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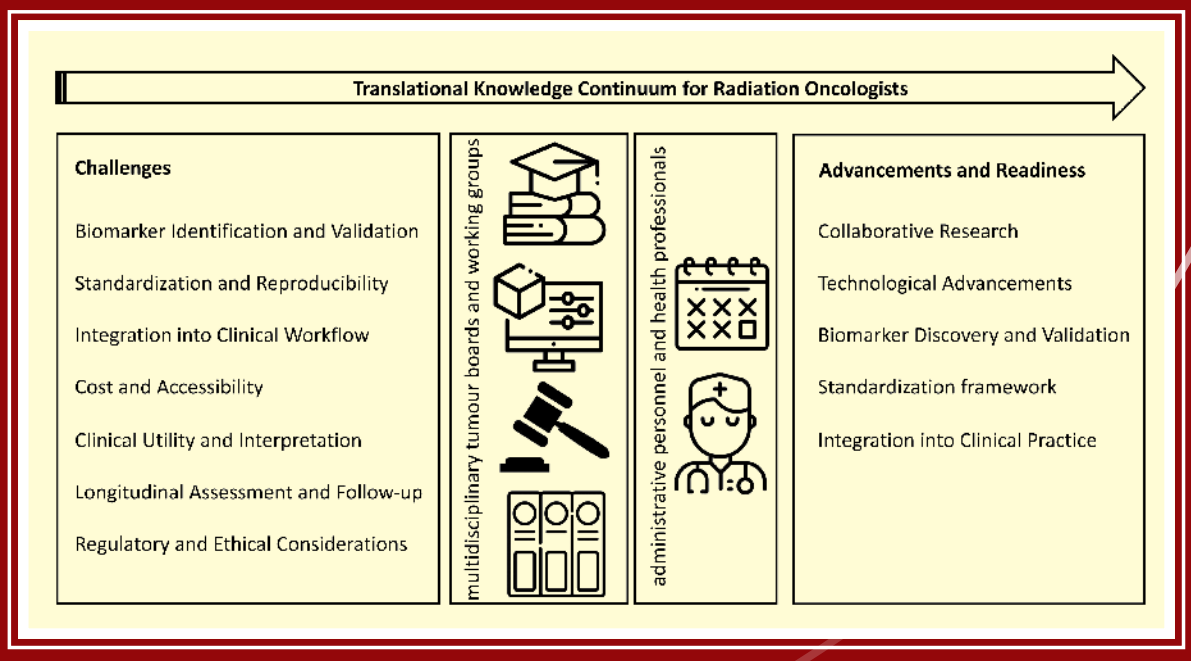

Radiation oncologists are ready to embrace translational biomarkers

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CONTENTS

Dear colleagues,

In the current issue, the editorial by Katsila et al. comments on the progress of radiation oncology and the active involvement of radiologists in the exploration and implementation of biomarkers in their field. The editorial by Finitsis et al. presents a timely update of the trials on thrombectomy for large ischemic brain infarcts up to 24 hours after symptom onset.

Moreover, this issue includes three review articles. The review article by Lazaris V. summarizes the latest data on the pathophysiology, risk factors, treatment, and prevention options regarding the acute chest syndrome. The review by Anagnostopoulou et al. aims to delineate the diagnostic process of dyspneic patients and presents the therapeutic options in the management of such patients. Also, it provides insights into the specific treatment algorithms of the most common causes of dyspnea. The review by Kalampoki et al. provides a comprehensive overview of data regarding the definition, prevalence, diagnosis, and treatment of occult hepatitis B infection, focusing on the risk of occult HBV infection in blood transfusion and in HBV elimination strategies.

Lastly, this issue includes the case report by Lagadinou et al. which presents an unusual case of *Datura stramonium* poisoning that occurred after eating accidentally *Datura* flowers. The patient was presented with encephalitis-like symptoms and was cured successfully.

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Are Radiation Oncologists ready to enter Biomarkers' World?

Theodora Katsila[1], Vivi Bafiti[1], Dimitrios Kardamakis[2]

INTRODUCTION

In the past 50 years, the subject of radiation oncology has expanded enormously, not only in the fields of treatment delivery technology (stereotactic techniques) and anatomical imaging of structures of interest (adaptive radiotherapy), but also in the incorporation of hybrid whole-body imaging modality (positron emission tomography, PET/computed tomography, CT) in the radiation treatment planning and the integration of molecular profile data of the tumour and the normal tissues in decision-making [1-3]. In modern oncology, significant progress has been made in prescribing the molecular characteristics of cancerous or normal cells, along with imaging data, serving as biomarkers with the hype to better inform clinical practice [4,5]. Radiation oncologists have been actively involved in the exploration and implementation of biomarkers in their field.

Molecular and image-based biomarkers in radiation oncology

Nowadays, molecular biomarkers are part of the comprehensive cancer patient care, allowing the prognosis of the disease, predicting patient response to a particular therapy, and allowing clinicians to apply personalised medicine [6,7]. Image-based biomarkers are also actively discussed. To name but a few: tumour size, shape, texture and volume; apparent diffusion coefficient; standardised uptake value; blood flow and perfusion; volumetric modulated Arc therapy parameters; and hypoxia imaging inform about tumour characteristics, treatment response and treatment-related toxicities [8,9]. As imaging techniques and analysis methods are emerging, the landscape of image-based biomarkers in radiation oncology continues to expand, providing opportunities for improved treatment planning, response assessment and personalised care.

The concept of Translational Precision Medicine calls for the application of molecular and digital (i.e., image-based) biomarkers in a way that is feasible and clinically relevant for clinical trials, accepted by regulators and of note, patients [10]. Even though molecular and image-based biomarkers refer to an objective medical state that can be measured with accuracy and reproducibility [11,12], unfortunately in real-world situations, several challenges are still to be overcome when combining molecular and image-based data with radiation oncology routine practice [4,13]. To this extent, artificial intelligence (AI) undeniably holds remarkable potential for revolutionising the field of radiation oncology in the coming years. The integration of AI into this domain has already showcased promising advancements, empowering radiation oncologists with enhanced precision, efficiency, and personalised treatment approaches [14]. By leveraging machine learning algorithms and data analytics, AI can assist in the identification and utilisation of biomarkers, both molecular and image-based ones, thereby facilitating improved patient risk stratification, treatment planning, and therapy response assessment. Furthermore, AI-driven technologies have the capacity to optimise treatment delivery, enabling real-time adaptation and ensuring optimal tumour targeting while minimising damage to surrounding healthy tissues. As the research and development in this area continue to unfold, embracing AI's capabilities

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Key words: *Radiation oncology; biomarkers; translational precision medicine*

and exploring its potential in radiation oncology will undoubtedly pave the way for innovative solutions, better patient outcomes, and the constant evolution of this vital medical discipline.

Are radiation oncologists ready for prime time?

As the field of biomarkers continues to advance, radiation oncologists play a critical role in incorporating these tools into their practice to enhance patient care and treatment outcomes. For the practicing radiation oncologist, a series of challenges arise from technical, clinical and logistical aspects.

Long waiting times for the results. The period between the referral of the patient and the results from the molecular analysis can delay the initiation of the therapy, putting the patient at an extra risk for relapse in cases of adjuvant treatment. Although we know that the association between a delay in starting radiation therapy (RT) and the outcome is complex and does not harm all patients waiting for RT [15], timely decision-making remains key. For the radiation oncologist to have the time to think, decide and act, a supporting framework of administrative and health professionals and digital tools and technologies alike shall be available for longitudinal assessment and follow-up.

Insufficient tumour and/ or normal tissue specimen for analysis. This is a real drawback for incorporating molecular analysis in the therapeutic algorithm. Radiation oncologists need to know the molecular profile of the normal tissues as well to predict the appearance and the severity of side effects. On the other hand, regarding the well described phenomenon of tumour heterogeneity, the molecular analysis of an insufficient tumour specimen may not represent the "true molecular profile". In any case, there are biomarkers that are considered as surrogates, as the information they provide cannot be used as the single variable defining disease type, staging, and response to RT. For image-based biomarkers, appropriate use must be based on knowledge of the relationship to the underlying biological processes, the physical origin of the biomarker signal as well as their strengths and limitations [16].

Results are presented in reports in a way not familiar to clinicians. This problem can be surpassed by using a template in reporting the results to the health care team in a way that fosters clinical significance. At the same time, oncologists need to obtain a basic level of understanding such molecular analysis reports by upgrading their training curriculum and putting emphasis on the molecular biology of cancer in their continuing medical education activities. Educational resources

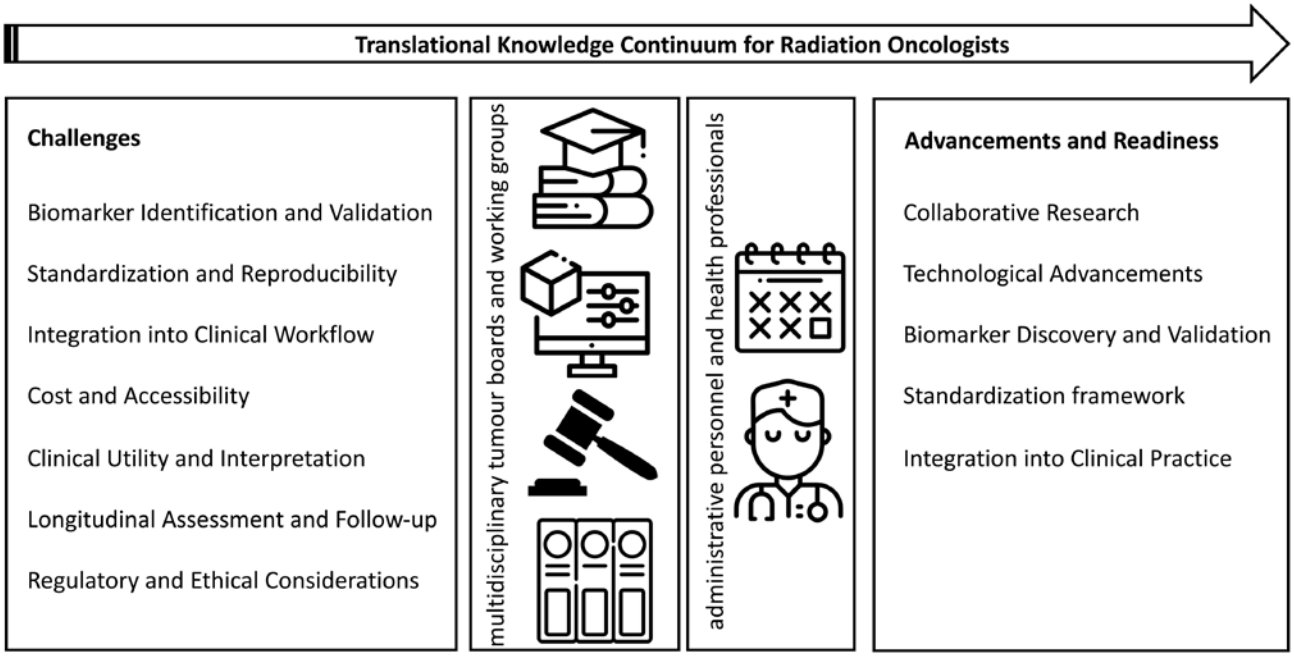

Figure 1. Radiation oncologists are ready to embrace translational biomarkers. Key challenges are clearly defined and hence, tumour boards and working groups are collectively putting forward implementation schemes. Such schemes may be translated in clinical routines if supported by administrative and health professionals that support radiation oncologists toward decision- and sense-making.

that are updated based on white papers and clinical guidelines describing molecular and image-based biomarkers, the techniques used to quantify them, their strengths and weaknesses within the context of their application to radiation oncology so as to ensure their appropriate use and application are vital. Here, the well-established roles of multidisciplinary tumour boards and working groups are extremely important in helping oncologists to read and interpret molecular and image analysis results [17-19].

