THE 5TH JAKARTA INTERNATIONAL CHEST AND CRITICAL CARE INTERNAL MEDICINE 2017

Editor Team:
Ceva Wicaksono Pitoyo
Gurmeet Singh
Indah Mastuti
Stephanie Gita Wulansari
Desy Safitri

Respirology and Critical Illness Division, Internal Medicine Department,
Faculty of Medicine Universitas Indonesia
Welcome Message

Dear Colleagues,

Welcome to The 5th Jakarta International Chest and Critical Care Internal Medicine, (JICCCIM) 2017 organized by the Division of Respirology and Critical Illness, Department of Internal Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital.

Following the success of JICCCIM 2016, we proudly present JICCCIM 2017 as the 5th annual international event in respirology and critical care. You will be given a big opportunity to get lectures, workshop and hands on (interventional pulmonology and critical care) in respiratory medicine and critical care internal medicine with our international and national caliber of medical experts and academicians.

We would like to express my appreciation for the contributions from various organizations, sponsors and individuals for their full support for this event. Finally, to all of participants, We hope you can enjoy and get benefits from all of our sequence of symposiums and workshops.

Regards,

[Signatures]

dr. Ceva W. Pitoyo, SpPD, KP, KIC, FINASIM
Chairman JICCCIM 2017

dr. Gurmeet Singh, SpPD, KP
Head of Organizing Committee
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Organizing Committee
The 5th Jakarta International
Chest and Critical Care Internal Medicine 2017

Patron Advisor : Dr. dr. Zulkifli Amin, SpPD, KP, FCCP, FINASIM
Dr. dr. C. Martin R, SpPD, KP, FCCP, FINASIM
Dr. Anna Uyainah ZN, SpPD, KP, MARS, FINASIM

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Treasurer : dr. Mira Yulianti, SpPD

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Dr. Anna Uyainah ZN, SpPD, KP, MARS, FINASIM
Dr. Ceva Wicaksono P, SpPD, KP, KIC, FINASIM
Dr. Telly Kamelia, SpPD, KP, FINASIM
Dr. Eric Daniel Tenda, SpPD
Dr. Mira Yulianti, SpPD
Dr. Herikurniawan, SpPD
Dr. Stephanie Gita
Desy Safitri, SKM

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Indah Mastuti, SKM

Workshop : dr. Mira Yulianti, SpPD
Dr. Herikurniawan, SpPD
Indah Mastuti, SKM
Zr. Ida Ayu Prastiti

Publication : dr. Stephanie Gita
Febriyanti, AMD
Fetty Novian Pulungan, AMD

Logistics : dr. Mira Yulianti, SpPD
Ns. Ita Juwita
Zr. Widya Rosliana Dewi
Muhammad Faiz
Krisna Adhi Wijaya
Sumawarni

Secretariat : Indah Mastuti, SKM
Desy Safitri, SKM
Fetty Novian Pulungan, AMD
Febriyanti, AMD

Registration : dr. Gurmeet Singh, SpPD, KP
Fetty Novian Pulungan, AMD
Febriyanti, AMD
Tegar Prasetyo
M. Yunus
Iswanto

Documentation : dr. Herikurniawan, SpPD
Syamsul Hadi

Poster Session : dr. Stephanie Gita
Desy Safitri, SKM
Moderators, Speakers And Facilitators
The 5th Jakarta International Chest and Critical Care Internal Medicine 2017

International Speakers
Chun-Hsing Liao (Taiwan)
Daniel S. Tan (Philipina)
Devanand Anantham (Singapore)
Maria Ercanita B. Limpin (Philipina)
Wen-Jue Soong (Taiwan)
Pallav Shah (UK)

Local Speakers
Achsanuddin Hanafie (Indonesia)
Arto Yuwono Soeroto (Indonesia)
Ceva Wicaksono Pitoyo (Indonesia)
Chrispian Oktafbipian Mamudi (Indonesia)
Didik Setyoheryianto (Indonesia)
Eko Budiono (Indonesia)
Eric Daniel Tenda (Indonesia)
Fera Ibrahim (Indonesia)
Gurmeet Singh (Indonesia)
I Made Bagiada (Indonesia)
Maria A. Witjaksono (Indonesia)
Mira Yulianti (Indonesia)
Rudi Putranto (Indonesia)
Soekamto (Indonesia)

Local Moderators
Anna Uyainah (Indonesia)
Aryanto Soewono (Indonesia)
Arto Yuwono Soeroto (Indonesia)
Asril Bahar (Indonesia)
Azhar Tanjung (Indonesia)
Ceva Wicaksono Pitoyo (Indonesia)
Cleopas Martin Rumende (Indonesia)
Telly Kamelia (Indonesia)
Yana Ahmad (Indonesia)
Zen Ahmad (Indonesia)
Zulkifli Amin (Indonesia)

