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BCG vaccination and Covid-19 protection

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Key words:
- Covid-19
- BCG
- Tuberculosis

The coronavirus pandemic, is an ongoing pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern on 30 January 2020, and a pandemic on 11 March 2020. Antiviral medications are under investigation for COVID-19, as well as medications targeting the immune response. None has yet been shown to be clearly effective on mortality in published randomized controlled trials.

In the absence of a specific vaccine the medical community investigates existing vaccines for potential general immunity augmentation, the so-called trained immunity. The antituberculous vaccine Bacille Calmette-Guérin vaccine (BCG) contains a live, weakened strain of Mycobacterium bovis, a cousin of M. tuberculosis. The vaccine is named after French microbiologists Albert Calmette and Camille Guérin, who developed it in the early 20th century. First used in humans in 1921, BCG is now one of the most widely used vaccines in infants and neonates, in whom its main utility is in the prevention of tuberculous meningitis and disseminated tuberculosis. Importantly, BCG is also used as adjuvant immunotherapy for patients with non-muscle-invasive bladder cancer. BCG, has been used in Greece by the Greek Red Cross since 1925, the vaccine being produced by the Greek Pasteur Institute in Athens. It prevents about 60% of tuberculosis (TB) cases in children on average, with large differences between countries. BCG vaccination has been suggested to have nonspecific beneficial effects in children from developing countries, reducing morbidity and mortality caused by unrelated pathogens.

NON-SPECIFIC EFFECTS OF VACCINES: CURRENT EVIDENCE AND POTENTIAL IMPLICATIONS

How it works

Several mechanisms by which BCG provides non-specific protection against respiratory infections have been a subject of active investigation. In general, when a pathogen enters the body, white blood cells of the innate immune system attack it first. The innate immune system, composed of white blood cells such as macrophages, natural killer cells, and neutrophils, was supposed to have no memory. If these cells fail, they call in the adaptive immune system, and T cells and antibody-producing B cells start to divide to fight. Key to this is that certain T cells or antibodies are specific...
to the pathogen. Once the pathogen is eliminated, a small portion of these pathogen-specific cells transform into memory cells that speed up T cell and B cell production the next time the same pathogen attacks. Vaccines are based on this mechanism of immunity9-13.

Molecular similarity between BCG antigens and viral antigens could lead, after BCG vaccination, to a population of memory B and T cells that recognize both BCG and respiratory pathogens. In addition, BCG could lead to antigen-independent activation of bystander B and T cells, a mechanism that has been termed heterologous immunity9-14. Finally, BCG could lead to long-term activation and reprogramming of innate immune cells. This last mechanism, which has been the subject of much interest in the past decade, has been called trained immunity5,9.

This process can explain the rapid effects of BCG vaccination and has been suggested to be mediated by epigenetic programming of monocytes or macrophages10,11. Monocytes undergo histone modification at promoter sites of genes encoding inflammatory cytokines, leading to long-term changes in their ability to respond to novel stimuli and resulting in an increasingly active immune response when they are reactivated. Monocytes from adults who receive BCG vaccination exhibit increased expression of various surface markers related to activation and produce cytokines, such as IL-1β, IL-6, IFNγ and TNF, in response to infection with various pathogens9-14.

Evidence

The idea that BCG offers protection against the novel coronavirus, or SARS-CoV-2, seems to stem from the vaccine’s ability to induce trained immune response, where the immune system of someone vaccinated with BCG, produces the ability to fight off other pathogens, including parasites and viruses15,16. There is weak evidence, but some previous studies have shown that the BCG-induced response can actually improve our ability to fight some unrelated viruses as well. It could prevent up to 30 per cent of all known infections, not only from viruses. The vaccine has demonstrated that it can protect against other viral infections of the respiratory tract such as influenza17. In a randomized placebo-controlled study published in 2018, the team showed that BCG vaccination protects against experimental infection with a weakened form of the yellow fever virus, which is used as a vaccine15.

Debate

At the moment, there is no evidence that those who have been administered the BCG vaccine have any immunization against Covid-19. It is debated that BCG, which is administered to children under one year of age, offers protection more than 15 years, and any effect might be just a correlation. The studies published have been criticized for their methodology18-22.

On 11 April 2020, WHO updated its ongoing evidence review of the major scientific databases and clinical trial repositories, observed that countries that routinely used the vaccine in neonates had less reported cases of COVID-19 to date. However, WHO believes that “such ecological studies are prone to significant bias from many confounders, including differences in national demographics and disease burden, testing rates for COVID-19, and the stage of the pandemic in each country”.

Recently, in a research letter in JAMA in a cohort of Israeli adults aged 35 to 41 years, BCG vaccination in childhood was associated with a similar rate of positive test results for SARS-CoV-2 compared with no vaccination. Because of the small number of severe cases, no conclusion about the association between BCG status and severity of disease can be reached23.

In the absence of convincing evidence, WHO does not recommend BCG vaccination for the prevention of COVID-1924.

Ongoing trials

Studies are in progress to determine whether BCG vaccination could protect against COVID-19 infection. Several trials involving BCG vaccination have commenced in Netherlands, Australia, Germany, and Greece19,20. Netherlands will recruit 1000 health care workers in eight Dutch hospitals who will either receive BCG or a placebo. Giamarellos has set up an open study in Greece to see whether BCG can increase resistance to infections overall in elderly people. The researchers will be blinded to which arm of the study—vaccine or placebo—a person is in. A research group in Melbourne and another at the University of Exeter are setting up a BCG study among health care workers. It is possible that BCG-Tokyo would be preferable to BCG-Danish. A team at the Max Planck Institute for Infection Biology will start a similar trial with VPM1002, a genetically modified version of BCG that has not yet been approved for use against TB. However, BCG vaccine is already in short supply, and indiscriminate use could jeopardize the supply needed to protect children against tuberculosis in high-risk areas or could engender a false sense of security. In addition, there is a possibility that up-regulation of immunity by BCG will exacerbate COVID-19 in a minority of patients with severe disease21.
UNANSWERED QUESTIONS

• First, how long does the heterologous immunity engendered by BCG last after vaccination?
• Second, what is the optimal time to vaccinate?
• Third, can it bridge the gap before a disease-specific vaccine is developed?
• Fourth, will the use of BCG to prevent COVID-19 affect its use to treat bladder cancer?

In conclusion, the vaccine probably won’t eliminate infections with the new coronavirus completely, but is likely to diminish its effect on individuals. The vaccine may confront textbook knowledge of how immunity works.

CONFLICT OF INTEREST

None.

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There has been extensive research into the regeneration of tissues and organs, and the restoration of damage done to them, with the use of stem cells.

**Primordial stem cells** are cells that are found in multicellular organisms. They are characterized by two basic qualities: the ability to divide and create similar cells as well as the ability to split and generate cells that are more specialized. That is, they possess the ability to generate multicellular subtypes, according to the cellular microenvironment. Depending on their source of origin, stem cells can be distinguished as **embryonic or adult** stem cells.

**Embryonic** stem cells are pluripotent cells which are derived from the inner mass of a blastocyst.

**Adult** stem cells refer to each type of cell in the body, which are characterized by the properties of self-regeneration and differentiation. Another term used for them is “somatic” and they can be found in both children and adults. Adult stem cells are located in many tissues playing a vital role in tissue development, maintenance and reparation. They are characterized by high plasticity, or, in other words, high differentiation capacity. Adult stem cells of mesenchymal origin have been isolated from a variety of sources, including the umbilical cord, bone marrow and, most recently, the adipose tissue, and they have been used not only for aesthetic purposes, but also for the treatment of numerous incurable chronic diseases, such as Parkinson’s disease, type 2 diabetes, congenital heart disease, inflammatory enteropathy, osteoarthritis and chronic kidney disease.

A significant number of clinical surveys have been published regarding the safety and effectiveness of mesenchymal stem cells used in the treatment of many chronic and acute diseases and they have had many promising results. Specifically, one study concerned their impact on incurable diseases of the respiratory system, such as idiopathic pulmonary fibrosis. In this study, mesenchymal stem cells were obtained by aspiration from adipose tissue.

As a result, it was certain that there would be references to the use of stem cells in research attempts to combat COVID-19 infections. One of the researchers’ aims is to treat the most serious complications resulting from a COVID-19 infection, viral pneumonia and ARDS.