Clinical utility is an old problem in oncology, yet unsolved. Data from *in vitro* and *in vivo* preclinical studies are difficult to be transferred to clinical situations. Translating biomarker findings into actionable clinical decisions can be complex. Radiation oncologists need to understand the clinical significance of biomarkers, if any, plus their limitations and how to integrate them with individual patient characteristics, treatment modalities and response patterns [20,21].

Most published data originate from chemotherapy studies and refer to biomarkers involving a "single gene" – "single drug" association. In the translational precision medicine era, the biomarker field is shifting toward biomarker signatures addressing best disease complexity and population differences. From such biomarker signatures, biomarker panels and companion diagnostics often arise. In radiation oncology, such efforts include the field of radiogenomics that involves studies on assessing gene – radiation effect relationships and radiomics, in which quantitative features from medical images are extracted and analysed [22]. Coupling molecular to image-based biomarkers holds promise easing integration into clinical workflows [8].

Lack of clear guidelines connecting the molecular biology and image findings with the clinical status of the patient and the stage of the disease. In modern radiation oncology practice, efforts are being made to individualise radiation delivery on the basis of genes associated with tumour and normal tissue radiosensitivity [23]. Same for proteins and lately, metabolites plus images. Standardisation is key for reproducibility, ensuring consistency and quality assurance measures among clinical settings [4].

The power of synergy

In summary, even though recently published surveys state that oncologists in general show a low self-esteem in integrating molecular analysis data and/or image data in clinical data, our personal beliefs are that radiation oncologists are ready to embrace biomarkers and hence, play an important role in advancing the field of precision oncology if they gain additional knowledge in areas such as molecular biology and bioinformatics and collaborate more closely with molecular biologists, biomedical engineers, bioinformaticians and pathologists [4,18,22-23]. Radiation oncologists need a support network of administrative personnel and health professionals as well as tumour boards and working groups for their translational knowledge continuum (Figure 1).

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Mechanical thrombectomy for the treatment of stroke in the extended time window: New Perspectives

Stefanos Finitsis

INTRODUCTION

Mechanical Thrombectomy (MT) is a safe and effective treatment for patients with acute ischaemic stroke (AIS) due to large vessel occlusion (LVO) in the anterior circulation since the appearance of six randomised trials in 2015 [1–6]. These trials established MT in the "early time window" (i.e., within six hours from symptom onset) but included very few patients beyond the 6-hour cutoff [3,7]. In 2018, treatment was further extended in the "late time window" (i.e., 6 to 24 hours from symptom onset) by two additional randomised trials, DAWN and DEFUSE 3 (Table 1) [8,9].

These trials, which provide the backbone for current AHA guidelines [10] in the extended time window, used a combination of clinical criteria and advanced imaging to select patients most likely to benefit from thrombectomy. According to these guidelines, CT perfusion (in addition to nonenhanced CT and CT angiography), or MRI (DWI and MRI perfusion), establish eligibility for thrombectomy (Evidence Level I, AHA guidelines). Central to the selection of patients is the evaluation of the volume of the infarct core, defined as the brain volume with a Cerebral Blood Flow (CBF) < 30% or an Apparent Diffusion Coefficient (ADC) < 620^{-3} x 10 mm^2/sec on MRI. The penumbral volume is defined as a Tmax > 6 sec on CT Perfusion or MRI [8,9]. The cutoff for these volumes is further adapted for the age and clinical deficit of the patient.

According to the DAWN trial criteria, which are applicable for patients from 6 to 24 hours after symptom onset [8] , patients younger than 80 years are further subdivided into patients with an NIHSS score > 20, in which case only patients with a core ≤ 50 ml are eligible for thrombectomy and patients with an NIHSS 10-20, in which case only patients with a core ≤ 30 ml are eligible, while patients with an NIHSS < 10 should not receive thrombectomy. For patients older than 80, thrombectomy is indicated only for those with a core ≤ 20 ml. According to the DEFFUSE 3 criteria [9], which are applicable for patients from 6 to 16 hours after symptom onset, thrombectomy is indicated in patients with a core ≤ 70 ml and a penumbra ≥15 ml or a mismatch ratio ≥1.8. Compared to medical therapy, the DAWN trial demonstrated an overall benefit of good functional outcome (mRS score 0-2) of 49% versus 13%, while the DEFUSE 3 trial showed a benefit of 44.6% vs. 16.7%. However, the imaging criteria used are restrictive, and there is growing evidence that several patients outside the DAWN and DEFUSE 3 eligibility criteria may still benefit from MT.

New randomised trials for the extended time window – A shift of perspective

Three new randomised trials (RESCUE Japan, SELECT-2 and ANGEL-ASPECTS) [11–13] on patients in the extended time window from 6 to 24 hours were concluded recently and present a shift in perspective in both imaging selection criteria and patient outcomes (Table 1). These trials enrolled patients presenting with large ischaemic strokes with ASPECTS as low as three and set the bar for a successful clinical outcome to an mRS of 0-3.

Key words: *Stroke; ischaemic; large vessel; thrombectomy; large core; extended time window*

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Table 1. *Overview of Randomized Control Trials comparing anterior circulation large vessel occlusion thrombectomy to best medial management in the extended time window.*

Year	Study	Time Window	Inclusion Criteria	mRS 0-2 at 90 days (Thrombectomy vs Best Medical Care)
2018	DAWN Trial	6-24 h	Advanced Imaging mismatch according to age (< 80 years, ≥80 years)	49% vs 13%
2018	DEFUSE 3	6-16 h	Infarct size < 70 ml or Advanced Imaging mismatch > 1.8	45% vs 17%
2022	RESCUE-Japan	Up to 24 h	ASPECTS 3-5 (up to 6 hours), or No FLAIR lesion (up to 24 hours)	14% vs 7.8%
2023	SELECT-2	Up to 24 h	ASPECTS 3-5, or Infarct size > 50 ml on perfusion CT or DWI	20.3% vs 7%
2023	ANGEL-ASPECTS	Up to 24 h	ASPECTS 3-5, or Infarct size 70-100 ml	30% vs 11.6%

RESCUE-Japan [12] focused on Japanese patients presenting with ASPECTS 3-5 (CT or MR) 6-24 hours from symptom onset or patients with no MR FLAIR changes up to 24 hours. Compared to medical therapy, patients undergoing thrombectomy demonstrated an overall benefit of independent ambulation of 31% vs. 12.7% (OR 2.43 95%CI 1.35-4.37, p=0.002), a higher rate of functional independence (OR 1.79, 95%CI 1.46-4.01) without an increased risk of symptomatic haemorrhage (9% vs 4.9%, RR 1.84, 95%CI 0.44-1.32, p=0.33). Rates of any intracranial haemorrhage were significantly higher in the thrombectomy group (58% vs 31.4%, RR 1.85 95% CI 1.33-2.58, p<0.001). The treatment effect persisted across all subgroups, signaling an even greater benefit in elderly patients.

SELECT-2 [11] was an international trial that focused on patients with a CT ASPECTS 3-5 or MRI 50 ml < ADC < 620 ml or core > 50 ml (CBF < 30%) within 24 hours of symptom onset. Compared to medical therapy, patients undergoing thrombectomy demonstrated an overall benefit of independent ambulation of 37.9% vs. 18.7% (OR 2.06 95%CI 1.43-2.96), a higher rate of functional independence (20.3% vs 7%, OR 1.79, 95%CI 1.46-4.01) without an increased risk of symptomatic haemorrhage (0.6% vs. 1.1%, OR 0.49, 95%CI 0.04-5.36). Of note, MT reduced the number of mRS 5 patients by more than half. The treatment effect persisted across all subgroups, especially in patients with very large ischaemic core volumes ≥ 150 ml, patients with large penumbras, and patients with small penumbras as 10 ml.

ANGEL-ASPECTS [13] was a randomised trial focusing on Chinese patients with a CT ASPECTS of 3-5 or a CBF<30% core of 70-100 ml within 24 hours of symptom onset. Compared to medical therapy, patients undergoing thrombectomy demonstrated an overall benefit of independent ambulation of 47% vs. 33.3% (OR 1.5 95%CI 1.17-1.91) and a higher rate of functional independence (30% vs. 11.6%, OR 2.62 95%CI 1.69-4.06) without an increased risk of symptomatic haemorrhage (6.1% VS 2.7%, p=0.21). In addition, MT reduced the number of mRS 5 patients by nearly half.

Implications of the new trials

The results of the three published large core trials provide preliminary evidence that infarction volume, even large, does not negatively modify the treatment effect of MT with no additional risk of symptomatic intracerebral haemorrhage. Furthermore, this effect is not modified by age or NIHSS. However, one could envision extreme scenarios, like elderly patients with very large cores where there may be no benefit from MT. Nevertheless, the treatment effect demonstrated in patients with ASPECTS ≥ 3 will likely render perfusion imaging unnecessary or reserved for extended-window patients with ASPECTS < 3.

The present trials also corroborate earlier concerns that ASPECTS and CT perfusion volumes are imperfect measures of the salvageable brain even with automated quantification [14]. ASPECTS has high interrater variability and does not consider the location of the infarcted regions and their weight in the final prognosis. Thus, the present results stress the need for more efficient methods to correlate CT hypodensities with the final functional outcome.

Other logistical questions include the need to repeat a head CT at the hub hospital after a transfer, the role of time windows in patient selections, and for which patient MT may be declared futile. A broader question pertains to the patients who do not reach ambulatory independence. In the present studies, only 2-3 out of 10 large core patients with MT get to be functionally independent, while 7-8 of 10 large core patients die or will need full-time nursing, adding to a high up-front cost. A cost-effectiveness analysis of the RESCUE-JAPAN trial found MT cost-effective with a cost-effectiveness ratio of $16 239/QALY [15]. The trials also denote a change in therapeutic perspective, reflecting the goal to avoid mRS 5, that is, avoid the outcome of a bedridden patient, which represents a dramatic increase in the cost of care and burden for the family and society.

The remaining additional large core trials, including LASTE (NCT03811769), TESLA (NCT03805308), and TENSION (NCT03094715), should provide further data to elucidate these questions.

CONCLUSION

The three published large core trials demonstrated a significant benefit of MT for large vessel occlusion in anterior circulation stroke in the extended time window. In addition, the treatment effect remained across all studied subgroups. Following these results and the results of other ongoing trials, a shift will likely occur regarding patient imaging triage resulting in an enlargement of the pool of patients who may benefit from MT.

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Acute chest syndrome in sickle cell disease. A brief review

Vasileios Lazaris

Abstract

Acute chest syndrome (ACS) is a severe complication of sickle cell disease. It affects all disease genotypes, leads to prolonged hospitalisations, and is a common cause of disease-attributed mortality. Prompt diagnosis plays a crucial role in the treatment of ACS patients. Hydroxyurea and infection prevention contribute to lower rate of ACS. Moreover, transfusions and supportive care alleviate the symptoms in the acute phase of the disease. This brief review presents all aspects of ACS, from the pathophysiology and risk factors to the treatment and prevention options.

Key words: *Acute chest syndrome; sickle cell disease; complications of sickle cell disease*

INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive inherited disease with very high prevalence, especially in sub-Saharan Africa [1,2]. The disease is caused by a single nucleotide mutation of the β-globin gene (HBB) that replaces glutamate with valine. The altered haemoglobin causes shape changes to the red blood cells (RBCs) resembling sickles. The misshapen RBCs are trapped in the small blood vessels causing vessel obstruction, tissue hypoxia, and severe pain.

The severity of the symptoms varies between the affected individuals. The most common symptom is the vaso-occlusive crisis (VOC), a painful event resulting from capillary obstruction. Some patients experience life-threatening complications such as splenic sequestration crisis, neurologic complications like haemorrhagic or ischaemic stroke, and acute chest syndrome. Acute chest syndrome (ACS) is a severe complication of SCD, mainly affecting respiratory capability. Chest pain, pulmonary infiltrates, dyspnoea, and fever characterise it.