Local Facilitators/Instructors
Achsanuddin Hanafie (Indonesia)
Cleopas Martin Rumende (Indonesia)
Eric Daniel Tenda (Indonesia)
Fauzar (Indonesia)
Gurmeet Singh (Indonesia)
Ita Juwita (Indonesia)
Ida Ayu Prastiwi (Indonesia)
Mira Yuliandi (Indonesia)
M. Ilyas (Indonesia)
Samsirun Halim (Indonesia)
Thomas Handoyo (Indonesia)
Wahyuni Indawati (Indonesia)
Widy a Dewi Rosliana (Indonesia)
General Information

Congress Name
The 5th Jakarta International Chest and Critical Care Internal Medicine.

Date

Congress Venue
JICCCIM 2017 will be held at Indonesia Kempinski Hotel, Jakarta, Indonesia.

Event Language
JICCCIM 2017 is in English.

Speaker’s Ready Room
The Speaker ready room will be located at the workshop venue and will be equipped high technology equipments.

PERPARI Meeting
The PERPARI Meeting will be held on 25th of March 2017 at Ballroom Indonesia Kempinski Hotel. This PERPARI Meeting will be hosted by The President of the Indonesian Society of Respirology and Critical Care.

Invitations Letter
An official invitation letter can be produced from the online registration system. Please contact the congress secretariat for any special request. This letter should not be considered as an offer of financial support from the organizers.

Certification on Attendance
All participants will be issued a certification of attendance. The certificate will be ready for collection from the registration desk on March 26th, 2017.
## Schedule of The 5th Jakarta International Chest and Critical Care Internal Medicine 2017

**Saturday, 25th March 2017**

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<td>07.00 – 08.00</td>
<td>REGISTRATION</td>
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<td>08.00 – 08.30</td>
<td>BPJS Policy on Patient Palliative Homecare</td>
<td>Director of Health / Vice</td>
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<tr>
<td>08.30 – 09.00</td>
<td>Patient Safety in Palliative Care in the Field of Respirology</td>
<td>dr. Maria A. Witjaksono MPaICI</td>
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<tr>
<td>09.00 – 09.05</td>
<td>Welcome Speech PB PERPARI*</td>
<td>Head of PERPARI/Vice</td>
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<td>09.05 – 09.10</td>
<td>Welcome Speech IDI*</td>
<td>Head of IDI/Vice</td>
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<tr>
<td>09.10 – 09.15</td>
<td>Welcome Speech PAPDI*</td>
<td>Head of PAPDI/Vice</td>
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<td>09.15 – 09.30</td>
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<td>09.30 – 09.50</td>
<td>Dual Bronchodilators : a New Phenomenon in COPD Treatment?</td>
<td>Prof. Daniel S. Tan, MD (Philipina)</td>
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<tr>
<td>09.50 – 10.10</td>
<td>Update GOLD 2017 : Refined ABCD Assessment Grid and Treatment Algorithm</td>
<td>dr. Ceva Wicaksono Pitoyo, SpPD, KP, KIC</td>
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<td>10.10 – 10.15</td>
<td>Discussion</td>
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<td>10.15 – 10.35</td>
<td>Diagnosis of Lung Cancer</td>
<td>dr. Eko Budiono, SpPD, KP (Yogya)</td>
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<td>10.35 – 10.55</td>
<td>Biomolecular Testing in NSCLC</td>
<td>dr. Didik Setyoheriyanto, SpPA, PhD (RS Sardjito)</td>
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<td>10.55 – 11.00</td>
<td>Discussion</td>
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<td>11.00 – 11.20</td>
<td>How to Choose Appropriate and Adequate Antibiotic for CAP Patients with Renal Dysfunction</td>
<td>Maria Ercanita B. Limpin, MD (Philipina)</td>
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<td>11.20 – 11.40</td>
<td>Pulmonary Infection in Palliative Treatment</td>
<td>dr. I Made Bagiada, SpPD, K-P (Denpasar)</td>
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<td>11.40 – 11.45</td>
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<td>11.45 – 12.05</td>
<td>Glutamine (GLN) supplementation in critically ill patients</td>
<td>dr. Chrispiam Oktahipian Mamudi, SpPD-KP (Manado)</td>
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<td>12.05 – 12.25</td>
<td>Nutrition in Palliative Care</td>
<td>dr. Rudi Putranto, SpPD, KpSi</td>
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<td>12.25 – 12.30</td>
<td>Discussion</td>
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<td>Interventional Pulmonology in Advanced Lung Cancer: Cryotherapy and IPC</td>
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<td>dr. M. Ilyas, SpPD, KP (Makassar)</td>
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<td>Ns. Iu Jiwita / Z. Ida Ayu / Z. Widya</td>
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<td>dr. Samsirun Halim, SpPD, KP, KIC (Jambi)</td>
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<td>CVC (Central Venous Catheter)</td>
<td>dr. Fauzar, SpPD, KP (Padang)</td>
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<td>Dr. dr. Cleopas Martin Rumende, SpPD, KP</td>
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<td><strong>Session 5 : Pulmonary MRSA and Fungal Infection</strong></td>
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<td>dr. Mira Yulianti, SpPD</td>
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<td>The Role of Serology and PCR in Diagnosing CMV</td>
<td>dr. Fera Ibrahim, SpMK</td>
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<td>Exacerbation in acute asthma</td>
<td>Dr. dr. Soekamto, S, SpPD, KAI</td>
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<td>Mechanical Ventilation in Acute Asthma</td>
<td>Prof. dr. Achsanuddin Hanafie, Sp.An, KIC</td>
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<td>Dr. Pallav Shah, MD (UK)</td>
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<td>The new novel diagnostics procedure of EBUS-TBNA : the importance of eligible sample</td>
<td>dr. Eric Daniel Tenda, SpPD</td>
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<td>13.30 – 17.00</td>
<td>Cryotherapy and APC</td>
<td>dr. Mira Yulianti, SpPD</td>
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<td>Bronchoscopy : Adult and Pediatric Populations</td>
<td>dr. Wahyuni Indawati, SpA (K) / Wen-Jue Soong MD / dr. Thomas Handoyo, SpPD (Semarang)</td>
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<td>BLVR (Bronchoscopic Lung Volume Reduction)</td>
<td>Dr. Pallav Shah, MD</td>
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<td>Invasive Mechanical Ventilation</td>
<td>Prof. dr. Achsanuddin Hanafie, Sp.An, KIC</td>
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SECTION 1