Clinical studies have shown the tropism of this virus for alveolar type 2 cells and capillary epithelium due to the high expression of ACE2 receptors in their cellular membranes, which allow the pathogen to enter. As a result of the impact of the virus, the so-called cytokine storm is activated, a consequence of the proliferation and interaction of immune cells, with
macrophage as the main cell agent. Cytokines (IL-2, IL-6, IL-7, INFγ, GSCF, IP10, MCP1, MIP1A, TNFa) promote inflammation, cause parenchymal damage with apoptosis and phagocytosis and irreversible lung tissue fibrosis, which clinically manifests as pulmonary edema, gas exchange disorder, ARDS and acute heart failure, with a high mortality rate.[12]

A vast number of surveys regarding the treatment of COVID-19 respiratory infection have commenced globally using mesenchymal stem cells (MSCs), MSC derived conditioned media (a complex of products that MSCs produce), extracellular vesicles (EVs) (particles that are surrounded by a cellular membrane and that contain proteins, lipids, metabolites, as well as organelles of the cell itself), and a few other cell populations.[13]

Scientists are looking into tackling the cataract of inflammation, the binding of ACE2, the utilization of EVs as a “means of transport” for antiviral drugs or other particles (RNA or proteins) and the regeneration of diseased tissues.

As a source of MSC, researchers used the following tissues: bone marrow, peripheral blood, adipose tissue (abdominal fat, infrapatellar fat pad, buccal fat pad) and embryonic tissue (placenta, umbilical cord, Warton’s jelly, amniotic fluid, fetal liver).

MSCs are activated with the binding of pathogen molecules (viral RNA) to the specific receptors on their cell surface, releasing a variety of mediators (anti-inflammatory cytokines (like TGFβ, HGF, LIF, VEGF, EGF, BDNF and NGF), antimicrobial peptides, angiogenic growth factors and EVs. With this mechanism, mesenchymal stem cells (MSCs) present immunomodulatory and regenerative properties,[7] as well as immediate antiviral activity, therefore they have the ability to mitigate the excessive immune response of the organism and prevent its devastating effects.[14,15]

There is evidence that most of the therapeutic properties of MSCs are due to the production of EVs.[10] Hence, new therapeutic approaches may be developed. The benefits of this method are: controlled extracorporeal production of EVs, the feasible use of EVs as a “means of transport” for antiviral drugs or other particles (RNA or proteins) for target therapy and the avoidance of systematic use, given that EVs can be inhaled directly into the airways through the nose or via inhalation. Moreover, EVs, “adorned” with spike proteins of the pathogen, bind ACE2 receptors to compete with the virus for cellular uptake.[16]

Leukemia inhibitory factor (LIF) - cytokine, which promotes cell growth and differentiation, and which belongs to the IL-6 group, plays an important role in the regeneration of damaged tissues, as well as in dealing with cytokine storm. It is produced by activated MSCs, yet with the aid of nanotechnology, synthetic stem cells (LIFNano), which can produce 1000 times the volume of LIF, this method reduces the cost of treatment.[17,18]

It is significant to understand the rationale and existing data that support and negate effectiveness of MSCs in COVID-19 and respiratory virus infections in general, as well as to delineate the targeted patient population and potential cell therapy approaches.[19] Currently, there is an increasing number of clinical investigations of stem cell therapy methodologies for COVID-19, using a range of different cell sources, doses, dosing strategies and targeted patient populations. It is unfavorably important to understand the suggested mechanisms of MSC actions in this patient population.[19]

In conclusion, in these difficult times, during the COVID pandemic, humanity needs to find an effective and safe treatment. Studies and clinical trials on treatments based on stem cells and their by products have begun all over the world[19-22], and the first results are optimistic, but they are nowhere near the final stage. In addition, it is noted that the trials must provide more information regarding the effectiveness and safety of this innovative and promising treatment.

CONFLICT OF INTEREST

None.

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Bacillus Calmette-Guerin: Established and emerging roles for an old friend

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Key words:
- BCG
- TBC
- Covid-19
- Lung Cancer
- Immunomodulation

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Bacillus Calmette-Guerin (BCG) has been used from the 1920s1 as a stimulant of the Th1 immune response in order to slow down tuberculosis (TB) dissemination2. Globally, almost 2 billion people are estimated to be infected and 10 million people have develop active disease every year. BCG vaccination is still one of the cornerstones for the prevention of the disease. It remains even today one of the most used vaccines globally3. In the region of eastern Mediterranean 87% of countries do have an active BCG vaccination plan in place, but inconsistency issues and high left out/dropout rates are still encountered4.

Three different BCG strains are globally most often used: the Moscow-368, Tokyo 172-1 and Sofia SL222 variants2. Vaccines contain dead and living bacilli as per WHO guidelines in terms of safety, quality and efficacy1,2. In previous decades many concerns have risen for its safety and efficacy with regards to pulmonary and extrapulmonary TB prophylaxis. All these have been grossly addressed by randomized control trials (RCTs) that showed significant protection rates of BCG vaccination of neonates, especially against meningeal and miliary TB. These protective properties of the vaccine were questionable, especially when performed at school-age children that have not been screened prior of the vaccination with a standard Tuberculin Skin Test (TST)4-6.

Following the initial perception that BCG vaccination protects against severe disease only, a recent meta-analysis revealed that BCG might as well have a role in protecting against primary infection from TB7, leprosy8 and non-tuberculous mycobacteria (NTM)9. On top of that, multiple immunomodulatory effects of BCG have been described over the last 3 decades, highlighting an additional role of BCG in reducing all-cause mortality especially in infancy and childhood. It has been documented that children have a relative risk of 0.70 for all-cause mortality when vaccinated10.

BCG vaccination’s beneficial effect is larger than somebody would expect from their direct effect on the disease that are directed against to. Interestingly, BCG vaccination is in vitro grossly protective against extensive lung injury from many pathogens that can reach alveolar space, like Influenza. This could occur by augmenting successful efferocytosis and preventing diffuse lung damage from Influenza A virus11. In other words, BCG vaccination seems to orchestrate the successful lung inflammatory homeostasis, promotes and maintains a balanced lung inflammation with minimal side
damage to the lung parenchyma per se, diminishing at the same time the subsequent development of fibrotic scarring11. BCG vaccination has also been associated with reduced infection rates from yellow fever, fungi like Candida spp, Plasmodium malariae and others12-14.

Of note, a recent a 60-year retrospective study revealed that BCG vaccinated children of Indian American and Alaska native origin had a lower lung cancer development rates in adulthood, after adjusted for significant epidemiological variables like sex, smoking habit and age15. Authors highlighted the fact that BCG protective effect against lung cancer was not related to its protective properties against tuberculosis per se, but seemed to be related to a direct immunomodulatory activity. This activity is of no surprise, since BCG is one of the mainstream immunotherapy treatments for non-invasive bladder cancer16 or even for stage III non operable in-transit melanoma as direct intralesional infusion17. In vitro incubation of various cancerous and non-cancerous cell lines with BCG seems to stimulate and regulate the release of numerous pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 among others. Previous reports for associations of BCG with lymphomas have been addressed and rejected by a recent metanalysis18. A BCG vaccination in early life could also shift the immune response towards Th1-type of inflammation that eventually would also be transiently protective against asthma19.

In view of the above mentioned immunomodulatory and broad-spectrum, lung protective, properties of BCG vaccination, recent studies report that widespread BCG vaccination may facilitate in flattening the curve of the increase of new COVID-19 cases20. BCG vaccination could be more effective against the COVID-19 infection if multiple doses are being administered21.

In conclusion, BCG vaccination might offer a widespread protection not only against TB, but also against other pathogens that affect respiratory tract and parenchyma, like severe respiratory syndrome related to COVID-19. BCG is also widely used against melanoma and bladder cancer and might have a favorable role in other chronic inflammatory disorders.

CONFLICTS OF INTEREST

No conflicts of interest to declare.

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Invasive Mechanical Ventilation: When and to whom?
Indications and complications of Invasive Mechanical Ventilation

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Key words: - Invasive mechanical ventilation - indications - complications

ABSTRACT
Although emergency endotracheal intubation and mechanical ventilation (MV) are undoubtedly a life-saving intervention, deciding when and whom to support remains challenging. Common indications include respiratory failure, shock, coma and operative procedures that require analgesia and sedation. Endotracheal intubation is well known for its potential difficulty and mechanical ventilation is associated with complications that may aggravate the critically ill patient. Although MV is used in intensive care units in order to maintain adequate gas exchange and decrease the work of breathing, these goals may be difficult to achieve if there is no proper interaction between patient and ventilator (patient-ventilator asynchrony). Therefore, it is important that clinicians suspect, recognize and resolve appropriately any adverse consequence associated with this intervention. Finally, with the widespread use of mechanical ventilation, ethical challenges arise; patients with terminal illnesses can be kept alive, with little to no prospect of having their underlying condition cured or improved. Of paramount importance is for chronically ill patients to partake in the decision to institute or withhold MV after being appropriately informed for its indications and limitations.


INTRODUCTION
The decision to intubate and apply mechanical ventilation to a patient is often challenging. Questions such as “who and when” remains a matter of ongoing debate. It is generally suggested that the patient should have a reversible underlying problem that can be resolved with the support of mechanical ventilation. However, the decision to initiate MV should be based upon clinical judgment, that considers the entire clinical situation.