It is known that over 50% of children with homozygous SCD (HbSS) will suffer from ACS at least once in their decade of life [3]. Furthermore, ACS is a common cause of hospital admission, with a mean length of stay over seven days and in-hospital mortality of just below 2% [4]. However, some older studies have reported mortality rates up to 3% in all ACS patients, 2% in the pediatric population, and 9% in adults [5]. ACS affects all SCD genotypes but is more common in those with homozygous SS and S/beta-thalassemia-null genotypes [6]. More specifically, the incidence of ACS ranges from 3.9/100 patient-years in the HbSβ+ population to 12.8/100 patient-years in the HbSS population [7]. Recurrent episodes of ACS may lead to debilitating lung disease [8].

ACS diagnosis & clinical manifestations

According to the British Society of Haematology (BSH), ACS is defined as an acute illness with a newly developed pulmonary infiltration accompanied by fever and/ or respiratory symptoms. The symptoms include cough, chest pain, wheezing, tachypnoea, and increased work of breathing, among others [9]. Older publications described ACS as a new pulmonary infiltrate on a chest radiograph [7] or as a condition that includes chest pain, increased leukocytosis, fever, and pulmonary infiltrate [10]. Hypoxia is a worrying clinical sign, and though

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it was not initially included in the definition of ACS, others consider it part of it [8]. Hypoxia which can be defined as PaO_2 less than 60 mmHg or relative hypoxia to baseline, which is defined as more than a 2% decrease in SpO_2 from a steady state on room air, is a worrying sign. Hypoxia may precede other clinical symptoms or X-ray findings. Moreover, the clinical manifestations of ACS depend on the patient's age; for example, younger patients usually do not experience chest pain. In addition, wheezing, cough, and fever were most common among children, whereas pain in the arms and legs and dyspnoea were more common among adults [5].

An ASC severity index was proposed by Ballas et al. in 2010 (Table 1) [11]. This index was mainly used in clinical research and is not widely validated in real-world settings [12].

ACS can occur during a VOC. A predictive score, including reticulocyte and leukocyte counts and spine and pelvic pain, can be used to identify the patients that will not develop ACS. Despite its high negative predictive value (98.8%), it has a low positive predictive value (39.5%). Nevertheless, it can be a helpful tool for the early discharging of low-risk patients [13]. Secretory phospholipase A2 was evaluated as a predictive marker for developing ACS during VOC in the PROACTIVE study but showed a 24% positive predictive value [14].

As may be noted, the preceding definition lacks specificity. The clinical signs of ACS resemble those of pneumonia. These two entities usually cannot be distinguished. As a result, all patients should be treated with antibiotics for severe community-acquired pneumonia. Furthermore, other urgent medical entities should be excluded. The differential diagnosis algorithm should include acute coronary syndrome, acute myocardial infarction, pneumothorax, pleural effusions, empyema, aortic dissection, and ARDS [8].

The initial workup of a patient with suspected ACS should at least include a chest X-ray, complete blood count, basic biochemistry, blood group, and screen or crossmatch, blood cultures, ABG measurement in cases with hypoxia, serology for atypical respiratory organisms and urine for Pneumococcal and Legionella antigen, sputum for bacterial culture and nasopharyngeal swab for virus testing [9]. Moreover, a lung CT scan will be needed in only a few cases as part of the initial workup because a chest X-ray can easily identify lung infiltrates [15].

Risk factors for developing ACS

High white blood cell (WBC) counts, low haemoglo-

Table 1. *The ACS severity index, as it is first described in Ballas et al [11].*

Mild ACS	Moderate ACS	Severe ACS	Very Severe ACS
Meets the diagnostic criteria above AND all of the following:	***Meets the diagnostic criteria above AND all of the following:***	***Meets the diagnostic criteria above AND 1 or more of the following:***	***Acute Respiratory Distress Syndrome (ARDS), as defined by the 3 criteria of the American-European Consensus Conference, includes:***
Transcutaneous oxygen saturation >90% in room air (FiO2 = 0.21)	Transcutaneous oxygen saturation ≥85% in room air (FiO2 = 0.21)	Respiratory failure (PaO2 <60 mmHg or PCO2 >50 mmHg) Mechanical ventilatory support required Transcutaneous oxygen saturation <85% in room air or ≤90% despite maximal supplemental oxygen	Acute onset of bilateral infiltrates on chest radiograph
Segmental or lobar infiltrates that involve no more than 1 lobe by chest radiography	Segmental or lobar infiltrates that involve no more than 2 lobes by chest radiography	Segmental or lobar infiltrates that involve 3 or more lobes by chest radiography	Pulmonary artery wedge pressure of <19 mmHg or the absence of clinical evidence of left atrial hypertension
Responsive to simple transfusion of no more than 2 units of red blood cells (or 15 cc/kg packed red blood cells)	Responsive to transfusion of ≥3 units of red blood cells (or more than 20 cc/kg packed red blood cells)	Requiring transfusion or exchange transfusion of red blood cells to achieve haemoglobin A ≥70%	PaO2/FiO2 ≤200 regardless of positive end-expiratory pressure (PEEP) level

bin F (HbF), young age, and more than 3 VOC episodes in the past years are well-established risk factors. Asthma and tobacco use are also related to ACS occurrence. Another risk factor is the genotype; individuals with more severe SCD (HbSS and HbSβ0) tend to develop more frequently ACS than those with mild SCD (HbSC and HbSβ+ genotypes) [16].

Acute chest syndrome pathophysiology

ACS is a type of acute lung injury. The exact events that lead to the syndrome manifestation are not fully known. The triggering causes contributing to the presentation of ACS are infections, pulmonary fat embolism, and pulmonary artery infarctions [17]. These events eventually lead to ventilation-perfusion mismatch, hypoxemia, and acute pulmonary artery and right ventricular pressure increases. At the microscopic level, there is vaso-occlusion, sickling of the abnormal red blood cells, adhesion of leukocytes, and inflammation of the pulmonary vascular endothelium. The inflammation is promoted to the nearby alveolar and small airway tissues [18].

Pulmonary infection is detected in up to 38% of patients with ACS. In children with ACS, the most typical cause is viral infections. The respiratory syncytial virus (RSV) is the main culprit. Moreover, atypical bacteria such as *Mycoplasma pneumoniae* can also be detected in children with ACS. Other bacteria, such as *Staphylococcus aureus* and *Streptococcus pneumoniae*, can be detected, especially in adult patients. Infections can induce excessive acute lung injury in a SCD patient. This is proven in SCD mouse models, which developed acute lung injury with a low dose of endotoxin, while the wild-type mice remained unaffected [19]. SARS-CoV-2 infection was identified as a triggering event of ACS. These two entities have overlapping symptoms and radiological signs. The patients that develop ACS usually have more localised infiltrates consistent with consolidation rather than a more diffuse pattern [20–23].

Pulmonary fat embolism is associated with ACS [24]. The emboli are derived from the infarcted and necrosed bone marrow. The fat is turned into free fatty acids in the lung's blood vessels, promoting inflammation and endothelial damage. Fat embolism is shown in autopsy studies. In the living, the diagnosis of pulmonary fat embolism is based on the presence of fat-laden macrophages in the bronchoalveolar lavage (BAL). However, BAL cannot be performed in every ACS case.

Pulmonary vessel infarction is another cause of ACS. The misshapen red cells obstruct the pulmonary vessel leading to exacerbations of hypoxemia. CT pulmonary angiogram (CTPA) is not routinely done in patients with ACS. However, Dessap et al., in a prospective study, have shown a 17% prevalence of pulmonary artery embolism detected by CTPA [25].

Management of ACS

There are no randomised clinical trials for the ACS. ACS is potentially fatal; therefore, early diagnosis and treatment are essential. The treatment aims to minimise irreversible lung damage that leads to long-term sequelae.

Oxygen supply should be given to maintain SpO_2 levels beyond 95%. SpO2 levels should be regularly monitored. ICU specialists should be informed in case of an increased need for oxygen support. Noninvasive ventilation (NIV) has been used in ACS cases with severe hypoxia. The NIV could reduce the need for intubation and mechanical intubation. Bilevel positive pressure (BiPAP), continuous positive pressure support (CPAP), and high-flow oxygen can be used in trained centers and wards [26,27]. NIV lowers the respiratory rate, raises PaO2, and reduces heart rate. Mechanical ventilation may be required in patients with worsening acute respiratory despite NIV or with a failing level of consciousness [9,28]. Furthermore, few reported cases of successful use of veno-venous extracorporeal membrane oxygenation (VV-ECMO) despite the increased risk of haemolysis and thrombosis from SCD [29,30].

Intravenous (IV) hydration should be provided to all patients with ACS. The amount of IV crystalloids needed depends on the patient's cardiopulmonary status. Fluid intake and outtake should be closely monitored to avoid fluid overload and acute pulmonary oedema.

In many cases, ACS is accompanied by VOC affecting the thoracic bones (sternum, ribs, and thoracic spines). The chest pain affects normal breathing and leads to lung atelectasis. Therefore, sufficient pain relief treatment can ameliorate breathing function. Acetaminophen, non-steroid anti-inflammatory drugs and opioids can be used. Other drugs, such as inhaled nitric oxide, have not been proven effective [31]. However, opioid overdose can lead to alveolar hypoventilation and ACS [32]. A strategy that can lead to lower doses of morphine is patient-controlled analgesia. It is a strategy in which the patients can titrate the analgesia by themselves, leading to lower cumulative doses of morphine [33].

Incentive spirometry can be combined with the

appropriate pain relief to reduce the incidence of ACS in case of thoracic bone infarction. It is studied in the pediatric population and post-operative setting [34–36]. Usually, ten inspirations every two hours when the patient is awake are sufficient. Despite the encouraging results in the pediatric population, incentive spirometry was not proven effective in adult patients. In a recently published small randomised trial, incentive spirometry did not significantly reduce the incidence of ACS [37].

As mentioned above, ACS cannot be distinguished from lower respiratory tract infections. Therefore, antibiotics are recommended in all cases [9]. Despite the lack of randomised controlled trials on this topic [38], all patients should receive community-acquired pneumonia treatment. It should be noted that the antibiotic regimen covers causes of atypical pneumonia, such as *Mycobacterium pneumoniae* and *Chlamydia pneumoniae*. Ceftriaxone plus a macrolide (azithromycin or clarithromycin) or a fourth-generation fluoroquinolone such as moxifloxacin or levofloxacin can be used [39].

The use of blood transfusions is a generally accepted clinical practice in the context of critically ill ACS patients [40]. However, no randomised clinical trials support this practice, except for one inconclusive trial due to a small group of participants [41]. Not all patients with ACS require a blood transfusion. The clinician should choose between a simple or top-up transfusion and an exchange transfusion. A simple transfusion can be used when the patient is anaemic. An exchange transfusion can be used when the patient is severely ill or continues to deteriorate despite the simple transfusion. A haemoglobin higher than 9 gr/dl before the exchange transfusion is preferred [9]. Most clinicians aim at haemoglobin S (HbS) levels lower than 30-40% when performing exchange transfusions.

Corticosteroids have been used in the treatment of ACS. The patients recovered faster but had higher readmission rates due to recurrent VOCs [42,43]. Moreover, a small retrospective study showed that inhaled corticosteroids do not decrease the morbidity of ACS [44]. Therefore, the use of corticosteroids is generally not suggested. Patients with ACS in combination with acute asthma or COVID-19 may be the exception [9,45,46].

ACS prevention

Hydroxyurea (HU) has been used for VOC prevention. The drug elevates the HbF levels, interrupting the elongation of deoxy-HbS polymers, decreases the adhesion of blood cells to the vascular endothelium, and finally improves vascular tone. It is shown that HU reduces the ACS in the first year of the treatment. The beginning dose is 15 mg/kg/day and gradually increases to the maximum tolerated dose (usually 30-35 mg/kg/day) [47,48]. If the HU is ineffective or cannot be tolerated by the patient, long-term transfusion may be a solution. It is shown that sickle cell patients that receive long-term transfusions for stroke prevention or silent cerebral infarct prevention have lower rates of ACS [49,50]. The major side effect of chronic transfusion is iron overload. Individuals receiving frequent transfusions should receive chelation therapy and monitor with MRI for liver haemochromatosis [40].

