duration of action of short acting inhaled anticholinergic agents is greater than that of beta 2 agonists (grade A). More recently, several studies have reported favourable effects with tiotropium a new long acting anticholinergic bronchodilator that must be inhaled once daily.

The duration of action of short acting anticholinergic agents is greater than that of short acting beta-agonists (grade A). The combination of beta agonists and anticholinergics is more effective and better tolerated than higher doses of either agents used alone (grade of recommendation A). The bronchodilator effects of short acting beta agonists (i.e. salbutamol) disappear within 4-6 hours; so for severe exacerbations is acceptable to increase the number of administrations. Table VI (modified from “COPDX plan: Australian and New Zeland guidelines for managements of acute exacerbation of COPD”) shows the use of bronchodilators according to the severity of COPD.

The duration of action of short acting anticholinergic agents is greater than that of short acting beta-agonists (salbutamol, terbutaline) (grade of recommendation A). The use of both of them is more effective and better tolerated than the use of each one alone (grade of recommendation A). Long-acting beta2-agonists (salmeterol and formoterol) provide bronchodilation for 12 hours and are the first line treatment of acute severe asthma. Moreover they provide sustained relief in moderate to severe exacerbation of COPD (grade of recommendation A).

**Table VI.**

<table>
<thead>
<tr>
<th>Severity</th>
<th>FEV₁</th>
<th>Suggested treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild COPD</td>
<td>60%-80%</td>
<td>Intermittent bronchodilators – salbutamol (200 µg) or ipratropium bromide (40 µg)</td>
</tr>
<tr>
<td>Moderate COPD</td>
<td>40%-59%</td>
<td>Intermittent or regular bronchodilators – salbutamol (200-400 µg four times daily) or ipratropium bromide (40 µg four times daily) Combination bronchodilators may be considered</td>
</tr>
<tr>
<td>Severe COPD</td>
<td>&lt; 40%</td>
<td>Regular combination bronchodilators – salbutamol (200-400 µg four times daily) and ipratropium bromide (40-80 µg four times daily)</td>
</tr>
</tbody>
</table>

Modified from GOLD [evidence level D]. FEV₁ = forced expiratory volume in one second. COPD = chronic obstructive pulmonary disease.
At the following dosage, salmeterol (50 microg twice daily) and formoterol (12 microg twice daily) improve the health related quality of life, lung function and symptoms.

**Theophylline**

Theophylline is a non selective inhibitor of phosphodiesterase. Besides bronchodilation it increases central respiratory drive, respiratory muscle endurance, mucociliary clearance, cardiac output and dilation of pulmonary arteries. Theophyllines are rarely used because of their narrow therapeutic index and the potential side effects (grade of recommendation A).

**Glucocorticoids**

Chronic treatment with oral glucocorticoids should not be used in COPD (grade of recommendation A). In fact their prolonged use do not modify the long term decline of FEV1. Systemic preferable oral glucocorticoids are beneficial in the management of acute exacerbation of COPD (grade of recommendation A). Probably they improve the rate of lung function during the first 72 hours. Many recent COPD guidelines recommend the use of a short course (two weeks) of oral glucocorticoids in a dosage of 0.5 mg of prednisone or prednisolone/kg body weight. Inhaled glucocorticoids should be considered in patients with a documented response or those who have severe COPD with frequent exacerbations (grade of recommendation B). Patients with clinically significant acute bronchodilator reversibility may benefit from long term inhaled glucocorticoid therapy.

**Oxygen Therapy and Ventilatory Support**

It’s indicated in patients with hypoxia to increase the oxygen blood saturation up to 90%. NIV has been shown to be an effective treatment for acute hypercapnic respiratory failure, particularly in patients with acute exacerbation of COPD in whom a respiratory acidosis persist despite maximum medical treatment on controlled oxygen therapy (grade of recommendation A). All the studies about the use of NIV in acute exacerbation of COPD have excluded patients deemed to warrant immediate intubation. NIV in fact should be undertaken as a therapeutic trial with a view to tracheal intubation if it fails. A decision about tracheal intubation should be taken before initiating NIV in each patient.