Summarizing the main objectives of invasive ventilation these aim in:
- Improving gas exchange, reversing hypoxemia, preventing acute respiratory acidosis and increasing lung volume.
- Decreasing oxygen consumption by reversing fatigue of respiratory muscles.
- Improving ventilation-perfusion ratio with prevention and reversal of atelectasis and improvement of lung compliance.
- Prevent further Ventilation Induced Lung Injury (VILI) damage.

INDICATIONS FOR MECHANICAL VENTILATION

Respiratory failure

Generally, arterial partial pressure of oxygen (PaO2) of less than 55mmHg, despite the delivery of the maximal possible fraction of inspired oxygen (FiO2) is an absolute indication for intubation1,2. According to ERS/ATS guidelines bilevel Non-Invasive Mechanical Ventilation (NIV) is recommended for patients with acute exacerbation of COPD with respiratory acidosis (pH ≤7.35), and bilevel NIV or CPAP for patients with acute respiratory failure due to cardiogenic pulmonary oedema because it reduces the need for endotracheal intubation and mortality (strong recommendation)3,4. However, increased partial pressure of carbon dioxide (PaCO2) with arterial pH less than 7.25 despite optimum pharmaceutical support, controlled oxygen therapy and application of NIV is another indication for intubation5. Other respiratory signs strongly suggestive of intubation are signs of respiratory muscle fatigue, tachypnea, bradypnea or apnea with respiratory arrest and alveolar-arterial gradient of oxygen tension (A-a DO2) with 100% oxygenation of greater than 450 mm Hg. Over the last decade, high flow nasal oxygenation (HFNO) has been widely adopted by intensivists for hypoxemic acute respiratory failure and its physiological benefits have been demonstrated. According to multicenter RCT FloRAL study6 that compared NIV, HFO and Oxygen mask for patients with non-hypercapnic acute respiratory failure, HFNO does not reduce intubation rate, but in post hoc analysis it shows significantly lower intubation rate for those patients with PaO2/FiO2<200. Moreover, high-flow oxygen therapy, as compared with standard oxygen therapy or noninvasive ventilation, resulted in reduced mortality in the ICU and at 90 days. Since guidelines regarding HFO for ARF do not exist, application of HFO should only be made in a controlled ICU environment in order to avoid late intubation and increased mortality.

Common diseases leading to inefficient gas exchange and need of intubation include Acute Respiratory Distress Syndrome (ARDS), COPD, Pneumonia, Asthma, Pulmonary Edema. In such cases, the effort required to maintain the elevated work of breathing may result in respiratory muscle fatigue and respiratory failure3,4. Mechanical ventilation can take over some or all of the increased work of breathing, allowing the respiratory muscles to recover from their fatigue. Moreover, neuromuscular disorders, central nervous system (CNS) diseases, chest wall deformities, and drug overdose may result in alveolar hypoventilation due to reduced respiratory drive or respiratory muscle weakness.

Several lines of evidence highlight that timing of intubation is crucial and thus, if a patient is worsening despite optimal care, intubation should be considered early and not be delayed until the need becomes emergent8. The criteria for initiating mechanical ventilation are summarized in Table 1.

Shock

Patients with shock refractory to fluid resuscitation could benefit from mechanical ventilation. In particular, mechanical ventilation unloads the diaphragm, saving about 15% of the cardiac output, reduces oxygen consumption (VO2), increases brain and renal perfusion and prevents respiratory arrest10,11.

<table>
<thead>
<tr>
<th>TABLE 1. Criteria for the initiation of invasive mechanical ventilation</th>
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<tbody>
<tr>
<td>Criteria for MV</td>
</tr>
<tr>
<td>Breathing rate (/min)</td>
</tr>
<tr>
<td>Vt (ml/Kg)</td>
</tr>
<tr>
<td>Pimax (cm H2O)</td>
</tr>
<tr>
<td>VC (ml/Kg)</td>
</tr>
<tr>
<td>VE (L/min)</td>
</tr>
<tr>
<td>Gas Exchange</td>
</tr>
<tr>
<td>PaO2 mmHg</td>
</tr>
<tr>
<td>PCO2 mmHg</td>
</tr>
<tr>
<td>A-a DO2 mmHg</td>
</tr>
<tr>
<td>Vd/Vt</td>
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</tbody>
</table>

Vt=Tidal volume, Pimax=Maximal inspiratory pressure, VE=Vital capacity, VE=Ventilation A-a DO2=Alveolo-arterial oxygen difference, (Vd/Vt)=Dead space (Vd)/Tidal volume (Vt)
1. Complications associated with intubation and existence of the tracheal tube

Endotracheal intubation, although widely regarded as a life-saving intervention, is notorious for its potential complications, especially in critically ill patients. The state of critical illness suggests a priori overt physiological dysregulation. As a result, the patient is at increased risk of complete cardiovascular and respiratory collapse when exposed to agents for induction of anesthesia, the peri-intubation apnoeic period or subsequent positive pressure ventilation. Pre-oxygenation of the patient with a markedly disturbed PaO2/FiO2 can never be optimal and a patient already on a high dose of vasopressors to maintain an adequate mean arterial pressure will be subjected to further hemodynamic compromise during intubation. Up to 30% of intubations in the ICU result in failure of “first pass success”, 25% experience severe hypoxemia (defined as SpO2 <80%) during the intubation procedure and around 6% have a predicted difficult airway. Additionally, major airway events in the ICU result in a 60-fold higher incidence of death and brain damage than in the operative room16. Interestingly, the majority of complications associated with endotracheal intubation seem to be related to the period after intubation; 82% of the airway device incidents in intensive care in the UK, reported to the UK National Patient Safety Agency, were post-placement and included blockage or displacement of the tube17. The most common complications are summarized in Table 218-21.

2. Mechanical ventilation effect on cardiovascular system

Positive pressure ventilation (PPV) frequently decreases cardiac output, which may cause hypotension. Several mechanisms contribute to that.

Decreased venous return – Intrathoracic and right atrial pressure increase during positive pressure ventilation, thereby reducing the gradient for venous return. This effect is accentuated by applied positive end-expiratory pressure (PEEP), auto-PEEP, or intravascular hypovolemia22.

Reduced right ventricular output – During PPV the pulmonary vascular bed is compressed and this increases pulmonary vascular resistance, thereby reducing right ventricular output. Applied PEEP artificially elevates central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) measurements23.

Reduced left ventricular output – Increased pulmonary vascular resistance can shift the interventricular septum to the left, impair diastolic filling of the left ventricle, and reduce left ventricular output. In contrast to these adverse

Coma

Every patient with Glasgow Coma Scale <8 should be intubated to protect the airway and avoid detrimental complications such as gastric fluid aspiration. The only exception is cases considered immediately reversible including hypoglycemia, opiate or benzodiazepine poisoning, thiamine deficiency, and acute alcohol intoxication12.

Scheduled operative procedures

Operative procedures often require high doses of analgesia and sedation. Thus, patients need to be intubated for a short period13.

Endotracheal Intubation: Advantages and contraindications

Mechanical ventilation in emergencies is usually applied through endotracheal intubation. The endotracheal tube bypasses and isolates the upper airways (up to the first third of the trachea). As a result, it protects the lungs from aspiration, releases airways from obstruction, reduces dead space and protects airways and stomach from positive pressures. Also, it enables aspiration of secretion and bronchoscopy. Finally, it ensures stable and secure patient-to-ventilation communication.

There are only relative contraindications to endotracheal intubation. These can be summarized into the following categories14,15:

- Increased risk of cervical spine injury or known spine injury or neck immobility (e.g. arthritis)
- Supraglottic or glottic pathology that prevents the placement of an endotracheal tube device e.g. blunt trauma of the larynx, anaphylaxis or burns
- Trauma of the upper airway (e.g. hematoma) or possible difficulties due to patient’s anatomic features
- Mallampati score classes III and IV which is the visual assessment of the distance from the tongue base to the roof of the mouth, and therefore the amount of space in which there is to work during direct laryngoscopy. A high Mallampati score is associated with more difficult intubation.

In all of the above cases, emergency cricothyrotomy is indicated. Other possible alternatives could be nasal intubation or surgical airway depending on the patient’s needs.

Complications of Mechanical Ventilation

Mechanical ventilation is often a life-saving intervention but carries potential complications.
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The extent to which hemodynamic effects occur varies according to the chest wall and lung compliance. The effect is greatest when there is low chest wall compliance (eg, fibrothorax) or high lung compliance (eg, emphysema); it is least when there is high chest wall compliance (eg, sternotomy) or low lung compliance (eg, ARDS, heart failure).

In general, fluid resuscitation seems to correct hypotension caused by PPV. On the other hand, pulmonary edema may occur after extubation because sudden removal of PEEP leads to a large venous return.

3. Ventilator Associated Lung Injury

Barotrauma

Barotrauma refers to alveolar rupture due to elevated transalveolar pressure. This can appear as pneumothorax, pneumoperitoneum, subcutaneous emphysema, pneumomediastinum and can sometimes progress to bronchopleural fistula or tension pneumothorax (Figures 1 and 2). High end inspiratory (plateau) pressures predispose to barotrauma. Patients with obstructive airway disease or diseases of the lung parenchyma with low compliance (like ARDS or interstitial lung diseases) are at greatest risk.