Another option, in case HU is not tolerated or is ineffective, is disease-modifying drugs such as crizanlizumab and L-glutamine. It is not proven that these drugs are effective in preventing ACS. However, they reduce the preceding VOCs. It is to be noted that the L-glutamine is not approved by the European Medicines Agency (EMA). Voxelotor is a recently approved drug that acts as an HbS polymerisation inhibitor. Voxelotor increases haemoglobin and reduces haemolysis. It is yet unclear whether the voxelotor improves the clinical symptoms of SCD [51].

Hopefully, new drugs are on the way, such as the first-in-class, oral, small-molecule allosteric activator of pyruvate kinase, mitapivat. This drug is being evaluated in clinical trials and is expected to increase haemoglobin levels and reduce VOCs and other complications like ACS, osteonecrosis, and nephropathy [52].

Another strategy for reducing the risk of ACS is infection prevention. The prophylactic use of penicillin V until at least the age of five years, pneumococcal vaccination, and annual influenza vaccination are highly recommended. Apart from the routine vaccination series with the pneumococcal conjugate vaccine PCV13, children with SCD should receive the pneumococcal polysaccharide vaccine PPSV23 at age of two years for additional protection against *S. pneumoniae* with a booster given at five years of age. The influenza vaccine should be started at the age of six months. There is no evidence for prophylactic antibiotics to prevent ACS in patients with VOC [9,36,53].

Long term complications

Interstitial lung disease and pulmonary hypertension were considered long-term complications of recurrent ACS, although no causation is documented [8]. Radiologic studies have shown increased scarring

and fibrotic lesions in patients with repeated ACS [54]. Furthermore, a case series study showed diffuse cystic lung disease in SCD patients, which has never been reported again, although a correlation with ACS was not established [55]. A relatively recent study from Nigeria in paediatric patients showed that abnormal lung function assessed by spirometry was correlated with repetitive ACS [56]. An older study in the adult population showed only a trend toward lower total lung capacity and haemoglobin-adjusted diffusing capacity in those with repeated ACS [57].

CONCLUSION

ACS is a complication and a common cause of death in patients with SCD [58]. However, mortality has decreased over the years with the introduction of antibiotics, vaccinations, hydroxyurea use, and therapeutic education for families. VOC prevention can lead to less ACS incidence and a better quality of life [59]. Hydroxyurea has shown effectiveness against the complications of SCD and ACS. New studies should address ACS's incidence, morbidity, and mortality in the post-hydroxyurea era. Furthermore, new drugs recently approved for SCD need to prove effective in preventing ACS. Apart from these classical treatment approaches, ongoing and planned gene therapy trials aim to cure SCD.

In addition, patients with suspected ACS should be aggressively treated. Oxygen supply, hydration, pain relief, and blood transfusions are the cornerstones in the management of ACS (Figure 1). The role of novel drugs in shortening hospital staying or ACS outcomes is unknown. Clinical trials regarding the optimal management of ACS are needed.

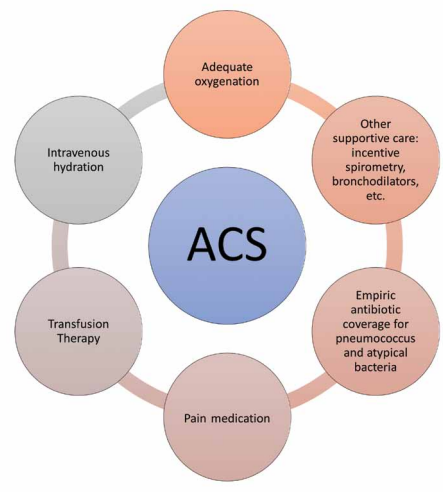

Figure 1. The main cornerstones in treating ACS.

Overall medical advances have changed the quality of life of SCD patients in the last decades, yet many aspects need improvement. Lastly, action should be taken to ameliorate the disparities between SCD patients with different socio-economic or racial statuses to have access to medical care and optimal management of their disease complications [60].

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Management of hospitalised patients with dyspnea

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Abstract

Dyspnea is one of the most common symptoms that can be presented in hospitalised patients. Its perception differs from individual to individual and can be described in many different ways. However, according to its definition, "dyspnea is a subjective experience of breathing discomfort that consists of qualitatively distinct sensation that varies in intensity" and represents a differential diagnosis problem for the clinical doctor. Its causes are variant, while the accompanying clinical signs may not be specific for the underlying condition. Thus, its diagnosis and treatment are challenging. In this review, we aim to delineate the diagnostic process and present the therapeutic options in the management of patients that are hospitalised in the Department of Internal Medicine and manifest the symptom of dyspnea. We also provide insights into the specific treatment algorithms of the most common causes of dyspnea such as pneumonia, pulmonary embolism, Chronic Obstructive Pulmonary Disease, and asthma.

Key words: *Dyspnea; hospitalized patients; management*

INTRODUCTION

Dyspnea, also known as shortness of breath or breathlessness, represents one of the most common cardinal symptoms in patients seeking medical care both at an outpatient and at an inpatient setting. The subjective nature of dyspnea, as it is a symptom and not a clinical sign, is responsible for the different descriptions patients use to express it: "difficulty of breathing, hunger of air, like breath hold, shortness of breath etc.". Its manifestation varies among individuals and its pathophysiology is very complex. The aetiological factors of dyspnea are based on multiple underlying physiological alterations, also on social conditions that may trigger this kind of individualised response. The spectrum of the disorders manifesting with dyspnea is very broad, with pulmonary and cardiovascular diseases taking the lion's share [1]. The differential diagnosis may be very challenging in daily clinical practice and, thus, an extensive clinical history and a thorough clinical examination are of the greatest importance. The evaluation and management of patients with dyspnea varies, depending mainly on the clinical setting. A specific clinical approach should be followed in hospitalised patients presenting the symptom of dyspnea, as the wide range and the severity of the related co-morbidities may cause life-threatening conditions. In this review, we aim to analyse the mechanisms and the different causes of dyspnea, the clinical manifestations and the management of patients in the inpatient setting of the Department of Internal Medicine in order to shed more light in the demanding approach of the hospitalised patients with dyspnea.

Definition of dyspnea

According to the Consensus Statement of the American Thoracic Society [2], the term dyspnea is defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity"

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and may be either acute or chronic. The characterisation of dyspnea as acute is "when it appears suddenly or within at most a few hours in a patient who has not previously complained of shortness of breath" and as chronic if "lasting longer than one month" [2,3]. The different sensations that patients experience and describe as dyspnea are the feeling of not enough air in inspiration, description of effort of breathing, chest tightness and inability of deep breathing [4]. The assessment of dyspnea should be evaluated by the severity of these sensations and the degree of the involved distress. Especially, in hospitalised patients, dyspnea is more likely of acute onset and its management depends mainly on the underlying cause.

PATHOPHYSIOLOGY OF DYSPNEA

Dyspnea occurs when there is a mismatch between the need for ventilation and the physical breathing. Every moment the brain assesses via the afferent receptors whether the efferent-motor commands to the ventilatory muscles are able to provoke the necessary lung movements in order to retain a normal airway pressure and air flow. If the correspondence to the motor command is not appropriate, then the dyspnea becomes more intense sending signals to the sensory cortex that are interpreted as a sensation of muscular effort and breathlessness [2,5,6].

CAUSES OF DYSPNEA

There is a wide range of conditions and diseases that can manifest with dyspnea with the following [3] being the most common ones that should be considered in differential diagnosis:

- *Upper airway obstruction*: This can be caused from a foreign body into the trachea, angioedema (most related to NSAIDS, ACE inhibitors), anaphylaxis (drugs, food allergies) and laryngeal, pharyngeal inflammation (epiglottitis, tonsillitis)
- *Lower airway disorders*: COPD, asthma, and aspiration (mainly due to mental status disorders, neurological dysphagia)
- *Conditions affecting the pulmonary parenchyma*: pneumonia, acute respiratory distress syndrome, neoplasms (superior vena cava syndrome, pneumothorax, pleural effusion)
- *Cardiac aetiology*: pulmonary embolism, aortic dissection, pulmonary hypertension, acute pulmonary oedema, acute myocardial ischaemia, acute valvular regurgitation, acute pericarditis, arrhythmias, cardiomyopathies
- *Neuromuscular diseases*: Myasthenia gravis, Guillain Barre syndrome, Duchene muscular dystrophy, stroke, motor neuron disease
- *Chest wall disorders:* Unstable chest, thoracic trauma
- *Anaemia*
- *Metabolic acidosis*
- *Sepsis*
- *Psychogenic causes (anxiety)*

However, during hospitalisation a patient will present most of the times the symptom of acute dyspnea, with the aetiologic causes being more specific. Acute central nervous system impairments (stroke), acute cardiac (acute coronary syndrome, pericardial effusion) and pulmonary causes (exacerbation of COPD, hospital-acquired infection, pulmonary embolism, pleural effusion) represent the most common causes of dyspnea in the inpatient setting. Other conditions, like musculoskeletal trauma (rib fracture), acute abdomen, ascites and allergic reaction may also provoke the symptom of dyspnea.

Clinical evaluation and management of hospitalised patient with dyspnea

The goal of the initial assessment of a patient with dyspnea is to recognise the characteristics of dyspnea, its type, and any accompanying symptoms. A detailed patient's medical and social history and a thorough clinical examination can provide much information regarding the type of dyspnea (acute dyspnea or exacerbation of a chronic condition), and its individual characteristics (orthopnoea, trepopnoea, platypnoea). By this way, the severity of dyspnea and the degree of urgency are determined. Warning signs that require immediate attention must be considered carefully as the cause of dyspnea may be life-threatening for the patient. These 'red flags' include dyspnea that occurs out of an emotional or exercise setting, mental status alterations, accompanying tachypnoea, chest wall retractions, hypotension, chest pain, cyanosis, stridor, unstable arrhythmia [4]. Nevertheless, under any circumstances and regardless of the cause of dyspnea the following steps are required:

1. Evaluation of patient according to ABCDE (Airway, Breathing, Circulation, Disability, Exposure)
2. Clinical stabilisation
3. Concomitant development of differential diagnosis algorithm for the determination of the cause of dyspnea

Clinical examination

In order to find the underlying cause of dyspnea, the

thorough clinical examination is of major importance and may provide crucial findings to help in the limitation of differential diagnosis. The most important findings from clinical examination and the associated underlying cause are presented in Table 1 [7].

Relevant special investigations

Laboratory tests

A Complete Blood Count and Metabolic Panel should be done in all hospitalised patients with dyspnea. Evaluation of inflammatory markers needs to be done for exclusion of inflammation. The NT pro BNP (B-type natriuretic peptide) can be also measured to rule out heart failure as a cause of acute dyspnea, High sensitivity Cardiac troponin to rule out ACS and D-Dimers can be used to exclude pulmonary embolism (PE). However, there is evidence that its negative predictive value is poor in hospitalised patients, especially after several days of hospitalisation, or in patients >60 years of age [4].