Symposium
Palliative Care in Respiratory Diseases Supports Patients Safety in the Health Care Quality Movement

Maria A. Witjaksono

Abstract

“The relief of suffering when cure is impossible should become the heart of all medical services. It is what every patient and family hopes for and has a right to expect. Therefore, each health care professional has responsibility to provide it when it is indicated”. Derek Doyle, 1999

Burden of disease experienced by most patients with lung cancer or non malignant chronic respiratory diseases potentially create suffering and poor quality of life.

Palliative Care aims to prevent and relieve suffering by controlling symptoms and to provide other support to patients and families affected by the diseases in order to maintain or to improve their quality of life. Although originally conceived and practiced as end of life care, integration of Palliative Care has been strongly endorsed by Thoracic Society such as ATS (American Thoracic Society) in all stages of disease as a simultaneously delivered approach adjunct to disease-focused treatment. The endorsement was based on evidence that earlier involvement of palliative care contribute to survival benefit.

The role of palliative care in respiratory diseases is to control symptoms along with or when causative treatment cannot be delivered, to support the patient and the family in various aspects of life including psychological, social and spiritual. It assists in communicating and making decision about the care, provides end of life care and bereavement care. For terminally ill patients, palliative care aims to achieve comfort, peace and dignity. Palliative care involves health and other professionals and volunteers.

Patients Safety has become an important aspect in Health Care Quality movement. Patient safety was defined as "the prevention of harm to patients." Emphasis is placed on the system of care delivery that (1) prevents errors; (2) learns from the errors that do occur; and (3) is built on a culture of safety that involves health care professionals, organizations, and patients.

The implementation of palliative care values and principles into daily practice is accordance with patient safety if it is performed by health care professionals who have appropriate level of competence in palliative care, supported by an adequate system and delivered with sensitive to the patients and families’ needs, as well as respectful of their cultural and spiritual values

Keywords: palliative care, respiratory diseases, patient safety

Background

Lung cancer and non-malignant chronic respiratory diseases such as COPD are debilitating disease that results in high disease burden and poor quality of life. The impact of these diseases on daily living is on all aspect of both patient’s and the family’s life and potentially create suffering. An integrated holistic service is required to relieve suffering, to achieve quality of life and to lighten family burden.

Integration of Palliative Care into Health Care System has been suggested as a pragmatic and humane answer to those affected by the disease (WHO, 1999) and an efficient approach in Health Care System. Although Palliative Care is an established medical specialty in many developed countries, its development in Indonesia is rather left behind other ASEAN countries due to various barriers.