To prevent barotrauma, it is recommended to maintain the end inspiratory (plateau) pressure below 30 cm H₂O. Most of the consequences of barotrauma need no intervention other than close monitoring. Pneumothorax needs closer observation because it can progress rapidly to tension pneumothorax and needs decompression with thoracostomy²⁵-²⁷.

Volutrauma

Alveolar overdistension, atelectrauma, and biotrauma are the principal mechanisms of ventilator induced lung

TABLE 2. Complications during and after endotracheal tube placement

<table>
<thead>
<tr>
<th>During Laryngoscopy</th>
<th>After Intubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sore throat</td>
<td>Laryngeal Injury including:</td>
</tr>
<tr>
<td></td>
<td>Inflammation and oedema, laryngomalacia vocal cord</td>
</tr>
<tr>
<td></td>
<td>paralysis, ulcerations, granulomas, stenosis</td>
</tr>
<tr>
<td>Traumatic blunt injury to the structures of the mouth, nose, pharynx and larynx</td>
<td>Tracheomalacia, tracheal granulomas, tracheal stenosis, tracheoesophageal fistula</td>
</tr>
<tr>
<td>Cervical Trauma</td>
<td>Sinusitis</td>
</tr>
<tr>
<td>Intubation of a main stem bronchus (3-9%)</td>
<td>Displacement or unplanned extubation</td>
</tr>
<tr>
<td>Intubation of the esophagus Aspiration of gastric content (8-19%)</td>
<td>Blockage of the endotracheal tube with secretions or blood</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Persistent cuff leak</td>
</tr>
<tr>
<td>Prolonged hypoxia – Hypoxic brain injury</td>
<td></td>
</tr>
<tr>
<td>Tachycardia/Bradycardia</td>
<td></td>
</tr>
<tr>
<td>Hypertension/Hypotension</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 1. Barotrauma due to mechanical ventilation. CXR and CT demonstrated pneumothorax, and extensive subcutaneous emphysema.
injury (VILI) during mechanical ventilation. Alveolar injury results in high alveolar permeability, interstitial and alveolar edema, alveolar hemorrhage, hyaline membranes, loss of functional surfactant, and alveolar collapse-findings similar to those observed in ARDS.\(^{27,28}\)

The alveolar injury caused by large tidal volumes is irrespective of airway pressures.\(^{29,30}\) Randomized trials found that mechanical ventilation using tidal volumes of \(\leq 6\) mL/kg of predicted body weight improved mortality in patients with ARDS.\(^{32}\) In patients intubated for reasons other than ARDS, overdistension from high tidal volumes has shown to increase the risk for VILI (odds ratio 1.3, 95% CI 1.12-1.51, for each mL above 6 mL per kg of ideal body weight).\(^{31}\) To investigate the potential effectiveness of low VT versus intermediate VT on patients without ARDS, the Protective Ventilation in Patients without ARDS (PReVENT) randomized control trial was conducted. A low-VT strategy was initiated in 475 subjects and defined as 6 mL/kg of predicted body weight. Comparatively, 480 individuals were assigned to a group with an “intermediate” VT of 10 mL/kg predicted body weight. Both groups had 21 (mean) ventilator free days with no significant differences in ICU length of stay or hospital length of stay. Other high-value outcomes of 28-d and 90-d mortality showed no significant differences between groups. However, by day 1, almost two-thirds of patients in the low tidal volume group received volumes >6 mL/kg PBW. Thus, insufficient differences between the achieved tidal volumes received by patients in both groups may have contributed to the lack of benefit.\(^{33}\)

Patients particularly prone to develop VILI are those receiving large tidal volumes, those with underlying restrictive lung diseases with ALI/ARDS, with acidemia (pH <7.35) and those who have received blood transfusions.\(^ {31}\) VILI can be prevented by applying two strategies. These strategies are based on studies on patients with ARDS (protective ventilation). The first is to prevent alveolar overdistension by applying low tidal volume ventilation and by limiting plateau pressure (Pplat) \(\leq 30\) cm H\(_2\)O. The general recommendation is to use tidal volumes of 4-8ml/kg of ideal body weight to get to the lowest tidal volume which the patient tolerates whilst providing acceptable oxygenation and ventilation. Mild acidosis and hypercapnia should be tolerated.\(^ {34}\) Finally, a recent observational study based on multiple RCTs demonstrated that low driving pressure (DP = plateau pressure – PEEP) is a better predictor of outcome in ARDS than either tidal volume or plateau pressure alone.\(^ {35}\) The second is to prevent collapse of alveoli during expiration and prevent cyclic atelectasis. The amount of PEEP needed to overcome cyclic atelectasis should be individualized.\(^ {34}\)

**Atelectrauma**

Even physiologic or low tidal volumes can lead to VILI in some patients. This is because, in patients with atelectasis, air tends to flow towards more compliant alveoli (i.e. the ones that are already open) and overdistend them. The prolonged contact of alveolar surfaces has been associated with local inflammation. Furthermore, those parts of the lung which are atelectatic but are being opened with each breath (cyclic atelectasis) are also prone to lung injury. Animal models have demonstrated that cyclic alveolar expansion and collapse creates forces that cause injury to adjacent alveoli and airways.\(^ {36,37}\)

This process is referred to as cyclic atelectasis or atelectrauma. Atelectrauma is generally managed using applied positive end-expiratory pressure (PEEP), although the optimal way to set the ideal level of PEEP is not clear.
Biotrauma - Inflammation

Biotrauma is characterized by ventilator-induced release of inflammatory mediators from cells within the injured lung. Both alveolar overdistension and atelectrauma in animals increase inflammatory cells including tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, IL-8, matrix metalloproteinase-9, and transcription factor nuclear factor (NF)-kappaB. In patients with ARDS ventilated with low volume strategies, randomized trials report a reduction in lavage and serum cytokines simultaneously with mortality benefit.

There is also evidence that injurious ventilatory strategies may lead to development of pulmonary fibrosis (in animals) and the development of multi-organ failure (in humans), although the precise mechanisms are unclear.

Ventilator induced diaphragmatic dysfunction (VIDD)

Mechanical ventilation causes diaphragmatic muscle atrophy, a phenomenon called ventilator induced diaphragmatic dysfunction (VIDD). Controlled mechanical ventilation may lead to diaphragmatic muscle fibers atrophy within the first day of mechanical ventilation. Long-term mechanical ventilation (defined as >24 hours) was associated with diaphragmatic muscle injury, atrophy, and proteolysis compared to short-term mechanical ventilation (defined as two to three hours). VIDD appears to be mediated by oxidative stress. VIDD may be associated with prolonged mechanical ventilation, difficulty weaning, prolonged ICU stay, and a higher risk of complications.

Diaphragm structure and function are very sensitive to high and low loading conditions. Goligher at al. studied invasively ventilated ICU patients and examined whether changes in the thickness of the diaphragm, as assessed by ultrasound, were associated with adverse outcomes, including prolonged ventilator dependence, re-intubation, and death. The results highlight that when diaphragm muscle thickness decreased by ≥10% this was associated with a lower probability of ventilator liberation, prolonged ICU admission, and respiratory complications (including reintubation and tracheostomy) compared with patients with a <10% change in diaphragm thickness. In 24% of the patients, diaphragm thickness increased by ≥10% in the first week of ventilation, and this was also associated with prolonged ventilation. The authors also demonstrated that the change in diaphragm thickness varied with diaphragm effort: low effort was associated with reduced thickness and high effort was associated with increased thickness.

4. Oxygen related complications

Oxygenation goals should be individualized and hyperoxia should be avoided. According to human and animal studies, high concentrations of inspired oxygen can cause a spectrum of lung injury, ranging from mild tracheobronchitis to diffuse alveolar damage (DAD). Hyperoxia appears to produce cellular injury through increased production of reactive oxygen intermediates (ROIs), such as the superoxide anion, the hydroxyl radical, and hydrogen peroxide resulting in inflammatory response and cell death. Moreover, high FiO₂ results in washout of alveolar nitrogen and the absorption of oxygen in alveoli cause absorptive atelectasis.

A meta-analysis of 25 randomized trials that compared a conservative oxygen strategy (FiO₂ 0.21; range 0.21-0.5) with a liberal oxygen strategy (median FiO₂ 0.52; range 0.28 to 1.0 for a median duration eight hours) in over 16,000 critical ill patients showed that a liberal oxygen strategy was associated with a small but increased hospital mortality (relative risk [RR] 1.21, 95% CI 1.03-1.43) and mortality at 30 days (RR 1.14, 95% CI 1.01-1.29). Importantly, as SpO₂ increased in the liberal strategy group, mortality also increased, indicating a dose-response relationship. For most critically ill patients, the lowest possible FiO₂ necessary to meet oxygenation goals should be used, ideally targeting a peripheral arterial saturation between 90 and 96 percent. This will decrease the likelihood of adverse events such as absorption atelectasis, accentuation of hypercapnia, airway injury, and parenchymal injury.