Imaging tests

Chest radiograph is the first line imaging modality that can be used to help the attending physician to identify the cause of dyspnea in the hospitalised patient [8]. This examination may confirm the diagnosis of pneumonia, pleural effusion, pneumothorax or cardiogenic

Table 1. *Clinical signs and underlying cause of dyspnea.*

Clinical sign	Underlying cause
1. Inspection	
1. a. accessory respiratory muscles use	ARDS, severe COPD, severe asthma exacerbation
1. b . jugular vein distention	
- with crackles in the lungs	Acute Heart failure, ARDS
- with normal auscultatory findings	Cardiac tamponade, massive pulmonary embolism
1. c. paleness of skin	Severe anaemia
1. d. peripheral oedema	Congestive HF
2. Chest Percussion	
2. a. Tympanic sound	Pneumothorax, emphysema
2. b. dullness	Consolidation, pleural effusion
3. Auscultation	
3. a. Of lungs	
- Diffuse crackles	Pulmonary edema
- Thick localized crackles	Pneumonia
- Medium late inspiratory crackles	Pulmonary fibrosis
- Decreased respiratory wheeze	Emphysema, severe asthma, hemothorax, pneumothorax, pleural effusion
3. b. Of heart	
- heart murmurs	Valvular disease
- reduce cardiac sounds	Cardiac tamponade
- intense S2 sound	Pulmonary hypertension
- pulsus paradoxus	Cardiac tamponade, massive PE, cardiogenic shock
4. Hemodynamic disorders	
4. a. Hypertension	Hypertensive crisis, ACS
4. b. Hypotension	Sepsis, massive PE

Abbreviations: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; HF, heart failure; PE, pulmonary embolism; ACS, acute coronary syndrome

pulmonary oedema. More specific investigations like V-Q scan and computed tomography of pulmonary arteries (CTPA) are proved to be useful to rule out the diagnosis of PE. A normal V-Q scan is reliable in the exclusion of PE, while a high probability V-Q scan has a positive predictive value of over 90% for the diagnosis of PE [9].

Other diagnostic tests

The heart ultrasound can be diagnostic for conditions like acute cardiogenic pulmonary oedema, valvulopathies, pulmonary hypertension, pericardial effusion, and restrictive pericarditis, which can be manifested with dyspnea. Also, spirometry is useful in the evaluation of obstructive airway disorders.

Management

The goal in a patient with dyspnea is to treat the underlying cause and relieve his/her symptoms. The latter can be achieved by placing the patient in the most appropriate position, providing supplemental oxygen, and adopting relevant medication maneuvers. The treatment of the underlying cause is condition specific.

We provide below the management algorithms for the most common causes of dyspnea in hospitalised patients in the Department of Internal Medicine.

Pneumonia

A hospitalised patient may suffer mainly from two types of pneumonia: Hospital-acquired pneumonia and Ventilator-associated pneumonia [10].

Hospital-acquired pneumonia (HAP) is diagnosed in patients with clinical features and imaging consistent with pneumonia, occurring >48 hours after admission to the hospital and excluding any infections present at the time of admission.

Ventilator-associated pneumonia (VAP) requires clinical features concerning new pneumonia with positive respiratory samples developing >48 hours following endotracheal intubation and mechanical ventilation.

When the physician suspects that the patients may suffer from one of these types of pneumonia, the first step in management is to proceed to new imaging tests after the onset of the new symptoms. A chest radiograph is easy to obtain and can provide with evidence of parenchymal lung involvement confirming the diagnosis. However, computed tomography (CT) scan is considered the gold standard for detection of pulmonary infiltrates, but its use is limited due to the inability to be performed at the bedside.

The laboratory tests are also of great importance in establishing the diagnoses and in monitoring the progress of the disease (inflammatory marker), while microbiology test can be of tremendous value in hospitalised patients, particularly those with severe sepsis or septic shock, as determining a causative organism can significantly improve mortality.

While no severity scoring system has been well validated in patients with HAP, once the diagnosis of pneumonia is established, antibiotic treatment should be initiated without delay. In patients with HAP, empiric antibiotic treatment should be adjusted to the individual risk factors for antibiotic resistance rather than disease severity. Empiric antibiotics should cover *S. aureus*, *Pseudomonas*, and nosocomial gram-negative bacilli, based mainly on the colonisation of each Department.

Adjunctive therapies to deal with dyspnea in patients with HAP should be considered. Non-invasive positive pressure ventilation and oxygen delivered through high-flow nasal cannula (HFNC) have been studied in patients with acute respiratory failure and they have been shown to decrease intubation rates and mortality. Venturi masks and nasal oxygen can also be used as alternatives, based on patients' clinical condition and medical history.

Hospitalised patients with impaired swallowing (chronic obstructive pulmonary disease, neurological diseases such as stroke), impaired consciousness (acute stroke, head injury, brain lesions), increased chance of gastric contents reaching the lung (reflux and tube feeding), and impaired cough reflex (medications, stroke, dementia) may develop pneumonia due to aspiration. Patients with this type of pneumonia may present with dyspnea as well. The same process with the other types of pneumonia should be followed for the diagnosis and treatment [11]

Pulmonary Embolism (PE)

PE should be considered in all patients with acute dyspnea. The most common clinical features are acute onset of dyspnea (> 75% of cases), tachycardia and tachypnoea (up to 50% of cases), sudden pleuritic chest pain (~ 20% of cases), cough and hemoptysis, and associated features of Deep Vein Thrombosis (DVT), e.g., unilaterally painful leg swelling [12,13].

The initial evaluation of patients with suspicion of PE typically includes laboratory studies, chest X-ray, electrocardiogram, blood gas, D-Dimers, CT chest, ventilation/perfusion scintigraphy (V/Q) scan and computed tomography pulmonary angiogram CTPA.

ECG

ECG related findings in patients with PE are sinus tachycardia, signs of right heart strain, SIQIIITIII-pattern, new right bundle branch block (incomplete or complete), T-wave inversion in V1–V4, atrial fibrillation.

D-Dimers

The normal value of D-dimers (Normal levels: < 500 ng/mL) has a high negative predictive value to exclude PE [14]. An increased value requires further testing as it may be present in other situations like myocardial infarction, pneumonia, sepsis, malignancies [15].

CTPA

CTPA is the most precise test for the diagnosis of acute PE in hospitalizsed patients (14). Intraluminal filling defects of pulmonary arteries are considered a direct finding of PE. Also, a wedge-shaped infarction with pleural effusion is almost pathognomonic for PE [16,17].

Ventilation/perfusion scintigraphy (V/Q scan)

V/Q scan is an alternative to CTPA in patients with contraindications for iodinated IV contrast. The absence of perfusion in normally ventilated areas of the lung (mismatch) suggests PE [14,16].

Chest x-ray

Characteristic findings at chest X ray in PE are the: [16]

Hampton hump: a wedge-shaped opacity in the peripheral lung with its base at the thoracic wall; caused by pulmonary infarction and not specific for PE

Westermark sign: an area of lung parenchyma lucency caused by oligaemia secondary to occlusion of blood flow

Normal chest X-ray in a patient with dyspnea and hypoxemia, raises the suspicion for PE.

Classification of PE

According to the American Heart Association (AHA) and American College of Chest Physicians (ACCP) guidelines PE is classified as: [18]

- Massive PE is defined as: persistent hypotension of systolic blood pressure (SBP) < 90 mm Hg lasting >15 minutes or requiring inotropic support, pulselessness, or bradycardia < 40 beats/ minutes.
- Sub-massive PE is: a PE without systemic hypotension (SBP >90 mm Hg) but with right ventricular (RV) dysfunction. RV dysfunction is based on either imaging (CTPA or transthoracic echocardiogram) or elevated biomarkers (BNP, NT-proBNP, or elevated troponin).
- Low-risk PE is: an acute PE without hemodynamic instability and without RV dysfunction.

Treatment of PE

As general principles, we should provide oxygen therapy in hypoxic patients and treat PE based on severity and bleeding risk as shown in Table 2 [19-21].

Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) is characterised by airway obstruction due to inflammation of the small airways [22]. COPD begins with chronic airway inflammation that usually progresses to emphysema, a condition that is characterised by irreversible bronchial narrowing and alveolar hyperinflation. These changes cause a loss of diffusion area, which can lead to inadequate oxygen absorption and CO2 release, re-

Table 2. *Pulmonary embolism treatment by severity and bleeding risk.*

Pulmonary Embolism Treatment by severity and bleeding risk		
	Bleeding risk	
	Low	High
Low-risk PE	- Anticoagulation in most patients - Outpatient management is often appropriate	- Consider a temporary IVC filter
Sub-massive PE	- Anticoagulation - Consider thrombolysis for PE	-Consider a temporary IVC filter -Consider embolectomy for PE
Massive PE	- Thrombolysis for PE followed by anticoagulation - Embolectomy for PE if thrombolysis fails	-Embolectomy for PE

Abbreviations: IVC, inferior vena cava; PE, pulmonary embolism.

sulting in hypoxaemia and hypercapnia. Most affected individuals present with a combination of dyspnea and chronic cough with expectoration [23].

Clinical presentation and lung function tests are the key for the diagnosis, and typically show a decreased ratio of forced expiratory volume (FEV) to forced vital capacity (FVC). The disease severity and the extent of possible complications can be assessed by imaging studies such as chest x-ray, but they are not required to confirm the diagnosis. The patient's oxygenation status can be assessed by aertial blood gas and pulse oximetry.

The staging system of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) should be used for the staging of patients with COPD. GOLD groups A-D are calculated based on the history of exacerbations and severity of symptoms (Table 3) [22].

Treatment

Treatment options depend on the GOLD group and mainly consist of short- and long-acting bronchodilators (beta-agonists and parasympatholytics) and glucocorticoids. Individuals with advanced disease may benefit from non-pharmacological treatment with oxygen supplementation and/or noninvasive ventilation [24].

More specifically, the treatment for each group is:

Group A: For a few symptoms and low risk of exacerbation the recommended treatment is a bronchodilator: LABA (Long-acting β2-receptor agonists) or LAMA (Long-acting muscarinic antagonists)

Group B: For many symptoms and low risk of exacerbation the recommended treatment is a bronchodilator: LABA or LAMA

Group C: For a few symptoms and high risk of exacerbation the recommended treatment is LAMA. During exacerbation LABA/Inhaled corticosteroids (ICS) is recommended

Group D: For many symptoms and high risk of exacerbation the recommended treatment is LAMA or LAMA + LABA or LABA/ICS.

Combination of LAMA + LABA is considered the best one for reduction of exacerbations.

In case of advanced disease long-term oxygen therapy (LTOT) and ventilatory support should be considered. LTOT increases survival in patients with COPD [22].

Asthma

Asthma is a chronic inflammatory disease of the respiratory system characterised by bronchial hyperresponsiveness, acute asthma exacerbations, and reversible airflow obstruction [25]. The cardinal symptoms of asthma are intermittent dyspnea, cough, and high-pitched expiratory wheeze. Symptoms remit in response to antiasthmatic medications or resolve spontaneously upon removal of the trigger.

The most common clinical features of asthma are dyspnea, orthopnoea, persistent dry cough, accessory respiratory muscles use and end-expiratory wheezes [26].

Management of a patient with asthma

The goals in the management of asthma are 1) to control the symptoms with antiasthmatic medication and adjunctive therapy, 2) to reduce the risk of exacerbations [27].

There are five levels of treatment with two "tracks" depending on the choice of reliever: ICS- formoterol (Track 1, preferred) or short-acting beta-agonists (SABA) (Track 2, alternative] [28]. All are described in Table 4.