One of the advantages of implementation of values and palliative care principles is to support patient safety. As demand of palliative care for patients with respiratory diseases is increasing, strong commitment from various stake holders is required to integrate palliative care in national health system.
Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems --- physical, psychosocial and spiritual. (WHO 2002)

Until recently, physicians tend to perceive palliative care as the alternative to life-prolonging or curative care —“what we do when there is nothing more that we can do” — rather than as a simultaneously delivered adjunct to disease-focused treatment. Although originally conceived and practiced as end of life care, integration of Palliative Care has been strongly endorsed by Thoracic Society such as ATS (American Thoracic Society) in all stages of disease as a simultaneously delivered approach adjunct to disease-focused treatment. The endorsement was based on WHO statement in 2005 that palliative care can be delivered from diagnosis to end of life and bereavement and the evidence that earlier involvement of palliative care contribute to survival benefit.

Palliative Care Principles
- Affirm life and regards dying as normal process (PC is not euthanasia)
- Aims to neither hasten nor postpone death
- Gives the patient a central role in decision making
- Provide relief from distressing symptoms
- Integrates the psychological, emotional, spiritual and social aspects of care for the patients, the family and carers in a culturally sensitive manner
- Avoids futile interventions
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family and carers coping during the patient’s illness and after the patient’s death
- Uses a team approach to address the needs of patients and their care givers

The Role of Palliative Care in Respiratory Diseases
The role of palliative care in respiratory diseases is to control symptoms along with or when causative treatment cannot be delivered and to support the patient and the family in various aspects of life including psychological, social and spiritual. It assists in communicating and making decision about the care, provides end of life care and bereavement care. For terminally ill patients, palliative care aims to achieve comfort, peace and dignity.

Interdisciplinary Team
Palliative care is a holistic approach involves a range of various disciplines and specialist in medical, psychological, social and spiritual domains who meet in a regular basis and perform formal clinical process of patient-appropriate assessment, diagnosis, planning, interventions, monitoring and follow up. It is distinguished from multidisciplinary team where individual work independently and may result in fragmented care. The team consists of a core group of professionals in medicine, nursing, and social worker, and may include chaplain, psychologist, pharmacist, dietician, physical, occupational art, play or music therapist and volunteers. Patients is regarded as both as a central of the care as well as a member of the team. Treatment should accordance to patient’s wishes after she/he choosing options offered by the team and must have his/her consent if possible. Patient’s family is important member of the team. They play a significant role in overall care, therefore their opinion should be included when designing management plan. The family is also target of care.

Patient Safety and Palliative Care

Patient Safety has become an important aspect in Health Care Quality movement. Patient safety was defined as “the prevention of harm to patients.” Emphasis is placed on the system of care delivery that (1) prevents errors; (2) learns from the errors that do occur; and (3) is built on a culture of safety that involves health care professionals, organizations, and patients.

The implementation of palliative care values and principles into daily practice is accordance with patient safety if it is performed by health care professionals who have appropriate level of competence in palliative care, supported by an adequate system and delivered with sensitive to the patients and families’ needs, as well as respectful of their cultural and spiritual values.
The core of Patient safety is prevention of harm. This can be achieved with the application of palliative care principles. Palliative care is not euthanasia. It emphasizes quality of whatever life remains for the patient. It affirms life by supporting the patient’s goal for the future regardless how short the future will be. Palliative Care intends neither to hasten nor postponed death. Assessment and treatment are comprehensively performed using patient-centered approach with a focus on central role of family unit in decision making. Palliative care team guides the patient and the family in making decision that enables them to work toward their goals. Therefore, communication is an essential aspect. Honest communication without losing hope requires special skills to help patients to understand and accept what is happening. Giving false hope in anticancer therapy is avoided as it only gives short advantage but long term difficulties.

Breaking bad news and discussion about prognosis, advance directives, resuscitation and terminal care is performed when initiated by the patients or when the patients agree to do so. Palliative Care respect patient’s right to be involved in the decision making. Prognosis discussions do not dampen hope. It empowers individual by providing realistic expectations and to help them make informed choices about their medical care.

Uncontrolled symptoms are one of the major causes of suffering. One of benefits of integrating palliative care is decreased symptom burden. The use of symptom assessment questionnaire will uncover more bothersome symptoms which need to be managed. The principles of symptoms management in palliative care include correct the correctable, non drug and drug treatment. Palliative Care anticipate problems that might arise and minimize the impact of the progressing illness so that allow the patients live actively as possible with maximum function and comfort until death.