5. Infection Related Complications (VAP)

Ventilator associated pneumonia (VAP) is defined as pneumonia which occurs after 48-hours of intubation and mechanical ventilation. The incidence is between 8–28% and it is associated with considerable mortality (up to 50%) . The tracheal tube allows pathogens to enter the trachea, damages cough and mucus clearance and favors retention of secretions. The risk rises with the duration of ventilation. Oropharyngeal secretions and leakage of secretions around the cuff are the primary routes of infection. Efforts should be made to minimize the risk of aspiration. Elevating the head of the bed to 30°, minimizing sedation or paralysis, frequent suctioning of subglottic secretions and maintaining the cuff pressure at least 20cm H₂O are measures that may limit aspiration. In addition, there is evidence that decontaminating the oral cavity with chlorhexidine swabs has reduced the incidence of VAP. Early recognition and treatment are important.
New onset of fever, purulent sputum, leucocytosis, and desaturation should prompt further investigation. In addition to a new infiltrate on radiography, they are enough to initiate empiric treatment. Antibiotics can be de-escalated or modified later based on cultures or response50.

6. AutoPEEP

AutoPEEP refers to hyperinflation of the lungs due to air trapping. It is caused by initiation of inspiration before expiration is complete. It can be caused by large tidal volumes, high respiratory rate (insufficient time for expiration), obstructive airway disease or narrow endotracheal tube. By looking at the flow versus time waveform, if inspiratory flow begins before expiratory flow has stopped, then autoPEEP will develop.

Unchecked autoPEEP can lead to barotrauma as well as worsening of the hemodynamic effects of positive pressure ventilation (PPV). Increased intrathoracic pressure leads to decreased venous return which in turn leads to decreased cardiac output and hypotension as mentioned above. This effect is further exacerbated in the hypovolemic patient. AutoPEEP can also worsen ventilation-perfusion (V/Q) mismatch by compressing capillaries in the healthy part of the lung and diverting blood to the diseased lung. Work of breathing may also be increased because in pressure support settings it makes it harder to trigger a breath52.

In patients with high minute ventilation, lowering the tidal volume, respiratory rate or increasing the inspiratory flow rate may help. In patients with obstructive airway disease, if bronchodilators or steroids are not helpful and the above strategies have also failed, applying PEEP may be useful. Applying external PEEP of 50-100% of measured static auto-PEEP keeps the airways from collapsing during expiration and may improve ventilation perfusion matching and oxygenation without any effect on cardiac output53.

7. Other

Gastrointestinal

Positive pressure ventilation for greater than 48 hours is a risk factor for gastrointestinal bleeding due to stress ulceration. Positive airway pressure (especially PEEP) is also associated with decreased splanchic perfusion. Other gastrointestinal complications include vomiting, pharyngeal irritation, and hypomotility mostly due to drugs like opiates54. It is uncertain whether these complications are due to mechanical ventilation or critical illness.

Renal

Mechanical ventilation is associated with the development of acute renal failure. In a prospective cohort study of 29,269 critically ill patients, positive pressure ventilation was an independent risk factor for acute renal failure (odds ratio 2.11, 95% CI 1.58-2.82)55. The mechanism for renal injury is likely multifactorial. Hypotheses include renal injury through the release of inflammatory mediators (eg. interleukin-6) and impaired renal blood flow due to decreased cardiac output, increased sympathetic tone, or activation of humoral pathways56.

Central nervous system

Positive pressure ventilation increases intracranial pressure (ICP). Positive pressure maintained in the chest may decrease venous return from the head, increasing intracranial pressure and this may cause deterioration of patients with brain injury and already elevated ICP.

Weakness

Systemic muscular weakness is common among patients who undergo mechanical ventilation. Potential causes include immobilization, prolonged use of sedatives, use of neuromuscular blocking agents, and critical illness. Early mobilization and exercise may increase the likelihood that the patient will return to an independent functional status57.

Sleep

Sleep disruption in the critically ill can be severe and is characterized by sleep fragmentation, abnormal circadian rhythms, increased light sleep and decreased slow-wave and rapid eye movement (REM) sleep58. Mechanical ventilation may disturb sleep by destabilizing the patient’s breathing and dyssynchronization between the ventilatory efforts of the patient and the machine. Indirect negative effects on sleep include discomfort related to endotracheal intubation, noise from the ventilator alarms, and the use of sedation and analgesia59. Some modes and ventilator settings may be more beneficial regarding sleep than others. Guidelines from the Society of Critical Care Medicine endorse the use of assist-controlled ventilation rather than pressure support ventilation during the night in critically ill patients60. Although newer modes such as proportional assist ventilation (PAV) and neurally-adjusted ventilation (NAVA), may improve ventilator asynchrony, strategies to fully optimize sleep are not fully known61.
VENTILATOR-PATIENT ASYNCHRONY

Patient-ventilatory asynchrony exists if the phases of breath delivered by the ventilator do not match that of the patient and it is common during mechanical ventilation (24% of mechanically ventilated patients). Patient-ventilator asynchrony exceeding 10% of the overall breath are considered clinically important and can cause dyspnea, may increase the work of breathing, prolong the duration of mechanical ventilation including higher rate of tracheostomy and increase intensive care unit (ICU) and hospital mortality. It is still unclear whether this relationship between asynchronies and poor outcome is causative, i.e. asynchronies are responsible for the worsened outcome, or asynchrony is a marker of severity of illness. However, identifying and correcting for asynchronies has been recognized as a crucial issue.

Ineffective triggering, also known as wasted efforts, may occur in case of a weak respiratory drive and/or effort, a high intrinsic positive end-expiratory pressure (PEEPi), an excessively low ventilator trigger sensitivity, higher levels of pressure support and higher tidal volumes.

Auto-triggering takes place when the ventilator delivers assistance unrelated to patient’s effort.

Double triggering, also named as breath stacking, occurs when a patient triggers a new breath before the completion of the prior ventilator-delivered breath because the ventilator inspiratory time is shorter than the patient’s inspiratory time.

A challenging approach to improve patient-ventilator synchrony is matching ventilator support to ventilator demand. For this purpose, two modes referred as proportional modes, are presently available for intubated patients: proportional assist ventilation (PAV) and neurally adjusted ventilatory assist (NAVA). PAV is a mode of ventilation that instantaneously delivers inspiratory support in proportion to patients’ generated flow (flow assist) and volume (volume assist). Therefore, an increased patient’s effort corresponds to increased support delivered by the ventilator. NAVA has the unique feature of controlling ventilator functioning through a non-pneumatic signal, assessed by diaphragm electrical activity (EAdi). The airway pressure applied by the ventilator depends on the magnitude of EAdi. Those models are promising for weaning, reducing the duration of mechanical ventilation.

ETHICAL CHALLENGES OF MECHANICAL VENTILATION

With the widespread use of mechanical ventilation - a medical technology of the latter half of the previous century- patients with terminal illnesses can be kept alive, without having their underlying condition cured or improved. When treating patients near the end of life, invasive mechanical ventilation and cardiopulmonary resuscitation (CPR) frequently pose questions regarding their appropriateness as forms of medical therapies. In the 1974 and 1980 CPR guidelines and standards, it is stated that “The purpose of CPR is the prevention of sudden, unexpected death. CPR is not indicated in certain situations, such as in cases of terminal irreversible illness where death is not unexpected” and “Resuscitation in some circumstances may represent a positive violation of an individual’s right to die with dignity.” Thus, clinicians, acting according to the principles of beneficence and non-maleficence, usually come across ethical decisions concerning the withholding of mechanical ventilation, in cases when it is considered to be futile.

A European survey in respiratory intermediate units, about end-of-life decision making, assessed the reasons for withholding and withdrawing treatment. These include low probability of hospital survival, poor predicted functional status after hospital discharge, patient’s preference and older age. There are cases where NIV is used as a ceiling of ventilatory care. However, this practice remains still controversial in patients with Do-Not-Resuscitation orders. On one hand, it can relieve dyspnoea, comfort the patient and provide him time to interact with his...
loved ones, but on the other hand, it prolongs the dying process and is not as effective in dyspnoea relief as other palliative measures77-79.

Interestingly, the attitude towards end-of-life practices in European ICUs was studied and data were compared during two different periods, 1999-2000 and 2015-2016 with Ethicus 1 and 2 prospective observational studies. They demonstrate that treatment limitations (withholding or withdrawing life-sustaining treatment or active shortening of the dying process) occurred significantly more frequently (89.7% vs 68.3%) in the second period, whereas death without any limitations in life-prolonging therapies occurred significantly less frequently (10.3% vs 31.7%). These findings suggest that end-of-life care practices in European ICUs changed from 1999-2000 to 2015-2016 with more limitations in life-prolonging therapies and fewer deaths without treatment limitations80.