Acute coronary syndrome (ACS)

Dyspnea can be present in patients with ACS. Supportive measures like oxygen therapy (2-4 L/min) provided with a face mask or nasal prongs should be considered in patients with severe dyspnea and signs of heart failure or shock. This support should aim to the

Table 3. *ABCD group assessment (GOLD report 2022).*

	Exacerbations in the past year	Severity of symptoms	
		mMRC dyspnea scale	CAT score
COPD group A	• 0	0–1	0–9
COPD group B	• Or 1 not leading to hospital admission	≥ 2	≥ 10
COPD group C	• ≥ 2	0–1	0–9
COPD group D	• Or ≥ 1 leading to hospital admission	≥ 2	≥ 10

Abbreviations: COPD, Chronic obstructive pulmonary disease; CAT, COPD Assessment Test

Table 4. *Levels of treatment for asthma patient.*

Controller and preferred reliever (Track1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever	**STEPS 1-2** As-needed low dose ICS-formoterol	**STEP 3** Low dose maintenance ICS-formoterol	**STEP 4** Medium dose maintenance ICS-formoterol	**STEP 5** Add-on LAMA Refer for phenotypic assessment +/- anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-formoterol	
	RELIEVER: As-needed low dose ICS-formoterol				
Controller and alternative reliever (Track2). Before considering a regimen with SABA reliever. Check if the patient is likely to be adherent with daily controller	**STEP 1** Take ICS whenever SABA taken	**STEP 2** Low-dose maintenance ICS	**STEP 3** Low-dose maintenance ICS-LABA	**STEP 4** Medium/high-dose maintenance ICS-LABA	**STEP 5** Add-on LAMA Refer for phenotypic assessment +/- anti-IgE, anti-IL5/5R, anti-IL4R Consider high-dose ICS-LABA
	RELIEVER: As-needed short-acting β2-agonist				
Other controller options for either track		Low-dose ICS whenever SABA taken or daily LTRA, or add HDM SLIT	Medium-dose ICS, or add LTRA, or add HDM SLIT	Add LAMA or LTRA or HDM SLIT, or switch to high-dose ICS	Add azithromycin (adults) or LTRA, add low-dose OCS but consider side-effects

Abbreviations: ICS, inhaled corticosteroids; SABA, short-acting beta-agonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonists; HDM SLIT, house dust mite- sublingual immunotherapy; OCS, oral corticosteroids

maximum oxygen saturation rates according to the patients' status and history. Also, pain relief medications (IV opioids) should be administered to relieve the pain and sedative drugs could be considered in agitated patients. Then the algorithm for the management of ACS should be followed [29].

Pleural effusion

Pleural effusion is often diagnosed using chest x-ray and ultrasound, but chest CT may be used for very small effusions [12]. Thoracentesis serves as both a diagnostic and therapeutic procedure: pleural fluid analysis can help identify the underlying cause and excess pleural fluid evacuation can provide symptomatic relief [30]. Treatment of pleural effusion often focuses on treating the underlying condition.

In unstable patients, e.g., those with dyspnea, respiratory failure, beginning of respiratory support should be considered along with urgent therapeutic thoracentesis [12,31].

Dyspnea in oncologic patient- Superior vena cava syndrome (SVC syndrome)

SVC syndrome is caused by the severe obstruction or occlusion of the SVC and can result in severe morbidity and mortality. Signs and symptoms of SVC syndrome are facial oedema, nonpulsatile distended neck veins, dyspnea and cough, arm oedema, syncope and headache, and confusion. Parenteral glucocorticoids and loop diuretic agents are commonly used medications in SVC syndrome to relieve symptoms. However, definitive treatment depends on the underlying condition and can include chemotherapy with or without radiotherapy, surgical bypass, or endovascular treatment such as angioplasty [32].

Dyspnea in critically-ill patients and in the context of palliative care

Dyspnea is one of the most common symptoms in critically ill patients, mainly in patients suffering from cancer, with an estimated prevalence close to 50% [33]. Dyspnea may also be the most challenging symptom to treat than other symptoms (i.e. pain) commonly seen in this category of hospitalised patients [34].

Several underlying mechanisms are related to the development of dyspnea in critically ill patients and the most common causes can be divided into:

a) malignant: direct tumour effects (i.e. bronchial compression), malignant effusions (i.e. pleural, pericardial effusion) and treatment-related (i.e. lobectomy or pneumonectomy)
b) Non-malignant: due to comorbidities (i.e. congestive heart failure, asthma, COPD)

The management of dyspnea begins by the correction of the underlying cause. However, in the patients with refractory dyspnea and especially in the cases of irreversible causes the cornerstone of treatment is opioids. Their effectiveness has been evaluated in multiple studies [35-37].

The use of supplementary oxygen may improve dyspnea in hypoxemic patients (SaO2 < 88%) but it appears to have little benefit in dyspneic patients with normal SaO2 [38]. Nevertheless, supplementary oxygen is prescribed in the majority of dyspneic patients despite the lack of evidence.

The role of bronchodilators and increased cortisol requirements (given orally or nebulised) are always considered reasonable treatment options. Antibiotic step up is necessary in deteriorating patients with severe lung infections. Finally, in the cases of severe illness with a compromised airway settings of non-invasive and invasive ventilation are needed.

Dyspnea and compromised airway

In some cases, dyspnea may be caused by a compromised airway and then intubation may be indicated. Severe respiratory destress in situations like airway trauma with oedema, angioedema, epiglottitis, severe asthma, cystic fibrosis, lung parenchyma impairment and chest trauma, dictates urgent need for keeping airway patency. In all the aforementioned situations the goal is to prevent or to manage appropriately the respiratory failure.

Psychogenic causes of dyspnea

Some psychiatric disorders may manifest with breathlessness. Patients who experience severe anxiety feel the need for more air or they have the impression that the air in the room is not enough. Panic Attacks are another cause of dyspnea. The temporary feeling of choking is common in people who experience panic attacks. These disorders become more intense in the hospital setting, as parameters like fear, stress, and pain interfere in the psychology of the patient. Thus, psychological causes of dyspnea may be more prominent in the hospitalised patients.

CONCLUSIONS

Dyspnea is a very common symptom among hospitalised patients in the Department of Internal Medicine. Its causes are various, and the differential diagnosis may be challenging. Physician should always have in mind that they have to deal with a multifactorial condition, due to the wide range of comorbidities that requires appropriate management. The tools of patient's history, clinical examination, and specific tests, as well as the management algorithms for each condition should be used effectively to lead to the treatment of the disorder that causes the symptom of dyspnea.

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Occult Hepatitis B virus (HBV) infection: A hidden threat

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Abstract

Occult hepatitis B infection (OBI) is described as the existence of detectable hepatitis B virus (HBV) DNA by polymerase chain reaction (PCR) in serum or liver, in patients who test negative for HBsAg. According to the presence of serum markers of HBV exposure, OBI can be categorised as seropositive or seronegative, based on serological profiles. Furthermore, OBI may occur because of the infrequent infection by strains that have escape mutations in the S gene, modifications that may cause structural abnormalities in HBsAg, making the infection difficult to detect by the commonly used serological detection tests. OBI's treatment is exceptionally difficult. Its purpose is to enhance patients' quality of life by delaying and preventing the development of liver failure, cirrhosis, and hepatocellular carcinoma. HBV DNA carriers with OBI may transmit HBV infection via blood transfusion. The more sensitive diagnostic tools used for blood screening can significantly reduce the risk of HBV transmission. To eradicate viral hepatitis by 2030, the World Health Organization adopted the Global Health Sector in 2016, but the current lack of effective treatment and detecting methods, challenge this goal. The need to discover new antiviral medications and treatment methods is the biggest problem facing HBV research today.

Key words: *Occult hepatitis B infection; OBI; HBV DNA; HBV surface antigen*

INTRODUCTION

HBV infection

Hepatitis B virus (HBV) is a hepatotropic virus that can provoke a persistent and chronic infection in individuals through immune anergy [1]. Approximately 33% of the current world population has previously been exposed to HBV. From those an estimated 240 million individuals are chronically infected, and approximately 800,000 people worldwide die each year from this infection [2]. Currently, 3.5% of the global population is chronically infected with HBV, although the incidence of HBV infections is decreasing owing to vaccination and, to a lesser extent, the use of antiviral therapy to reduce the viral load of chronically infected individuals [1]. Well-defined serum and liver biopsy diagnostic markers allow the evaluation of disease severity, viral replication, risk stratification for a patient, and the appropriate treatment decisions. Current treatment includes antiviral agents that directly affect viral replication and immunomodulators [1].

There are ten unique genotypes of HBV (A-J), and the geographical distribution of each HBV genotype is distinct. Different genotypes of HBV infection are linked to different chronicity after infection, disease progression, and IFNα treatment responses; nonetheless, the approved HBV vaccines are effective against all genotypes [1].

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A silent evolution characterises HBV infection's natural history, because typically, the disease is diagnosed decades after infection. An immunoenzymatic assay or a rapid test can detect HBV infection [3]. The presence of HBsAg in the serum is the key serological maker of both acute and chronic hepatitis B [1]. Laboratory confirmation is essential because it is impossible to distinguish hepatitis B from other viral hepatitis types clinically. Notably, HBV infection is asymptomatic in 80% of infected individuals. If the result is positive, the diagnosis is confirmed by carrying out complementary tests, such as liver biopsy, to search for other markers or using molecular tests to directly detect HBV DNA [3].

Acute HBV infection is characterised by the presence of HBsAg and an immunoglobulin M antibody for the core antigen. The HBeAg is found in the initial phase of infection. An immune-tolerant phase is characterised by a typically high viral load in the blood that is responsible for high infectivity [3].

Chronic infection is marked by the persistence of HBsAg for at least six months (with or without HBeAg), while the load of HBV DNA determines the rest serologic profile and, consequently, the need for treatment. The persistence of HBsAg is the main risk factor for the development of liver cirrhosis and hepatocellular carcinoma (HCC) [3].

Taking into consideration the presence of HBeAg, HBV DNA levels, alanine aminotransferase (ALT) values and the existence or absence of liver inflammation, chronic HBV infection can be classified into five stages (Table 1).

i) **HBeAg-positive chronic HBV infection** is characterised by the presence of serum HBeAg, very high levels of HBV DNA (>10^7 IU/m) and ALT within the normal range. In the liver, there is no or minimal liver necroinflammation or fibrosis but a high level of HBV DNA integration and clonal hepatocyte expansion. Due to high levels of HBV DNA, patients are highly contagious [4].
ii) **HBeAg-positive chronic hepatitis B** is characterised by the presence of serum HBeAg, high levels of HBV DNA (10^4 -10^7 IU/ml) and elevated ALT. In the liver, there is moderate or severe liver necroinflammation and rapid development of fibrosis [4].
iii) **HBeAg-negative chronic HBV infection** is characterised by the presence of anti-HBe, HBV DNA levels < 2,000 IU/ml and normal ALT. In the liver, minimal necroinflammatory activity and low fibrosis [4].
iv) **HBeAg-negative chronic hepatitis B** is characterised by the lack of serum HBeAg, normally with detectable anti-HBe, and moderate to high levels of serum HBV DNA (>2.000 IU/ml), alongside elevated ALT values. As regards the liver, there is necroinflammation and fibrosis [4].
v) **HBsAg-negative phase** is characterised by serum negative HBsAg and positive anti-HBc, with or without detectable anti-HBs. This phase is widely known as "occult HBV infection". In this phase, we have normal ALT values and ordinarily undetectable serum HBV DNA. HBV DNA (cccDNA) can be detected often in the liver [4].

Occult HBV infection

Definition of Occult HBV infection

HBV DNA can be found only in serum or the liver in cases of occult hepatitis B infection (OBI) where hepatitis B surface antigen testing is negative. This is described as the existence of detectable HBV DNA by polymerase chain reaction (PCR) in patients who test negative for HBsAg. According to the international Taormina statement, occult HBV infection is defined as the presence of replication-competent HBV DNA (i.e. episomal HBV

Table 1: *Stages of chronic HBV infection, classified by the presence of HBeAg, HBV DNA levels, ALT values and the existence or absence of liver inflammation.*

	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	+	+	-	-
HBV DNA	>10^7 IU/ml	10^4 -10^7 IU/ml	<2.000 IU/ml	>2.000 IU/ml
ALT	Normal	Elevated	Normal	Elevated
Liver disease	None or minimal	Moderate/severe	None	Moderate/severe

Abbreviations: HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase

covalently closed circular DNA [cccDNA]) in the liver - in individuals who test negative for HBsAg (whether or not HBV DNA is present in the blood or liver) [5].

OBI may occur as a result of the infrequent infection by strains that have escape mutations in the S gene; these modifications cause structural abnormalities in HBsAg, making the infection difficult to detect by the commonly used serological detection tests. OBI may also result from mutations (substitutions, deletions, and insertions of nucleotides) in the pre-S1 and pre-S2 regions, which reduce or prevent HBsAg expression [3].