Palliative Care avoids futile intervention. Patients who are referred to palliative care early in the course are more likely to perceive and retain accurate information about prognosis and are less likely to receive aggressive treatment at the end of life. It is believed that overtreatment can cause preventable suffering. Invasive procedures in terminally ill patients often fail to change the course of the disease. Interventions can become inappropriate overtreatment if they result only in disease related and iatrogenic harm to the patient. To facilitate appropriate care and to avoid inappropriate interventions, doctors need to anticipate discordance between their views and those of patients and surrogates. In a hospital setting where the culture is focused on “cure”, continuation of invasive procedures for investigations or treatments directed to patients in advanced disease may not produce the benefits sought by the patient, may results in very short term benefits that offers no realistic change of improvement and may prolongs the dying process which potentially create suffering to the patients, burden to the family and inefficient Health Care System.

Integrating psychological, emotional, spiritual and social aspects of care for the patients, the family and carers in a culturally sensitive manner is an important value applied in palliative care. The stress associated with advanced cancer or other respiratory diseases inevitably induces suffering and may increase other aspects of suffering- pain or other physical symptoms, social difficulties and spiritual problem. On the other hand, untreated pain and other symptoms, social difficulties and spiritual problem will aggravate psychological stress. Therefore, psychological, social and spiritual care must be an integrated part of overall care.

Palliative Care offers a support system to help the family and carers coping during the patient’s illness and after the patient’s death. The relatives of patients with advanced and terminal diseases are subject to considerable emotional, physical, social and spiritual distress, as well as physical tiredness, particularly if the patient is being cared at home. As the success of palliative care is also depend on the family’s ability to cope, attention must be paid to their needs. Emotional support, help with daily tasks and respite are examples of supports to the family.

Summary

Palliative Care aims to prevent and relieve suffering by controlling symptoms and to provide other support to patients and families affected by the diseases in order to maintain or to improve their quality of life. Although originally conceived and practiced as end of life care, Integration of Palliative Care has been strongly endorsed by Thoracic Society such as ATS (American Thoracic Society) in all stages of disease as a simultaneously delivered approach adjunct to disease-focused treatment. The endorsement was based on evidence that earlier involvement of palliative care contribute to survival benefit. The implementation of palliative care values and principles into daily practice is accordance with patient safety.
Palliative Care in Respiratory Diseases Supports Patients Safety in the Health Care Quality Movement

Reference

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Update GOLD 2017: Refined ABCD Assessment Grid and Treatment Algorithm

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Introduction
The management of chronic obstructive pulmonary disease (COPD) has been guided by a global consensus called global initiative for chronic obstructive lung disease (GOLD). The latest revised of the guideline has been published in 2017. The structure and manuscript flow of the guideline are still similar to the 2011 guideline. So are the classification of degree of airflow obstruction (grades 1-4) and the treatment goals for stable COPD, still unchanged. The grouping of A, B, C, D are still existing, but with modifications.

The definition of COPD has been revised by emphasising persistent respiratory symptoms and airflow limitation. There are refinement of ABCD assessment, focusing on respiratory symptoms and exacerbations alone to assign ABCD groups. The role of spirometry is now mainly focused on establishing the diagnosis. Spirometry is no longer recommended for pharmacological treatment decisions (but for non-pharmacological treatments). The importance of assessment and regular evaluation of inhaler technique is also has been highlighted in the 2017’s guideline. There are also updated evidences on non-pharmacologic management.

An exacerbation is now defined as an acute worsening of respiratory symptoms resulting in additional therapy. Symptoms and future risk of exacerbations are now serve as basis for treatment decisions. There is also introduction of strategies for escalation and de-escalation of pharmacotherapy.

Detailed hospital discharge and follow-up criteria are added in GOLD 2017, including integrated team care. Management of comorbidities (cardiovascular diseases in particular) are also discussed in more detail.

Revised Definition of COPD
Previous definition of COPD is a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

Actually the FEV1 decline is not invariably progressive over years in COPD. After all by the UPLIFT study we learned that 8% of subjects had annual increase of >20mL/year.3 The phrase ‘persistent airflow limitation’ has been revised in GOLD 2017. In GOLD 2017, COPD become a common preventable and treatable disease, characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