Of paramount importance is for patients, especially the chronically ill, to partake in the decision to institute or withhold mechanical ventilation. As this process requires thought, it should be done timely, and preferably before respiratory failure demands an urgent answer79,81.

It is also important to explore family perception about palliative care and ventilator withdrawal for the chronically ill and prolonged ventilated patient. Because the majority of those patients have poor consciousness level, decisions about their support often fall to their relatives. When family opinion was studied, the vast majority agreed to palliative care and half of the family members regretted having chosen prolonged mechanical ventilation82. Poor patient quality of life (QoL) and higher family member knowledge of palliative care were found to significantly increase the willingness to receive palliative care and withdraw life-sustaining treatments in the terminal stage of life. These findings imply that physicians should thoroughly discuss mechanical ventilation benefits and burdens and poor QoL should be more effectively communicated to families in order to have realistic expectations. Withholding futile interventions does not mean abandoning the patient; on the contrary, appropriate treatment aims to alleviate the patient’s discomfort and not merely prolong suffering.

CONFLICTS OF INTEREST

Authors have no conflicts of interest

ΠΕΡΙΛΗΨΗ

Επεμβατικός μηχανικός αερισμός: Πότε και σε ποιόν;
Ενδείξεις και επιπλοκές του επεμβατικού μηχανικού αερισμού

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Η επείγουσα διασωλήνωση και ο επεμβατικός μηχανικός αερισμός είναι αδιαμφισβήτητα μία σωτήρια παράμβαση, όμως η απόφαση ποιος και πότε θα υποστηριχθεί παραμένει μια πρόκληση. Οι ενδείξεις περιλαμβάνουν την αναπνευστική ανεπάρκεια, το shock, το κώμα και χειρουργικές παρεμβάσεις που απαιτούν αναληψία και καταστολή. Η ενδοτραχειακή διασωλήνωση μπορεί να είναι δυσχερής και ο μηχανικός αερισμός συνοδεύεται και από επιπλοκές που ισχυρίζονται τον ήδη ασταθή ασθενή. Επιπλέον, αν δεν υπάρχει συγχρονισμός μεταξύ ασθενούς και αναπνευστήρα είναι δύσκολο να επιτευχθεί επαρκής ανταλλαγή αερίων και να υποστηριχθεί το εργα της αναπνοής. Ο κλινικός ιατρός είναι επιφορτισμένος να αναγνωρίζει και να επιλέγει τυχόν επιπλοκές του μηχανικού αερισμού. Τέλος, με την ευρεία διάδοση του μηχανικού αερισμού προκύπτουν και ηθικά διλήμματα; ασθενείς με τελικό στάδιο νόσημα μπορεί να παραμείνουν εν ζωή χωρίς την προοπτική βελτίωσης του υποκείμενου νοσήματος. Σε αυτές τις περιπτώσεις είναι σημαντικό οι ίδιοι οι ασθενείς να συμμετέχουν στην απόφαση για περαιτέρω υποστήρι-
Επεμβατικός μηχανικός αερισμός, Ενδείξεις, Επιπλοκές

Λέξεις - Κλειδιά: Επεμβατικός μηχανικός αερισμός, Ενδείξεις, Επιπλοκές

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COVID19 alert
Do we know our enemy?

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Key words:
- Covid-19
- Review

ABSTRACT
SARS-coronavirus 2 (SARS-CoV-2), the etiologic agent of the new lung disease COVID-19 is closely related to SARS-CoV, and together with MERS-CoV are three new human coronaviruses that emerged in the last 20 years. Clinical presentations range from asymptomatic or mild symptoms to severe illness. The prevalent cause of mortality is pneumonia that progresses to ARDS. Such a devastating health burden worldwide has imposed intensive international scientific interest to be focused on the emergence of new therapeutic regimens. Pending the availability of a vaccine, there is a critical need to identify effective treatments and a number of clinical trials have been implemented worldwide. Trials are based on repurposed drugs that are already approved for other infections, have acceptable safety profiles or have performed well in animal studies against the other two deadly coronaviruses. In this review, we summarize the main points of clinical papers published in the current literature employed in epidemiology, clinical trials and intensive care unit (ICU) in COVID-19 disease.

including cordons sanitaire, traffic restriction, social distancing, home quarantine, centralized quarantine, and universal symptom survey was temporally associated with reduced effective reproduction number of SARS-CoV-2 (secondary transmission) and the number of confirmed cases per day across age groups, sex, and geographic regions. These findings may provide great information about public health in other regions of the world to fight the global pandemic of COVID-19. It seems that monitoring infection rates and effective reproduction numbers continuously makes nonpharmaceutical interventions a valuable tool for controlling COVID-19. Moreover, future studies that will be focused in genetic analysis of infected patients will be crucial, in order to further analyze the genetic background of different populations. For example, in a population-based study in Iceland, children under 10 years of age and females had a lower incidence of SARS-CoV-2 infection than adolescents or adults and males. The proportion of infected persons identified through population screening did not change substantially during the screening period, which was consistent with a beneficial effect of containment efforts.

THERAPEUTIC ISSUES

On March 11 2020, the World Health Organization (WHO) declared the SARS-CoV-2 outbreak a pandemic. On March 18th the World Health Organization launched the SOLIDARITY trial and soon after an add-on trial, a European initiative of the Reacting consortium, the DISCOVERY trial was announced. Currently, there are no approved therapies specific for any human CoV. Trials are based on repurposed drugs that are already approved for other diseases, have acceptable safety profiles or have performed well in animal studies against the other two deadly coronaviruses, which cause SARS and MERS. SOLIDARITY includes research looking at four possible therapeutics with direct antiviral actions: remdesivir; chloroquine and hydroxychloroquine; lopinavir plus ritonavir; and lopinavir plus ritonavir and interferon-beta while chloroquine will not be included in the DISCOVERY trial. Additionally, the DISCOVERY trial will include a placebo arm with standard of care while the SOLIDARITY trial will not be blinded and patients will know they received a treatment that would cause a placebo effect as stated by Ana Maria Henao Restrepo, a medical officer at WHO’s Department of Immunization Vaccines and Biologicals. Additional information regarding lung imaging and blood gases will be monitored in the DISCOVERY trial besides data on hospitalization length and requirement for oxygen or ventilation that will be collected by the SOLIDARITY trial.

Important considerations in the successful testing and use of currently available and future therapies for COVID-19 are the timing of the treatment, the viral load of the patient and markers predictive of lung injury. Antiviral treatment is more efficient as a prophylactic measure and at earlier times during the infection, when virus replication is at its peak. Conversely, immunomodulatory and anti-inflammatory treatments may be more effective later and may be combined with careful monitoring of the patient viral loads.

OUTCOME IN THE ICU

Unfortunately a large proportion of infected patients need intensive care admission and management however, the knowledge about the clinical characteristics of those patients is generally limited. Grasselli et al reported the largest case series of patients with COVID-19 and severe illness who required admission to the ICU in Lombardy Region, Italy. The majority of patients (68%) had at least 1 comorbidity and 49% had hypertension. 99% needed respiratory support (88% mechanical ventilation and 11% noninvasive ventilation) and the ICU mortality was 26%. However, the above study has different limitations, such as a large number of patients reported were still intubated at the publication date.

The number of critically ill patients presenting to hospitals highlights the fragility of health care systems to care for the most severely ill patients in even the wealthiest countries. Fortunately, pandemics do not affect all locations with the same intensity at the same time. The pandemic burden may be attenuated only when an effective multifaceted response with collaboration and support is demonstrated by all countries. Patients with severe disease not considered suitable for escalation to intensive care, i.e. those who are frail or have multiple comorbidities, are at very high risk of dying, with an estimated death rate of 15–22%. We have a moral obligation to provide good symptom control to prevent avoidable suffering. Thus, comprehensive care of the patient with COVID-19 requires identification of patients at increased risk of dying, who would benefit from a parallel approach to management. This encompasses optimal symptom management for those with severe disease but who will...
survive, and expert symptom management and end of life care for those that are deteriorating and in their last days–hours of life.

Health care professionals often face fear and anxiety during this period. The 8 sources of anxiety after asking them can be organized into 5 requests from health care professionals to their organization: hear me, protect me, prepare me, support me and care for me. It is important that leaders understand the sources of concern and assure them that their concerns and their daily fight with the invisible enemy are recognized. Health care workers want to see that their leaders make an effort to develop approaches that mitigate those concerns to the extent that they are capable of.