In a small minority of OBI subjects, the absence of serum HBsAg can be associated with an infection with HBV genetic variants containing mutations at the S gene level that result in the production of modified HBsAg which cannot be detected even by commercially sensitive testing. In these cases, serum HBV DNA levels may be as high as those normally detected in subjects with "overt" HBsAg-positive infection. Also, HBV DNA can be integrated into the host's genome in individuals with OBI. However, integrated viral sequences are not involved in HBV replication, and their existence does not affect the diagnosis of OBI, as OBI usually occurs in cases with persistence of replication-competent HBV DNA [5].

According to the presence of serum markers of HBV exposure, occult hepatitis B can be categorized as seropositive or seronegative OBI, based on serological profiles. About 80% of all instances of OBI are referred to be seropositive, which is defined as those who have antibodies to the HBV core antigen (anti-HBc) and/or antibodies to HBsAg (anti-HBs) that are detectable in the serum. A smaller proportion (between 1% and 20% of instances) of OBIs are referred to as seronegative OBIs [3,5].

Albeit the clinical features that distinguish OBI-seropositive from OBI-seronegative cases remain completely cryptic, OBI can be exhibited in one of three clinical forms:

(a) during an acute HBV infection window period, (b) detectable HBV DNA and undetectable HBsAg in patient serum without an overt HBV infection previous history, (c) in individuals who have a history of chronic HBV infection [6].

The main reason behind the growing interest in OBI is related to accumulating evidence of its clinical impact. Indeed, (a) it can be transmitted to the recipient, primarily through blood transfusion or liver transplant; (b) in case of immunosuppression, it may result in viral reactivation; (c) it might have a detrimental effect on the progression of chronic liver disease of various causes into more advanced clinical stages; (d) It significantly contributes to the development of HCC [7].

Prevalence of Occult HBV infection

Although occult hepatitis B infection was first described more than 30 years ago [8], there are several important aspects of this disease, including its natural history, factors involved and effective diagnostic tools, that have not been fully elucidated yet. Occult hepatitis B infection is widespread worldwide, with high prevalence in high-risk populations for HBV or living in areas where HBV infection is prevalent [3].

Occult hepatitis B infection is commonly associated with classical hepatitis B in infected individuals consistent with the expected clinical picture (i.e. with typical serological and clinical patterns of infection). It can occur in multiple clinical situations, such as cases where HBV infection is reactivated after the development of an immunodeficiency, which can result in acute hepatitis or fulminant hepatitis [9]. The sensitivity of HBsAg and HBV DNA assays, the existence of risk factors for HBV exposure, the prevalence of HBV among the general population in different geographic areas, the existence and adherence of anti-HBV vaccination programs in various countries, and the presence and severity of liver disease in the examined populations are just a few of the many factors that influence the worldwide epidemiology of OBI [6].

In fact, the majority of studies on OBI prevalence have been carried out on liver disease patients and blood donors, so, they do not truly represent the population as a whole. There are a few studies that indicate a low OBI prevalence in Asian and African regions with high endemicity of HBV infection, despite the fact that OBI prevalence is higher in areas of the world where hepatitis B is endemic. High OBI prevalence has been found in groups of patients with risk factors for HBV infection, for instance, intravenous drug users (45%), subjects with HCV co-infection (15-33%) or HIV co-infection (10-45%), patients on dialysis (27%), and patients with co-existing liver disease, for example, those with HCC (63%), cryptogenic cirrhosis (32%), or liver-transplant patients (64%) [7]. The relatively high prevalence reported in HCV or HIV-infected populations and HCC patients may be biased by the fact that clinical investigations are being conducted more frequently in these populations. Hepatitis B virus serological profiles suggest that the estimated OBI rate in anti-HBc- positive patients varies between 4% and 25% [3,5].

Risk of Occult HBV infection-Transmission - Blood Transfusion

Numerous studies have demonstrated that HBV DNA carriers with OBI may transmit HBV infection via blood transfusion, resulting in typical hepatitis B in the recipient. The more sensitive diagnostic tools used for blood screening have significantly reduced the risk of HBV transmission over the past 30 years through blood transfusion [7]. However, despite the widespread availability of anti-HBc tests and nucleic acid testing (NAT), the transmission of HBV from OBI blood donors remains a significant public health concern in low- and middle-income nations [7]. Because the minimum dose of infectious HBV DNA is below the lower limit of detection of the NAT assays that are currently in use, there is still a minimal risk of OBI transmission through transfusion in developed countries [7].

If the donor is an OBI carrier, the transmission relies upon many variables, for example, how much plasma is transfused, the immune status of the recipient, and the HBV serology status of both donor and recipient [10]. Additionally, an OBI carrier may be intermittently infectious due to the fact that OBI is characterized by periods of transient viremia alternated with phases of absence of serum viral replication [10]. HBV DNA positive OBI donors with an isolated anti-HBc serological marker have been shown to be more infectious than anti-HBs positive OBI carriers, and the recipient's anti-HBs positivity significantly lowers the risk of infection [10].

Diagnosis of Occult HBV infection

The detection of HBV DNA in the blood or liver of individuals who test negative for HBsAg is necessary for the diagnosis of OBI. The detection of HBV genomes in DNA extracts from the liver is regarded as the gold standard [7]. HBV DNA testing in the blood, on the other hand, is a much more common diagnostic method and generally easier to perform. Anti-HBc testing may be used as a substitute marker for the diagnosis of OBI primarily for the purpose of identifying potential seropositive OBI subjects in cases of blood, tissue, or organ donation and when immune suppressive therapy has to be initiated [7].

Currently available HBsAg assays have a limit of detection of 0.05 IU/mL, and some recent studies showed that between 1% and 48% of samples testing negative in these assays resulted positive using more sensitive HBsAg assays with a lower limit of detection of 0.005 IU/mL [11,12]. Another issue is the different ability of commercial HBsAg assays to detect S-escape variants [9]. The lower limit of detection of most currently available commercial HBV DNA assays is 10 to 20 IU/mL. In addition, HBV DNA is usually present at low levels in people with OBI and can only be detected intermittently, so blood samples collected at multiple time points and testing DNA extracts from no less than 1 mL of serum or plasma, is recommended for the diagnosis of occult HBV infection [5]. Furthermore, NAT assays that are highly specific (99.9%) and sensitive (LLOD 2–4 IU/mL) are used for blood donations. However, sensitivity significantly decreases when NAT screening is performed on minipools of multiple donations [7].

Reliable methods for detecting OBI include nested PCR techniques, real-time PCR methods whereas digital techniques include droplet PCR assays. NATs are increasingly being applied using primers containing three or more, conserved regions covering the S, X and core genes [3,13].

Escape mutations in the S region is a main challenge in OBI detection. HBsAg assays that are insufficiently sensitive or unable to detect variants in this region, usually give false negative HBsAg results and therefore misdiagnosis. Molecular tests for HBV may also be inadequately sensitive. There is currently no standardized and validated test in order to detect OBI. Several studies have attempted to standardize a technique based on internal tests, but differences in sensitivity and specificity have limited their successful application [3,5].

Treatment of occult HBV infection

Indications for treatment in chronic HBV infection are based on the levels of serum HBV DNA, ALT and severity of liver disease. Treatment indications are typically similar for HBeAg-positive and HBeAg-negative diseases [7]. Treatment is generally indicated for those with HBV DNA levels >2000 IU/mL, and elevated levels of liver enzymes, 1-2 times the upper limit of normal [14]. In the presence of cirrhosis, treatment is frequently advised in cases of detectable HBV DNA levels independent of the ALT levels. Furthermore, patient's age, a family history of liver cancer, comorbidities, risk of HBV transmission and extrahepatic manifestations of hepatitis B, are some factors we can take into consideration for the indication of treatment. Treatment for acute HBV infection is primarily supportive, and antiviral treatment is often not necessary unless patients have fulminant liver failure [7].

OBI is exceptionally difficult to be treated because current HBV therapeutic strategies fail to eliminate the

HBV minichromosomal reservoir (cccDNA / integrated HBV DNA) from all infected cells [3]. In order to find a cure for HBV, the current research and clinical trials aim to develop novel antiviral strategies. It is probably impossible to completely sterilize all tissues with the elimination of cccDNA and integrated HBV DNA. As a result, the current focus is on achieving functional cure, which is defined as HBsAg clearance in a high percentage of patients after a limited course of treatment [15].

In patients with chronic HBV infection, spontaneous or treatment-induced HBsAg clearance has been shown to reduce liver necroinflammation and, consequently, the risk of cirrhosis, HCC, and HBV-related mortality [5].

However, HBV DNA positive patients with elevated levels of liver enzymes, during or after direct acting oral antivirals (DAA) therapy should be monitored at regular intervals (once every 4 weeks) for possible reactivation of HBV [3].

To eradicate HBV from people with OBI, HBV infected hepatocytes would either need to be eliminated or cured. Theoretically, there are several options:

-Elimination of cccDNA within infected hepatocytes, using cccDNA targeting procedures like CRISPR/Cas9 technologies or gene editing techniques [5].

-Killing infected hepatocytes by using strategies directed at restoring HBV-specific T cell responses, therapeutic vaccination strategies, engineered T cell treatments like chimeric antigen receptor (CAR-T) cell technologies or HBV-T cell receptor (TCR) engineered T cells to kill the remaining infected liver cells [5].

This would require not only adapting these innovative technologies to this clinical application, but also gaining a deeper comprehension of the biology of cccDNA and immune control, along with the number of infected hepatocytes in the case of occult HBV infection [5].

With the primary goals of: (a) stopping treatment with no risk of virological relapse and no risk of liver disease progression; and (b) further decreasing the risk of HCC, numerous research programs are currently underway to develop new treatment concepts that concentrate on the clearance of HBsAg in a significant proportion of patients [16].

Direct antivirals and immunotherapeutic drugs can be used to classify the innovative treatment alternatives currently undergoing pre-clinical and early clinical research. HBV entry inhibitors, drugs aiming at cccDNA destruction or silencing, approaches targeting viral transcripts by siRNA or anti-sense oligonucleotides, nucleocapsid assembly modulators, approaches to decrease HBsAg release in serum are all examples of direct-acting antivirals. This list is not meant to be comprehensive as many viral targets are currently being screened for drug discovery. First phase clinical trials are ongoing for several of these agents [16].

Occult HBV infection and challenges to the HBV elimination strategy

To eradicate viral hepatitis by 2030, the WHO adopted the Global Health Sector Strategy (GHSS) in 2016. With this strategy WHO aims to decrease by 2030 the frequency of hepatitis to 0.9 million cases and will reduce annual deaths because of hepatitis from 1.4 million to 0.5 million [2].

The WHO is assisting a number of nations in the development of hepatitis control programs in this regard. In order to eliminate hepatitis by 2030, five strategic areas are listed in the GHSS document. Due to our current lack of an effective treatment, most of them target HBV. The following are the focus areas: (a) expansion of HBV vaccination coverage (b) prevention of transverse transmission of HBV (c) parental transmission care (d) reducing harm and co-infection, and (e) broadening the availability of HBV and HCV testing and treatment [2].

CONCLUSION

The WHO proposes increasing early HBV diagnosis and treatment in addition to expanding preventive vaccination coverage [2]. To aid in the treatment of OBI, coordinated clinical studies of therapies that eliminate cccDNA are required. The detection of "false OBI" would also benefit from an increase in diagnostic sensitivity for HBsAg detection. One of the main challenges associated with OBI and the elimination of HBV, is the significant unmet need to develop specific, sensitive and standardized tests for the detection of OBI. Screening for anti-HBc, HBV DNA NAT with a LOD of 0.8 copies/ml (0.15 IU/ml), or pathogen reduction of blood components, are some methods that can increase HBV blood safety. Treatment is not necessary for OBI unless it is complicated [3].

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An unusual presentation of *Datura Stramonium* intoxication mimicking encephalitis in Western Greece

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Abstract

Datura stramonium, also known as Thorn Apple or Jimson Weed, is an alkaloid-containing plant that is entirely toxic. The active toxic constituents of the plant are atropine, scopolamine and hyoscyamine. Herein, we present an unusual case of *Datura stramonium* poisoning that occurred after eating accidentally *Datura* flowers. The patient was presented with encephalitis-like symptoms and was cured successfully.