Based on post-bronchodilator FEV1, GOLD classifies the severity of airflow limitation by 4 groups. Group GOLD 1 is where the FEV1 still at least 80 % of predicted. GOLD 2 is when the FEV1 50 – 79 % of predicted. When FEV1 is 30 – 49 % predicted, it categorized as GOLD 3. GOLD 4 is when the FEV1 below 30 % of predicted. In the first era of GOLD, this classification used to define the severity of COPD and thus guide the treatment. Hurst et al in 2010 showed that exacerbation history is the most powerful single predictor of exacerbations (independent of GOLD Stage).4 GOLD 2011 was then using exacerbations as a component to classify COPD patients. The FEV1 classification in GOLD 2011 was used to stratify airflow limitation but not the patients. In GOLD 2011, patients of COPD were stratified into 4 groups. The A and B patients are they who suffer less airflow limitation, where FEV1 is more than 50 % predicted. Patients with FEV1 less than 50 % predicted or more than 50 % but have two exacerbations or more in the last year are categorized as C or D. In the case where there is no spirometry, the number of exacerbation may replace FEV1 criteria. The A and C groups consist of patients with less symptoms whilst the B and D groups cover patients with more symptoms. The treatment of chronic stable COPD patients is then guided by this grouping.

In GOLD 2017, FEV1/FVC post-bronchodilator less than 70 % is used to diagnose COPD. But FEV1 is not used to classify COPD patients into ABCD grouping anymore. Classifying ABCD is done by number of exacerbation and the score of symptoms. FEV1 is used to do prognostication and non-medication treatment algorithm. Thus
therapy recommendations are based exclusively on respiratory symptoms and exacerbation history. In assessing respiratory symptom, both mMRC (Modified MRC dyspnoea scale) or CAT (COPD Assessment Test) can be used.

As a preferred choice, all group A patients should be offered a short- or a long-acting bronchodilator (dependent on its effect on breathlessness). Continuation with treatment should be done if symptomatic benefit is documented. When symptomatic benefit is not well documented, physicians should stop or try alternative class of bronchodilator.

For group B patients, either LAMA or LABA can be used. No evidence which is superior in this group of patients. If symptoms persist, LAMA/LABA combination is than recommended. LAMA/LABA combination is also recommended since the start of treatment in patients with severe breathlessness. To step back down to 1 bronchodilator has to be considered if the second medication does not improve symptoms. By this recommendation, treatment of group A and B are completely ICS-free.

Starting therapy with a LAMA is the recommendation for group C patients. In case of persistent exacerbations addition of a LABA so the treatment become LAMA/LABA combination is the first choice. Combination of LABA/ICS could be an alternative but patients are on higher risk for developing pneumonia.

Combination LAMA/LABA is recommended from the start in group D since a LAMA/LABA combination was superior to a LABA/ICS combination in preventing exacerbations and other patient reported outcomes in group D patients. For patients with a history and/or findings of concurrent asthma or raised eosinophil count, LABA/ICS may be the first choice. For patients who develop further exacerbations on LAMA/LABA two alternatives are suggested: escalation to triple therapy or switch to LABA/ICS (but no evidence). If triple therapy is inadequate for symptom control, physician may add roflumilast (especially ini chronic bronchitis with low FEV1).

A practical impact of the new ABCD assessment grid exemplified by GOLD group D patients, one may see if we consider two patients – both patients with FEV1 < 30% of predicted and CAT scores > 10, one patient who has < 2 exacerbations in the past year, will now be considered as group B while the other patient who has > 2 exacerbation will still be considered as group D patient.

Further statements/preliminary recommendations

There are also further statements/preliminary recommendations in GOLD 2017 regarding triple combination LAMA/LABA/ICS. At present, evidence is lacking to draw conclusions on the benefit of triple therapy compared to LAMA/LABA. In Group D patients with LAMA/LABA treatment who are still suffering from exacerbations an escalation to triple therapy can be considered to have LAMA/LABA/ICS. If the patients treated with LAMA/LABA/ICS still have exacerbations the addition of the following options may be considered:

- Roflumilast in patients with FEV1< 50% predicted and chronic bronchitis
- A macrolide in selected patients. The best existing evidence of macrolid is azithromycin.

Withdrawal of ICS

GOLD 2017 endorse stopping ICS in case of a lack of efficacy or increased risk of adverse effects (including pneumonia). The discussion on this issue is regarding ICS withdrawal. At present results from ICS withdrawal studies are assessed as inconsistent regarding consequences on lung function, symptoms and exacerbation rates. Nevertheless in GOLD Group D patients the withdrawal of ICS is recommended in patients on triple therapy who do not clearly benefit from ICS.