**Antibiotic Therapy**

Antibiotics should be used in patients with purulent sputum and should be administered according to the stage of the disease (mild, moderate or severe) and appropriate to the bacterial agents probably involved. So in the mild stage with a suspected infection by *Streptococcus pneumoniae, Haemophilus influenzae, Chlamydia pneumoniae, Mycoplasma pneumoniae, Moraxella catarrhalis* the recommended treatment is amoxicillin-clavulanic acid (or other more inhibiting beta-lactams available such as ampicillin-sulbactam and amoxicillin-sulbactam), at dosage of 875/125 mg/12 h for ten days or cefuroxime (500 mg/12 h for 10 days) with azithromycin (500 mg/day for three-five days) or clarithromycin (500 mg twice daily for 1 week). If patients have one or more risk factors add moxifloxacin/gatifloxacin/levofloxacin (respectively 400 mg/day, 400 mg/day and 500 mg/day for 7 days) and telithromycin (800 mg/day for 5 days). If patients have a moderate or severe condition intravenous treatment may sometimes be necessary. The first line therapy, if enteric bacteria or penicillin resistant *streptococcus* is involved are quinolones, piperacillin-tazobactam and, if there is a suspected infection by *Pseudomonas aeruginosa*, ceftazidime, imipenem or meropenem or cefepime.

**Management of Acute Asthma**

A recognized definition of acute asthma must be still developed, despite numerous clinical definition have been proposed in different workshops, working group, consensus conferences and national and international guidelines. The following table shows the major and minor criteria established by the American Thoracic Society in 2000, to define severe asthma.

According to consensus guideline, a severe episode is characterized by almost one of the following events:

1. Accessory muscle activity;
2. Paradoxical pulse exceeding 25 mmHg;
3. Heart rate > 110 beats per minute;
4. Difficulty talking;
5. Hypoxia with saturation below 90%.

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4. Respiratory rate > 30 breaths per minute; 
5. Arterial saturation less than 90%.

This clinical features are associated with a forced expiratory volume or a peak expiratory flow rate less than 50%. In fact the sine qua non of an episode of acute asthma is the reversible, non uniform increase in airway obstruction that induces diminished flow rate, hyperinflation of the lung and premature airway closure. Moreover with the increase in work of breathing and in expiratory effort the dynamic hyperinflation rises and auto-positive end expiratory pressure (PEEP) develops.

Arterial blood gas examination: it typically shows hypoxemia, hypocapnia, respiratory alkalosis. The more severe is the attack, the lower is the arterial oxygen saturation. However most asthmatic patients don’t develop marked hypoxemia and, also in severe attacks, it’s very infrequent that oxygen tension decrease under 50 mmHg. Respiratory acidosis follows hypercapnia. With extreme flow limitation metabolic acidosis develops. In fact, if cardiac output is compromised develops lactic acidosis because of the hypoperfusion of peripheral tissue; in addition the increased oxygen consumption by respiratory muscles also contributes. It may also be induced by aggressive administration of non selective sympathomimetics.

Managements

In hospital settings for asthmatic patients the driving gas should be oxygen for acute ill patients. Moderately short-acting beta2-adrenergic agonists such as salbutamol and terbutaline have rapid onset of action and provide more bronchodilation than do methylxanthines and anticholinergics, making them the first line treatment for acute illness. Adult patients with acute asthma should be given 2.5-5 mg of salbutamol or 5-10 mg of terbutaline (Grade of recommendation B23). There is evidence that additional benefit can be obtained by adding anticholinergic treatment such as ipratropium bromide 500 microg (Grade of recommendation A). Treatment should be repeated if patient is non responsive to the therapy. In near fatal asthma, the use of intravenous salbutamol (5 microg/min) and adrenaline (1 mg repeatable for three times each 15 minutes), is effective.