Key words: *Datura Stramonium; poisoning; encephalitis; misidentification; alkaloids*

INTRODUCTION

Toxic plant exposures have become more and more frequently, due to increased interest in exploring the surrounding environment. That has created health concerns, especially for nature adventurers [1]. Accordingly, identification mistakes contribute to accidental significant toxicity.

Datura Stramonium (also known as Thorn Apple, jimson weed, devil's snare) is a characteristic example of misidentification in toxic plant exposure. It belongs to the belladonna alkaloid family. It is found in temperate and subtropical regions across the world, including Europe, North Africa, North America, eastern and northwestern Asia [1].

Datura Stramonium has been widely reported to be very toxic. Its frequent poisoning effect (intentional or accidental) may be intricately linked to its ubiquitous nature, ease of contaminating foodstuffs and portable water [2]. On the other hand, the plant also has anti-inflammatory and stimulatory effects on the central nervous system (CNS), active clearing effect on the respiratory tract thereby aiding the respiratory system as well as keeping the teeth and skin healthy.

Herein we present an unusual case of *Datura stramonium* poisoning that occurred after eating accidentally *Datura* flowers. The patient appeared with neurological symptoms that were resolved after supportive care.

CASE PRESENTATION

A previously healthy 71-year-old male was referred from a local medical centre to the Emergency Department of the University Hospital of Patras, in Western Greece, for further investigation due to acute onset of confusion and speech disturbances.

Upon admission, the patient showed exclusively confusion, tachycardia, and mydriasis. No concomitant symptoms such as fever, headache, nuchal rigidity, photophobia, vomiting and weakness, were reported. Specifically, signs of meningeal irritation (Kernig and Brudzinski) could not be elicited. The rest of the physi-

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cal examination was unremarkable. The patient was haemodynamically stable and respiratory competent.

The emergency laboratory work-up with complete blood count with differential, full biochemical profile, coagulation studies, inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) and urinalysis were normal (Table 1). An arterial blood gas analysis did not show any abnormalities.

The chest X-ray and electrocardiogram were also normal. A contrast enhanced Computed Tomography (CT) of the head demonstrated no abnormalities such as recent ischaemic stroke or cerebral haemorrhage (Figure 1).

Lumbar puncture was performed with normal cerebrospinal fluid analysis results. The patient underwent further investigation with electroencephalogram (EEG), which did not reveal any epileptiform activity.

The patient was empirically treated with acyclovir (10mg/kg every 8h) and crystalloids intravenously and a brain magnetic resonance imaging was scheduled for the next day. After five hours, the patient's neurological state improved dramatically, and he became fully alert and oriented without any neurologic deficit. He recalled consumption of cooked *Amaranthus blitum* about one hour before symptom onset. In Greece, *Amaranthus blitum* is not rarely grown together with other widely distributed toxic plants like ***Datura stramonium,*** **therefore,** the suspicion of poisoning with the later plant was raised. The patient remained hospitalised for 24 hours without any further treatment and was discharged healthy. He was asked to bring us some photographs of the plant he had collected,

Table 1. *Laboratory parameters upon admission and discharge day.*

	Admission Day	Discharge Day	Reference rates (Units)
WBC	7,48	5,70	4,0 – 11 K/ml
Hematocrit	41,10	40,30	36,0 - 52,0mg/dl%
Hemoglobin	13,80	13,00	11,8 - 17,0 g/dl
PLT	276,00	255,00	150 – 400 K/µl
Glucose	130	100	75 – 115 mg/dl
Sodium	141,0	139,0	134 – 152 mmol/l
Potassium	4,7	4,4	3,8 – 5,5 mmol/l
Urea	32	21	15 – 54 mg/dl
Creatinine	0,8	0,9	0,9 - 1,6 mg/dl
SGOT	13	15	5 – 40 U/l
SGPT	11	12	5 – 40 U/l
ALP	49	59	34 – 104 U/l
LDH	153	156	120 – 230 U/l
γGT	10	10	10 – 50 U/l
CPK	41	73	< 190 U/l
CRP	0,40	0,81	>0,80 positive
TotalBilirubin	0,39	0,80	0,1 - 1,3 mg/dl
Albumin	4,5	4,5	3,5 - 5,5 g/dl
Arterial Blood Gas:	PH: 7.42 PO_2: 79.9, PCO_2: 37.6 HCO_3: 24.6	—	PH: 7.35-7.45 PO_2: 100mmHg PCO_2: 35-45mmHg HCO_3: 23-27 mmol

Abbreviations: WBC: white blood cells, RBC: red blood cells, PLT: platelets, SGOT: serum glutamic- oxaloacetic transaminase, SGPT: serum glutamic- pyruvate transaminase, ALP: alkaline phosphatase, CPK: creatine phosphokinase, LDH: lactate dehydrogenase, γGT:gamma- glutamyl transferase, CRP: C- reactive protein

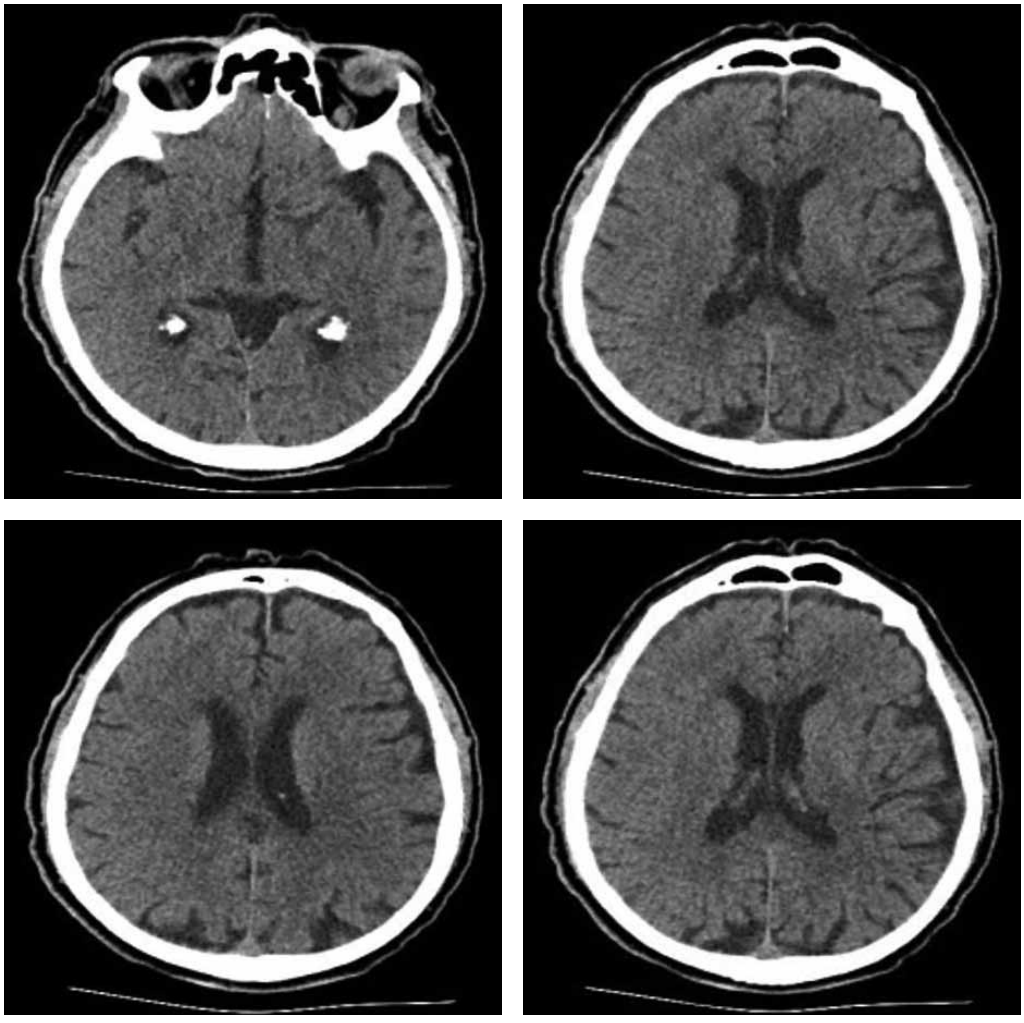

Figure 1. Brain CT demonstrated no abnormalities.

which confirmed the diagnosis of poisoning by *Datura stramonium* (Figure 2).

DISCUSSION

Datura is one of the oldest and most frequently abused psychoactive plant species. It causes anticholinergic toxicity since it contains atropine, scopolamine and hyoscyamine [3]. *D. stramonium* is toxic by attacking various organs, such as the liver, heart, kidney, and brain. Its toxicity varies and depends on the solvent used for its extraction [2]. Typical clinical symptoms of its intoxication are those of atropine intoxication, which are ataxia, impaired short-term memory, disorientation, confusion, hallucinations (visual and auditory), psychosis, agitated delirium, seizures, coma, respiratory failure, and cardiovascular collapse [4]. These symptoms result from the inhibition of central and peripheral muscarinic neurotransmission [5]. One hundred units of *Datura* seeds contain approximately 6 mg atropine, which may be fatal. Half a tea spoon of Datura seeds contains approximately 0.1 mg atropine, on average. Although atropine is present in all parts of the plant, the highest concentration is in the seed and the root [3].

The seeds of *Datura stramonium* appear similar to tomato seeds since its seeds are flat, disk shaped, and brown too. Moreover, this widely distributed plant in the Greek rural areas, is often grown concomitantly with other toxic plants like *Amaranthus blitum* and can be accidentally harvested for cooking together with blitum leaves. In 2006, seven people in Greece were hospitalised after having consumed a salad of *Amaranthus blitum*. Public health authorities discovered the toxic plant *Datura stramonium* harvested among the normally cultivated blita in the Megara region west to Athens and sold in supermarkets [6].

We report herein a case of accidental poisoning by *D. Stramonium* manifested exclusively with symptoms of

Figure 2. Images from *Datura Stramonium* from the area our patient visited.

encephalitis. In our case, poisoning occurred as a result of collecting *Datura stramonium* plant after confusing it with *Amaranthus blitum*. The similar appearance of the *Datura* flowers and the *Amaranthus blitum* flowers may have led to the accidental poisoning.

Interestingly, our case is similar in many aspects to the case reported by Oberndorfer et al. [7]. This could be explained assuming that, comatose patients, because of *Datura* intoxication, demonstrate a rather stereotyped pattern of neurological findings. Moreover, this unusual presentation of *Datura stramonium* should draw attention to the fact that *Datura stramonium* intoxication may present even in a coma.

There are many cases of *Datura* poisoning with neurological manifestations in the literature. In a 2008 study published by Wiebe et al, delirium developed in four patients due to *Datura stramonium* poisoning [3,8]. Seung-Han Suk et al, reported poisoning in two elderly women who were brought to the emergency department because of anticholinergic syndrome. The patients displayed agitated behaviour, confusion, urinary retention, dry mouth, and dilated pupils within three hours of ingesting the dried seeds of *Datura stramonium*. Patients were discharged with a complete recovery after receiving conservative therapy for five days [9].

Specific antidote for tropane alkaloid toxicity is physostigmine salicylate, a reversible acetylcholinesterase inhibitor capable of directly antagonising CNS manifestations of anticholinergic toxicity. The patient improved without administration of any specific antidote treatment. Its role has been controversial in the management of *D. Stramonium* poisoning. This is due to its potential adverse effects secondary to acetylcholine accumulation [8,10].

Datura Stramonium may be accidentally used as a food ingredient. Since its poisonous effects are not known to the public, the general population should be informed and warned. Educational public health programs should be organised for preventing poisoning associated with *Datura Stramonium*.

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Author Contributions: *ML, ST, CD: wrote the manuscript, PG: treated the patient, SS, MM: revised and approved the manuscript*

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