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Cutaneous neurofibromas resembling parenchymal lung nodules

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It regards a 79-year-old Caucasian male patient smoker 40 pack-year cigarette with already diagnosed and clinically evident Neurofibromatosis type I (NF1) referred to our department for possible pulmonary involvement. On chest radiograph, multiple soft tissue nodules appeared in all lung fields (Figure 1a), a finding that was further clarified by the chest computerized tomography (CT) scan as the superimposition on the plain films of the dermal and subdermal neurofibromas (Figure 1b). CT of the chest further disclosed mild to moderate emphysema more prevalent in the upper lung fields both paraseptal and centrilobular type (Figure 1b) as well as kyphoscoliosis (Figure 1c). No evidence of interstitial lung or neoplastic disease was found.

FIGURE 1. (a) Posteroanterior chest radiograph showing multiple soft tissue nodules in all lung fields. (b) Chest computerized tomography (CT) scan revealing numerous well-defined cutaneous and subcutaneous nodules with soft-tissue attenuation in a configuration characteristic of neurofibromas as well as emphysema, predominantly in subpleural distribution at the upper lobes characteristic of paraseptal (distal acinar) emphysema. (c) Chest computerized tomography (CT) scan (coronal view) revealing severe deformity of the thoracic spine with marked kyphoscoliosis. Pulmonary function tests revealed a significant reduction in total lung capacity and functional residual capacity.
Renal Tuberculosis

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Key words:
- Intravenous pyelography
- Calyceal dilatation
- Percutaneous nephrolithotomy

Fifty-five year old patient complaining about hematuria, dysuria and left flank pain. No history of tuberculosis, just an uncontrolled diabetes, smoked one pack of cigarettes per day for the last ten years. Laboratory results: glucose 130 mg/dL, creatinine 1.1 mg/dL, white blood cells 7500/µL, hemoglobin 12.1 g/dL, hematocrit 37%; urine analysis: 28 leukocytes, nine erythrocytes per field. No bacteria grown in urinary culture. Normal chest radiography. On intravenous pyelography both kidneys were simultaneously functional, discontinuity between the left ureter and pelvis, calyceal dilatation in the left kidney and multiple renal calculi. The patient undertook percutaneous nephrolithotomy and because morphology and endoscopic view of the renal calyx was asymmetrical, biopsy was performed. A histopathologically positive result was identified by a granulomatous reaction, which included Langerhans cells and caseification necrosis. Negative for infection with human immunodeficiency virus. Started orally antituberculous therapy based on actual body weight with Isoniazid, Rifampin (Rifadin, Rimactane), Ethambutol (Myambutol), Pyrazinamide associated with Vitamin B-6 (pyridoxine). His condition improved over the course of the next weeks.

FIGURE 1. Computed tomography showed multiple cyst with some calcification in left kidney with a minimal expansion of the calyx.

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Tubercular meningitis

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Key words:
- Cerebrospinal fluid
- Polymerase chain reaction
- Neck stiffness

Twenty-two year old man, was admitted with a nine day history of fever, chills, sleepiness, headache and neck stiffness. Known for excessive consumption of alcohol, the patient appeared dehydrated and malnourished. He had a dental implant surgery five days before admission. On admission: temperature was 41 degrees, Glasgow coma scale 13 with marked neck stiffness. Cerebrospinal fluid was clear with an opening pressure of 38 cm and 610 white cells per cubic millimeter (65% neutrophils, 35% lymphocytes). The glucose cerebrospinal fluid/blood ratio was 0.9/7 mmol/l, cerebrospinal fluid lactate was 8.8 mmol/l, and cerebrospinal fluid protein was 182 mg/dl. Normal chest radiography. Tuberculin skin test was negative. Serum quantiFERON TB Gold was negative. Negative for infection with human immunodeficiency virus. Mycobacterium tuberculosis complex polymerase chain reaction was obtained from cerebrospinal fluid and was positive. He started antituberculous therapy and his headache and confusion improved over the course of the next few days.

FIGURE 1. Magnetic Resonance Imaging- in the right temporal lobe and thalamus the strengthened T1+ T2 signals could be noticed, which stipulated that a sizeable part of the brain nodules encounter meningeal enhancement.
Twenty-three year old man was admitted for assessment of lightheadedness, increased heart rate and recurrent back pain of four months duration associated with progressive numbness and stiffness of both legs and feet, causing trouble in rising and in climbing stairs. During this period, because of loss of appetite, he lost 20 kilograms, and 2 weeks prior to admission he experienced difficulty in urination and erection. Physical examination revealed kyphosis, a "hunchback" deformity, muscle atrophy, decreased tonicity and weakness of the lower extremities followed by decreased vibratory and position sense, decreased rectal tone and saddle anesthesia. Tuberculin skin test was positive. Normal chest radiography. The cerebrospinal fluid showed a high protein of 1121 mg/dl. The patient underwent immediate surgery. Histopathology revealed areas of consolidation with central caseating necrosis (caseating granulomas) and Langhans giant cells. Cultures taken at the time of surgery were positive for Mycobacterium tuberculosis. Negative for infection with human immunodeficiency virus. Postoperatively, the patient regained normal neurologic function and started prompt antituberculous therapy.

*Key words:*
- Caseating granulomas
- Langhans cells
- Hunchback deformity

*FIGURE 1. Magnetic Resonance Image showing destruction of vertebral bodies (L2, L3) with intraosseous and epidural abscess resulting in spinal canal stenosis.*
Physiotherapy Management for COVID-19 in the Acute Hospital Setting: Recommendations to guide clinical practice

ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a highly contagious new coronavirus that emerged in 2019 and causes Coronavirus Disease 2019 (COVID-19). The Section of Cardiovascular and Respiratory Physiotherapy - Rehabilitation (CRPR) of the Panhellenic Physiotherapists’ Association in Greek language after permission the “Physiotherapy Management for COVID-19 in the Acute Hospital Setting: Recommendations to guide clinical practice” (Thomas et al., 2020) (http://www.tkafa.gr/img/enimerosi_files/0659202001586446489100000.pdf) (March, 2020). These recommendations inform physiotherapists and the rest of the hospital’s healthcare staff about the role of physiotherapy in the acute phase of hospitalization in the management of patients with confirmed and / or suspected COVID-19 and the individual protective equipment (GDP) required duration of physiotherapy.

Physiotherapy may be beneficial in the respiratory treatment and physical rehabilitation of patients with COVID-19. Although a productive cough is a less common symptom, physiotherapists may provide airway clearance techniques for ventilated patients who show signs of inadequate airway clearance and they can assist in positioning patients with severe respiratory failure associated with COVID-19, including the use of prone position to optimise oxygenation. First of all, it is necessary to record the equipment of respiratory physiotherapy, mobilization and exercise, in order to prevent the movement of the equipment between infectious and non-infectious areas of the hospital. Avoid sharing equipment. Physiotherapists are required to have specialised knowledge, skills and decision making to work within the ICU. It is necessary to increase the required physiotherapy workforce by allowing additional shifts for part-time staff, or recruit a pool of casual staff. Physiotherapy interventions should only be provided when there are clinical indicators, so that staff exposure to patients with COVID-19 is minimised and PPE supplies may be reduced. Physiotherapists should meet regularly with senior medical staff to determine indications for physiotherapy.

review in patients with confirmed or suspected COVID-19 and screen according to set/agreed guidelines (if they have pneumonia, mild symptoms or severe symptoms, lower respiratory tract infection). Physiotherapy may be indicated, particularly if weak cough, productive and/or evidence of pneumonia on imaging and/or secretion retention. Patients should wear a surgical mask during any intervention. Staff uses airborne precautions. Patients will be provided treatment in isolation rooms. A Senior PT will screen patients with COVID-19 in consultation with an ICU medical Consultant before the physiotherapy program. The use of nebulised agents (e.g. salbutamol, saline) for the treatment of non-intubated patients with COVID-19 is not recommended as it increases the risk of aerosolization and transmission of infection to health care workers in the immediate vicinity. In adult patients with COVID-19 and severe ARDS, prone ventilation for 12–16 hours per day is recommended. Closed inline suction catheters are recommended. Physiotherapy respiratory interventions (or chest physiotherapy) include: Airway clearance techniques, positioning, active cycle of breathing, manual and/or ventilator hyperinflation, percussion and vibrations, positive expiratory pressure therapy, mechanical insufflation-exsufflation (MI-E). Techniques to facilitate secretion clearance should be followed i.e., assisted or stimulated cough manoeuvres, and airway suctioning. BubblePEP is not recommended for patients with COVID-19. There is no evidence for incentive spirometry in patients with COVID-19. Physiotherapists also play an integral role in the management of patients with a tracheostomy.