Nebulized corticosteroids have been used as a substitute of oral corticosteroids in moderate exacerbations of adult asthma; they have been shown to have an oral steroid sparing effect (Grade of recommendation A). Patients that are resistant or slowly responsive to beta-agonists need corticosteroids more urgently. Methylprednisolone should be administered at dosage of 1 mg/kg of body weight during the acute attack. The US guidelines recommend 120-180 mg daily of methylprednisolone given intravenously (in three or four doses). It must be repeated for 48 hours in those admitted, followed by 60-80 mg/day until the FEV1 reach the 70% of normal. Oral prednisone (60 mg/day) can be substituted.

Methylxanthines, although may have antiinflammatory properties, are considerably less effective than the sympathomimetics and produce more significant side effects.

Compared to COPD, insufficient evidence exists to recommend the use of NIV for asthma patients; there is also insufficient evidence to recommend Continuous Positive Airway Pressure (CPAP) in acute asthma (Grade of recommendation C). The role of NIV is not yet clear established and it could delay the use of endotracheal intubation when it is necessary.

E – Approach to Patients with Hypoxemic ARF

a – Pulmonary Oedema

The definition of “pulmonary oedema” is the overflow of fluid from the lung’s capillary to the alveolar spaces. We can distinguish two different entities of this pathology: cardiogenic pulmonary oedema and non-cardiogenic pulmonary oedema. The acute cardiogenic pulmonary oedema is a hydrostatic oedema due to an impaired function of left ventricle caused by coronary artery disease, myocarditis, cardiomyopathy, hypertension, congenital heart diseases. It occurs when the pulmonary capillary pressure rises to value exceeding plasma colloid-os-
motic pressure (approximately 25 mmHg). Clinical examination reveals a low flow state with wet crackles, jugular venous distention, third tone (S3 gallop), cardiomegaly. Concerning laboratory tests, ECG could shows signs of ischemia or infarction. There could be an increasing in cardiac enzymes and, at the radiography, perihilar distribution of oedema and the appearance of Kerley lines. Pulmonary capillary wedge pressure exceeds 18 mmHg.

The treatment of acute pulmonary oedema is based on the use of oxygen, nitrates, diuretics and, if coexists cardiogenic shock, inotropes. Furosemide and nitrates (10 microg/min) are the first line of medical treatment and should be administered, together with morphine, if arterial systolic blood pressure exceed 100 mmHg. They promote diuresis and vasodilation and so act both on the pre-load and on the post-load of the heart, reducing cardiac work and improving the ejection fraction. If arterial systolic blood pressure is between 70 and 100 mmHg dobutamine (2-20 microg/kg/min) improves the contractility and reduces peripheral resistances avoiding arterial vasoconstriction (it acts only on beta receptors). If there are signs of cardiogenic shock, dopamine (5-15 microg/kg/min) increases the contractility and improve the arterial blood pressure, acting both on alpha and beta peripheral receptors and, at low dosage, on dopaminergic receptors in the renal glomerule promoting diuresis.

Oxygen could be administered with face masks with Venturi system or with reservoir to reach high concentration of oxygen until 100%. During the last ten years the use of NIV for treatment of acute pulmonary edema is developing with modality of CPAP. CPAP has been shown to be effective in patients with cardiogenic pulmonary oedema who remain hypoxic despite maximal medical treatment (Grade of recommendation B)\textsuperscript{10,59-62}. CPAP permits higher inspired oxygen content, increases mean airway pressure and improves ventilation recruiting collapsed areas of the lung.