High blood eosinophil counts may be of help to predict the effects of ICS on exacerbations. Findings of post-hoc analyses of two clinical studies in COPD patients suggest blood eosinophil counts can serve as a biomarker of exacerbation risk in patients with an exacerbation history5. It may also become predictor of the effects of ICS on exacerbation prevention6. Other post-hoc analyses have shown an association between blood eosinophil counts and exacerbation preventio7. Prospective trials are demanded to validate the use of blood eosinophil counts to predict the ICS effect. A similar trial are demanded to to determine a cut-off threshold for eosinophil counts to predict future risk of exacerbations in COPD patients with an exacerbation history and for ICS response. In accordance to this issue, trials also needed to clarify cut-off values that can be used in clinical practice.

ACO(S)

Neither a chapter nor an appendix regarding ACO(S) is present in the current GOLD report 2017. In the context of “differential diagnoses” there is a short note that “the diagnosis Asthma-COPD Overlap Syndrome (ACOS) or Asthma-COPD-Overlap (ACO) has been coined to acknowledge that this represents overlap of common disor-
ders causing chronic airflow limitation rather than a distinct syndrome”. In patients with a history and/or find-
ings suggestive of ACO(S), ICS/LABA treatment may be the first choice.

Management of exacerbations

In GOLD 2017, the guidance on exacerbation is is relatively unchanged, but guidance on exacerbation is extending to hospital discharge. The inclusion of hospital discharge criteria are:

- Full review of all clinical and laboratory data
- Confirmed maintenance therapy and understanding
- Reassessed inhaler technique
- Reassessed need for long-term oxygen
- Documented capacity to do physical activities and activities of daily living
- Documented symptoms by using CAT or mMRCV
- Determined status of comorbidities
- Measured spirometry: FEV₁

GOLD 2017 also recommend 1-4 weeks of follow up and then 12-16 weeks of follow up. Evaluation to patients ability to cope in the usual environment has to be assessed. In the follow up a complete review has to assess the understanding on treatment regimen, reassess of inhaler technique, reassess of long-term oxygen therapy, document the capacity to do physical activity and activities of daily living, document symptoms using CAT or mMRC, determine status of comorbidities and measure spirometry, i.e. the FEV₁.

Comorbidity

Strategies for the management of cardiovascular and other important comorbidities are presented in detail in GOLD 2017. The other important comorbidities are osteoporosis, anxiety and depression, lung cancer, metabolic syndrome and diabetes, gastroesophageal reflux (GERD), bronchiectasis, obstructive sleep apnea, COPD as a part of multimorbidity.

The significance of the assessment and evaluation of inhaler technique has been considerably enhanced in GOLD 2017. Inhaler technique needs to be assessed regularly to improve therapeutic outcomes. Importance of education and training cannot be over-emphasised. Choice of inhaler device has to be individualised and will depend most importantly on patient’s ability and preference. Instructions and demonstration of a proper inhalation technique are essential also a re-check at each visit to ensure a correct use of the inhaler. Inhaler technique (and adherence) should be evaluated before a treatment is assessed as insufficient.

At last, in GOLD 2017, management of stable COPD should be predominantly based on individualised assessment of symptoms and future risk of exacerbations. Appropriate non-pharmacologic interventions should complement pharmacologic treatments.

Summary

Overall key points of new GOLD strategy 2017 are:

- Management strategy for stable COPD should be predominantly based on the individualised assessment of symptoms and future risk of exacerbations.
- The main treatment goals are reduction of symptoms and future risk of exacerbations.
- Management strategies are not limited to pharmacological treatments, and should be complemented by appropriate non-pharmacological interventions.
- All individuals who smoke should be strongly encouraged and supported to quit.
- The ABCD assessment grid has been refined to utilize exclusively respiratory symptoms and exacerbation history to assign groups.
- For each GOLD category more precise treatment recommendations are given, resulting in a shift towards a more personalized approach to treatment, with strategies for escalation and de-escalation of pharmacotherapy.
- Bronchodilator (LAMA, LABA, LAMA/LABA) therapy is key for COPD treatment across the spectrum of patients with COPD in GOLD stage B-D.
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Diagnosis of Lung Cancer

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Background

Lung cancer is the leading cause of cancer death in the United States. In 2015, an estimated 221,000 new cases (115,610 in men and 105,590 in women) of lung and bronchial cancer will be diagnosed, and 158,040 deaths (83,380 in men and 71,660 in women) are estimated to occur because of the disease. Only 17.4% of all patients with lung cancer are alive 5 years or more after diagnosis.

However, much progress has been made recently for lung cancer such as screening, minimally invasive techniques for diagnosis and treatment, advances in radiation therapy (RT) including stereotactic ablative radiotherapy (SABR), targeted therapy, and immunotherapy. Common symptom of lung cancer includes cough, dyspnea, weight loss, and chest pain; patients with symptoms are more likely to have chronic obstructive pulmonary disease (National Comprehensive Cancer Network 2016).