Physiotherapists are responsible for the early mobilization of the patients including passive, active assisted, active, or resisted joint range of motion exercises to maintain or improve joint integrity and range of motion and muscle strength, bed mobility, sitting out of bed, sitting balance, sit to stand, walking, tilt table, standing hoists, upper limb or lower limb ergometry. Only where there are significant functional limitations (e.g. (risk for) ICU-acquired weakness, frailty, multiple comorbidities, advanced age) should the requirement for direct physiotherapy interventions is considered. It is recommended COVID-19 patient’s, ideally, be treated in a Class N negative pressure single room. Airborne precautions are followed including: an N95/P2 mask, fluid resistant long-sleeved gown, goggles/face shield, gloves, hair cover for AGPs, shoes that are impermeable to liquids and can be wiped down.
Φυσικοθεραπευτική Παρέμβαση σε COVID-19 στον χώρο της Οξείας Φάσης Νοσηλείας: Συστάσεις οδηγιών κλινικού έργου

Α. Χρηστάκου, Σ. Ανδρεάδου, Α. Ζαμπλάρα, Δ. Καραδήμου, Α. Κούστα, Π. Μπεμπελέτση, Δ. Παναγοπούλου, Ε. Πατσάκη, Π. Σακελλάρη, Α. Σεϊταρίδη

ΠΕΡΙΛΗΨΗ


Κατ’ αρχάς σύμφωνα με τις συστάσεις σχεδιασμού και προετοιμασίας του προσωπικού της φυσικοθεραπείας, απαιτείται αυτό να διαθέτει εξειδικευμένες γνώσεις για παροχή φυσικοθεραπείας στο χώρο της ΜΕΘ. Επιπρόσθετα, κρίνεται αναγκαίο η απογραφή εξοπλισμού της αναπνευστικής φυσικοθεραπείας, της κινητοποίησης και της άσκησης, ώστε να αποτρέπεται η διακίνηση του εξοπλισμού μεταξύ μολυσματικών και μη μολυσματικών περιοχών του νοσοκομείου.

Οι ασθενείς με COVID-19 εμφανίζουν συμπτώματα παρόμοια με τη γρίπη και τα ποσοστά εισαγωγής τους στη ΜΕΘ για μηχανική υποστήριξη της αναπνοής είναι υψηλά. Η αναπνευστική και η μυοσκελετική φυσικοθεραπεία σε ασθενείς με COVID-19 είναι υφιστάμενη. Παρόλα αυτά, οι φυσιοκαθαριστικές παρεμβάσεις θα πρέπει να παρέχονται μόνο όταν υπάρχουν κλινικές ενδείξεις, ώστε να ελαχιστοποιείται η έκθεση του προσωπικού σε ασθενείς με COVID-19. Η μη αναγκαία παρέμβαση στο χώρο απομόνωσης αυτών των ασθενών θα έχει επίσης αρνητικό αντίκτυπο στις προμήθειες του ΑΕΠ του νοσοκομείου. Σε ασθενείς με ήπια συμπτώματα, ή/και πνευμονία και με κλινικά στοιχεία εξιδρωματικής πύκνωσης,
ή/και αδυναμία κινητοποίησης εκκρίσεων από τους ιδίους (λ.χ., αδύναμο, μη αποτελεσματικό, υγρό βήχα, ψηλαφητές δονήσεις παραγόμενες κατά τη διόδο του αέρα από μεγάλο βρόγχο πλήνεις, υγρό ήχο φωνής, ρεγχάζοντες ρόγχους) δύναται να υπάρχει παραπομπή φυσικοθεραπείας για κάθαρση αεραγωγού. Οι φυσικοθεραπευτικές παρεμβάσεις περιλαμβάνουν: (α) τεχνικές καθαρισμού των αεραγωγών, (β) μη επεμβατικό αερισμό (NIV) και αναπνοή θετικής εισπνευστικής πίεσης (IPPB), (γ) τεχνικές διευκόλυνσης απομάκρυνσης των εκκρίσεων, (δ) τοποθέτηση των ασθενών με σοβαρή αναπνευστική ανεπάρκεια σχετιζόμενη με το COVID-19 σε διάφορες θέσεις με συμπεριλαμβανομένης και της πρηνού θέσης μιας και διεθνείς έρευνες αναφέρουν ότι είναι μία αποτελεσματική στρατηγική σε μηχανικά αεριζόμενους ασθενείς και (ε) πρώιμη κινητοποίηση και άσκηση εξαιτίας της ανάπτυξης της μυϊκής αδυναμίας αποκτηθείσα στη ΜΕΘ (όταν αυτή κρίνεται ασφαλής με ατομικούς χρήσιμο εξοπλισμό). Ο φυσικοθεραπευτής δύναται να εκτελέσει ασκήσεις εύρους τροχιάς των αρθρώσεων, παθητικές, ενεργητικές υποβοηθούμενες ενεργητικές ή με αντίσταση, κάθισμα εκτός κρεβατιού, καθιστική θέση – ισορροπία, ορθοστάτηση, βάδιση, να κάνει χρήση ορθοστάτη τύπου tilt-table, αλλά και ανυψωτήρα ορθοστάτη με στόχο τη διατήρηση ή βελτίωση της ακεραιότητας και του εύρους τροχιάς των αρθρώσεων, της μυϊκής ισχύος, κ.λπ. Επίσης οι φυσικοθεραπευτές έχουν αναπόσπαστο ρόλο στη διαχείριση ασθενών με τραχειοστομία.

Εξαιτίας κινδύνου δημιουργίας αερογενούς μετάδοσης του COVID-19 κατά τη διάρκεια της φυσικοθεραπείας απαιτείται να εκτιμάται ο κίνδυνος της κάθε παρέμβασης και να εφαρμόζεται ο αντίστοιχος ενδεικνυόμενος ΑΕΠ, καθώς και μέτρα αναπνευστικής προστασίας του βήχα, όπως ο ασθενής να γυρίζει το κεφάλι από την αντίθετη πλευρά του βήχα και την απόχρεμψη ή την «παγίδευση» του βήχα με μαντήλι, ή/και όταν είναι εφικτό ο φυσικοθεραπευτής να βρίσκεται σε απόσταση ≥2 μέτρων από τον ασθενή και μακριά από την «ζώνη έκρηξης» του βήχα του.

Σε ασθενείς με COVID-19 δεν υπάρχουν ενδείξεις χρησιμότητας του σπιρόμετρου κινήτρου. Επαναχρησιμοποιούμενος αναπνευστικός εξοπλισμός θα πρέπει να αποφεύγεται κατά το δυνατό. Οι φυσικοθεραπευτές δεν θα πρέπει να εφαρμόζουν εφύγρανση - νεφελοποίηση χωρίς τη συμβουλή και τη σύμφωνη γνώμη του ιατρού. Γενικά, διαδικασίες παραγωγής αερολύματος δημιουργούν τον κίνδυνο αερομεταφερόμενης μετάδοσης του COVID-19 και δεν συνιστάται η χρήση νεφελοποιημένων παραγόντων για τη θεραπεία ασθενών με COVID-19, καθώς αυξάνει τον κίνδυνο αερολύματος και μετάδοσης της λοίμωξης. Η συνήθης χρήση του μη επεμβατικού αερισμού (NIV) δεν συνιστάται. Συνίστανται οι κλειστού τύπου καθετήρες αναρρόφησης, ενώ οποιαδήποτε αποσύνδεση του ασθενούς από τον αναπνευστήρα για λήψη δείγματος βρογχικών εκκρίσεων θα πρέπει να αποφεύγεται. Εάν απαιτούνται φυσικοθεραπευτικές παρεμβάσεις για τη διευκόλυνση της λήψης δείγματος θα πρέπει να χρησιμοποιηθούν αερογενείς προφυλάξεις. Η διαχείριση των δειγμάτων πτυέλου θα πρέπει να γίνει σύμφωνα με τις οδηγίες του εκάστοτε νοσοκομείου.

Για τα επιβεβαιωμένα κρούσματα, τα ελάχιστα μέτρα προφύλαξης από σταγονίδια είναι η χρήση μιας μάσκας Ν95/P3, η αδιάβροχη μακρυμάνικη φόρμα, γυαλιά/ασπίδα προσώπου, γάντια, κάλυμμα μαλλιών και αδιάβροχα παπούτσια. Να χρησιμοποιείται η διαδικασία ένδυσης και απομάκρυνσης του ΑΠΕ βήμα προς βήμα, σύμφωνα με τις οδηγίες που υπάρχουν ανά νοσοκομείο. Τα δωμάτια αρνητικής πίεσης χρησιμοποιούνται για την απομόνωση ασθενών με COVID-19, ως μέτρο πρόληψης της διασποράς.
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*n/a: not applicable; *excluding References, Tables, Acknowledgements and Figure Legends
Introduction
The rationale for the study should be summarized and relevant background material outlined. The Introduction should not contain findings, methods used or conclusions.

Methods
Methods should be described in adequate detail to assure the reader as to how the results were obtained. In manuscripts reporting human research, the authors should report approval by the Review Board or Ethics Committee and that written informed consent was obtained from patients. The location (city, state, country) of a manufacturer listed in the text should be provided. Units should conform to SI conventions. Generic names of drugs should be used instead of trade names. Statistical methods should be meticulously described and referenced.

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Acknowledgements
Acknowledge the persons who provided a true contribution and who endorse the data and conclusions. Acknowledge any funding sources.

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