ARDS is defined by non cardiogenic pulmonary oedema, characterized by severe hypoxemia, new bilateral pulmonary infiltrates at radiography, without elevated left atrial pressure. The American - European Consensus Conference on ARDS defined the severity of the pathology by the ratio of PaO$_2$/FiO$_2$: a ratio of 300 or less defines the acute lung injury (ALI); a ratio of 200 or less defines ARDS regardless of the amount of PEEP needed to support oxygenation\textsuperscript{65}. The pathogenesis is due to the lung damage, that causes an increasing in permeability of capillary endothelium and an alteration of lung alveolar-capillary barrier with overflow of fluid into the alveolar and interstitial space, without increasing in pulmonary circulatory pressure. The damage involves both the endothelial and epithelial surface; the activated endothelium participates and partly drives the neutrophil inflammatory response that contributes to edema formation and fibrosis\textsuperscript{64}. The most common cause of ARDS is a severe infection and it accounts for approximately half of cases. It could present as a localized or systemic disease and the most common agents involved are gram-negative bacteria, that are often associated to multiple organ failure. The last syndrome is the major cause of death with a mortality of about 40%\textsuperscript{65-68}. Other frequent causes of ARDS are: trauma, disseminated intravascular coagulation (DIC), acute haemorrhagic pancreatitis, aspiration of gastric contents, inhalation of foreign bodies, acute radiation pneumonitis, inhalation of toxic gases (smoke, ozone, cadmion, chlorine, nitrogen dioxide) or circulating foreign substances (alloxan, alpha-naphthyl thiourea). Special forms of ARDS are showed in the table below\textsuperscript{69} (Table VII).

<table>
<thead>
<tr>
<th>Table VII. Special forms of ARDS.</th>
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<tbody>
<tr>
<td><strong>Pharmaceutical</strong></td>
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<tr>
<td>- Narcotic overdose</td>
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<tr>
<td>- Chemotherapy</td>
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<tr>
<td>- Salicylate intoxication</td>
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<tr>
<td>- Hydrochlorothiazide</td>
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<tr>
<td>- Contrast fluid</td>
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<tr>
<td>- Calcium antagonists overdose</td>
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<tr>
<td>- High altitude</td>
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<tr>
<td>- Neurogenic</td>
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<td>- Pulmonary embolism</td>
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<td>- Eclampsia</td>
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<tr>
<td>- Post cardioversion</td>
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<tr>
<td>- Post anesthesia</td>
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<tr>
<td>- Post cardiopulmonary bypass</td>
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</tbody>
</table>

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Management

The main life threatening problem of ARDS is hypoxemia, that should be alleviated by recruiting and ventilating collapsed alveolar spaces and reducing the shunt. Hypoxemia cannot be corrected by the simple administration of oxygen. Mechanical ventilation via endotracheal intubation should be initiated as soon as possible. PEEP improves oxygenation reducing the intrapulmonary shunt. In general 5 to 20 cm H₂O provides a reasonable balance among potential effects. In fact the heterogeneity of lung damage, due to the different disposition of areas of consolidation and atelectasis, causes that a certain amount of PEEP is appropriated in one region, too much in a normal region and too low in a more damaged region. The traditional ventilation included high flow with elevated tidal volume (12 ml/kg) and high plateau pressure (50 cm H₂O), inducing ventilator-induced lung injury. A low tidal volume (6 ml/kg) and a low plateau pressure (max 30 cm H₂O) decreased ARDS mortality from 40% to 31%.

Clinical Manifestation

The clinical definition of common acquired pneumonia includes such typical signs and symptoms of lower respiratory tract infection, shared by both pneumonia and acute exacerbation of COPD.

- Pleural pain, cough with purulent expectoration, dyspnoea, tachypnoea, and other local symptoms; high fever or chills, headache, arthritis, muscular pain.
- New focal signs at the physical examination of the chest.

The chest radiography shows pleural effusion, areas of consolidations and/or atelectasis. For the diagnosis of pneumonia, the presence of an infiltrate or a consolidation in chest radiography is necessary.

We define nosocomial pneumonia if it occurs in patients admitted since at least 48 hours or discharged no more than 8 days before the onset of symptoms, or for outpatients or visitors that attended the hospital at least during the past 48 hours. The most frequent pathogens are aerobi bacteria Gram negative such as Enterobacter, Acinetobacter, Pseudomonas, Klebsiella, etc.; in the immunocompromised patients most frequently, Staphylococcus aureus and Legionelle. Table VIII shows the risk factors for nosocomial pneumonia.

The aspiration pneumonia due to the entrance of fluids from stomach or upper respiratory tracts into the lower respiratory tracts, can be classified in consideration of the three different pulmonary damages: toxic, obstructive or infective. Table IX, from IDSA guidelines, shows in synthesis clinical manifestations and therapeutic approach to the different forms.

Atypical pneumonia is defined for the unusual manifestations with majority of systemic signs and symptoms (fever,
arthralgias, headache, etc.) and a poor pulmonary and chest manifestations (cough without purulent sputum, no signs of consolidation at chest radiography). The more frequent agents involved are *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia psittaci*, *Coxiella burnetii*. Several studies have shown that clinical, laboratory and radiographic features cannot reliably differentiate between different causative pathogens. The diagnosis of *Chlamydia pneumoniae* is made serologically or by polymerase chain reaction techniques; both *Chlamydia* and *Mycoplasma* are relatively often detected in mixed infections with *Streptococcus pneumoniae* and *Haemophilus influenzae*, thus making difficult to define under what circumstances they could be considered the cause of pneumonia. Treatment is often empiric (Grade of recommendation A II): macrolide, doxycyclin, and ciprofloxacin (Grade of recommendation B III).

The first step in a patient with a diagnosis of pneumonia is to assess the severity of illness and the need for hospital admission that were identified by the American Thoracic Society (ARS) and the British Thoracic Society (BTS) in 2001. The ATS rule is based on the presence of at least one major criterion (need for mechanical ventilation, an increase in the size of infiltrates by > 50% within 48 h, septic shock or the need of vasopressors for > 4 hours, and acute renal failure), or two minor criteria (respiratory rates > 30 breaths per minute, PaO₂/FiO₂ < 250, bilateral/lobar pneumonia, arterial blood pressure 90/60 mmHg). The BTS rule is based on the presence of 2 main risk factors; if only one is present clinician should evaluate pre-existent comorbidities (age more that 50 years, congestive heart failure –Ib-, ictus –Ib-, coronary artery disease –III-, diabetes mellitus –Ia-, neoplasm –Ib). There are 4 prognostic negative factors: mental confusion non pre-existent, Urea > 7 mmol/l, Respiratory rate > 30 breaths/min, systolic Blood pressure < 90 (or diastolic < 60 mmHg) (CURB).

**Management**

If oxygen blood parzial pressure is less than 70 mmHg, oxygen should be administered to obtain an increasing in saturation major that 90%. If obstructive pulmonary diseases don’t coexist, the inspiration fraction of O₂ should be greater than 0.35. In seriously ill patients, if oxygen therapy is not necessary to maintain saturation between 85 and 90%, despite maximum medical treatment, NIV could be used to improve oxygenation,
Table X.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Modifying factors/comments</th>
<th>First choice</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER</td>
<td>LRTI&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Aminopenicillin</td>
<td>Tetracyclines, cephalosporins respiratory quinolones, macrolides</td>
</tr>
<tr>
<td>Canadian</td>
<td>No modifying factor COPD, no recent antibiotics or oral steroids</td>
<td>Macrolide New macrolide</td>
<td>Doxycycline</td>
</tr>
<tr>
<td></td>
<td>COPD, antibiotics or oral steroid within 3 months</td>
<td>Respiratory FQ</td>
<td>Co-amoxiclav 2nd GEN cephalosporin + macrolide</td>
</tr>
<tr>
<td>IDSA</td>
<td>No modifying factor</td>
<td>Macrolide/doxycycline/cefuroxime/co-amoxiclav</td>
<td>Respiratory FQ</td>
</tr>
<tr>
<td>ATS</td>
<td>No modifying factor Cardiopulmonary disease or other modifying factor</td>
<td>β-Lactman + macrolide or doxycycline</td>
<td></td>
</tr>
<tr>
<td>Hospital treated general ward</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERS</td>
<td>β-Lactman + macrolide</td>
<td>Respiratory FQ</td>
<td>2nd-4th GEN cephalosporin + macrolide</td>
</tr>
<tr>
<td>Canadian</td>
<td>Respiratory FQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDSA</td>
<td>β-Lactman + macrolide</td>
<td>FQ</td>
<td></td>
</tr>
<tr>
<td>ATS</td>
<td>Azithromycin i.v.</td>
<td>β-Lactman + doxycycline or FQ alone</td>
<td></td>
</tr>
<tr>
<td>ICU-treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERS</td>
<td>2nd-3rd GEN cephalosporin + macrolide or FQ + rifampicin</td>
<td>β-Lactman + macrolide</td>
<td></td>
</tr>
<tr>
<td>Canadian</td>
<td>P. aeruginosa not suspected</td>
<td>Respiratory FQ + β-lactman</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P. aeruginosa suspected</td>
<td>Ciprofloxacin + antipseudomonas β-lactman or AG</td>
<td></td>
</tr>
<tr>
<td>IDSA</td>
<td>P. aeruginosa not suspected</td>
<td>Extended spectrum β-lactman + FQ or macrolide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Structural lung disease</td>
<td>Antipseudomonas β-lactman + ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td>CDC</td>
<td>P. aeruginosa not suspected</td>
<td>β-Lactman + macrolide or FQ</td>
<td>Respiratory FQ</td>
</tr>
<tr>
<td>ATS</td>
<td>P. aeruginosa suspected</td>
<td>β-Lactman + macrolide or FQ</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antipseudomonas β-lactman + ciproflaxacin</td>
<td></td>
</tr>
</tbody>
</table>

ERS: European Respiratory Society; IDSA: Infection Diseases Society of America; CDC: Center for Disease Control and Prevention; ATS: American Thoracic Society; LRTI: lower respiratory tract infection; FQ: fluoroquinolone; GEN: generation; P. aeruginosa: Pseudomonas aeruginosa; AG: aminoglycoside. <sup>1</sup>: no distinction was made between community-acquired pneumonia and other LRTIs; +: depending on local resistance situation and underlying factors; §: risk factors for penicillin-resistant pneumococci or Gram-negative bacteria; /: risk factors for penicillin-resistant pneumococci or Gram-negative bacteria, including nursing home patients.
Table XI. Suggested strategy for empirical outpatients treatment of community acquired pneumonia in the immunocompetent adult. (Modified from Eur Respir J)84.

<table>
<thead>
<tr>
<th>Clinical/epidemiological data indicating atypical pneumonia</th>
<th>No clinical/epidemiological data indicating atypical pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolide or doxycycline</td>
<td>Younger and previously well</td>
</tr>
<tr>
<td>Penicillin V or amoxicillin</td>
<td>Older, COPD and or other severe chronic illness</td>
</tr>
<tr>
<td>Amoxicillin ± clavulanic acid</td>
<td>Therapy failure</td>
</tr>
<tr>
<td>Macrolide or doxycycline</td>
<td>Doxycycline or respiratory fluoroquinolone</td>
</tr>
</tbody>
</table>

Table XII. Suggested strategy for empirical inhospital treatment of community acquired pneumonia in the immunocompetent adult. (Modified from Eur Respir J)84.

<table>
<thead>
<tr>
<th>Patient to moderate CAP</th>
<th>Probable pathogen (cover required)</th>
<th>Choice of empirical therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate CAP</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Benzylpenicillin or amoxicillin clavulanic acid</td>
</tr>
<tr>
<td>All cases</td>
<td></td>
<td>Cefotaxime/ceftriaxone if high rate of highly</td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus influenzae</em> and</td>
<td>penicillin-resistant pneumococci</td>
</tr>
<tr>
<td></td>
<td><em>Moraxella catharralis</em></td>
<td>Co-amoxiclav, or 2nd/3rd generation</td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td>cephalosporin (iv)</td>
</tr>
<tr>
<td>Chronic pulmonary</td>
<td><em>Legionella</em></td>
<td>2nd/3rd generation cephalosporin (iv)</td>
</tr>
<tr>
<td>or post-influenza</td>
<td></td>
<td>Respiratory FQ, or macrolide + data</td>
</tr>
<tr>
<td>pneumonia</td>
<td></td>
<td>benzylpenicillin/amoxicillin clavulanic</td>
</tr>
<tr>
<td>and drug added</td>
<td></td>
<td>or 2nd/3rd generation cephalosporin (iv)</td>
</tr>
<tr>
<td>Epidemiological</td>
<td><em>Mycoplasma pneumoniae</em> and</td>
<td>Macrolide or doxycycline</td>
</tr>
<tr>
<td>chemical data</td>
<td><em>Chlamydia pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td>indicating <em>legionella</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidemiological clinical data indicating other atypicals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-negative cover nor routinely necessary (irrespective of patient's age, or whether nursing home resident)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Severe CAP             | *Streptococcus pneumoniae*         | Cefotaxime ceftriaxone macrolide rifampicin |
| All cases              | *Haemophilus influenzae*,          | or benzylpenicilli respiratory FQ          |
|                        | *Moraxella catharralis*,           |                                           |
|                        | *Staphylococcus aureus*,           |                                           |
|                        | “atypical” agents and              |                                           |
|                        | Gram-negative enteric bacilli      |                                           |

FQ: fluoroquinolone.
reduce respiratory rate and lessen dyspnoea. Moreover, NIV can be used as an alternative to tracheal intubation if patient became hypercapnic (Grade of recommendation C)\(^{11}\).

Patients should have arterial systolic pressure > 90 mmHg and the diuresis (0.5-1 ml/kg/hour).

The empirical antibiotic treatment recommended by international guidelines is summarized in Table X (from ERJ)\(^{84}\).

It differs between outpatients and inhospital patients, and it’s based on severity of illness and the most likely pathogen involved in various patients categories (Table XI).

Most of the outpatients should be treated with monotherapy, most often with beta-lactam alone (amoxicillin ± clavulanic acid or second and third generation intravenous cephalosporin). If therapy fails, *Mycoplasma* and/or *Chlamydia pneumoniae* may be involved and so treatment with doxycycline/macrolide or fluoroquinolone should be initiated (Table XII).

The inhospital patient should be treated within 8 hours from the admittance, with empirical therapy (amoxicillin ± clavulanic acid or second and third generation intravenous cephalosporin): it should not be delayed while waiting for the results of the examinations (hemocultures, culture of sputum, first of all). If patient has structural lung disease *Pseudomonas* should be suspected: piperacilline, piperacilline-tazobactam, cefepime, imipenem, meropenem should be administered. If aspiration pneumonia is suspected, a therapy against anaerobic bacteria should be initiated (beta lactamic antibiotics plus inhibitor of beta lactamase, clindamycin, metronidazol). If *Pneumococcus* is suspected, beta lactamic antibiotics plus inhibitor of beta lactamase (1 g each 6 hours), cefotaxime (1 g each 8 hours), ceftriaxone (1 g each 24 hours) should be administered, or, if patient is allergic, fluoroquinolones or quinopristin/dalfopristin, or still linezolid or vancomycin.

In general, it is important for efficacy, as well as to avoid development of resistance, that high enough or frequent enough dosing is used rather than extending therapy for > 7-10 days (except for treatment of the Legionnaires’ disease, where 2-3 weeks’ duration is recommended).

References


29. COMBIVENT INHALATION AEROSOL STUDY GROUP. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. Chest 1994; 105: 1411-1419.

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