Risk Factor of Lung Cancer

Different cancers have different risk factors. Some risk factors, like smoking, can be changed. Others, like a person's age or family history, can't be changed. Some risk factors of lung cancer (American Cancer Society 2016):

1. Tobacco smoke
   Smoking is by far the leading risk factor for lung cancer. About 80% of lung cancer deaths are thought to result from smoking. The risk for lung cancer among smokers is many times higher than among non-smokers. The longer and the more packs a day someone smoke, the greater the risk. Secondhand smoke: If someone don't smoke, breathing in the smoke of others (called secondhand smoke or environmental tobacco smoke) can increase the risk of developing lung cancer. Secondhand smoke is thought to cause more than 7,000 deaths from lung cancer each year.

2. Exposure to radon
   Radon is a naturally occurring radioactive gas that results from the breakdown of uranium in soil and rocks. Radon is the second leading cause of lung cancer in USA, and is the leading cause among non-smokers.

3. Exposure to asbestos
   People who work with asbestos (such as in mines, mills, textile plants, places where insulation is used, and shipyards) are several times more likely to die of lung cancer. Lung cancer risk is much greater in workers exposed to asbestos who also smoke. It's not clear how much low-level or short-term exposure to asbestos might raise lung cancer risk. People exposed to large amounts of asbestos also have a greater risk of developing mesothelioma, a type of cancer that starts in the pleura (the lining surrounding the lungs).

4. Exposure to other cancer-causing agents in the workplace
   Other carcinogens (cancer-causing agents) found in some workplaces that can increase lung cancer risk include:
   - Radioactive ores such as uranium
   - Inhaled chemicals or minerals such as arsenic, beryllium, cadmium, silica, vinyl chloride, nickel compounds, chromium compounds, coal products, mustard gas, and chloromethyl ethers
   - Diesel exhaust

5. Air pollution
   In cities, air pollution (especially near heavily trafficked roads) appears to raise the risk of lung cancer slightly. This risk is far less than the risk caused by smoking, but some researchers estimate that worldwide about 5% of all deaths from lung cancer may be due to outdoor air pollution.

6. Previous radiation therapy to the lungs
   People who have had radiation therapy to the chest for other cancers are at higher risk for lung cancer, particularly if they smoke. Examples include people treated for Hodgkin disease or women who get radiation after a mastectomy for breast cancer. Women who get radiation therapy to the breast after a lumpectomy do not appear to have a higher than expected risk of lung cancer.
7. Personal or family history of lung cancer

Classification

WHO divides lung cancer into 2 major classes based on its biology, therapy, and prognosis:

1. **Non Small Cell Lung Cancer (NSCLC)**
   - NSCLC accounts for more than 83% of all lung cancer cases, and it includes 2 major types:
     - Non squamous carcinoma (including adenocarcinoma, large cell carcinoma, and other cell type).
       - Adenocarcinoma is the most common type of lung cancer seen in the United States and Asia, and is also the most frequently occurring histology in non-smokers.
     - Squamous cell (epidermoid) carcinoma.

2. **Small Cell Lung Cancer (SCLC)**

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**Figure 1.** Non Small Cell Lung Carcinoma (left), Small cell lung carcinoma (right)
Diagnostic and Staging clinical pathway

Patient presents with features fitting criteria for either chest x-ray or immediate referral for suspected lung cancer

Chest x-ray normal?

Yes

Low suspicion of lung cancer

Yes

Observe manage

No

CT thorax, upper abdomen and lower neck with intravenous contrast administration

Diagnostic and Staging Assessment

Respiratory physician takes history and examines patient including illness assessment, spirometry and basic blood test. Lung Cancer Nurse Specialist is available to support the patient and care's. May include co-ordinators and radiologist. All respect be wishes of the patient.

Choose investigation(s) that give maximum diagnostic and staging information with least risk. Discuss at Lung cancer MDT if complex. Fitness of patient may influence choice and extent of investigations.

CT negative or inconclusive

Peripheral lesion without enlarged mediastinal nodes (<10 mm short axis; low probability of malignancy)

Further investigations or observation depending on clinical/radiological features

Peripheral of central lesion with enlarged lymph node(s) that may determine treatment with curative intent

PCT-CT

If suitable for potentially curative treatment, otherwise skip this step

Peripheral lesion with enlarged lymph node(s) that may determine treatment with curative intent

Mediastinal nodes 10-20 mm short axis i.e. intermediate probability of malignancy

Peripheral of central lesion with enlarged lymph node(s) that may determine treatment with curative intent

Mediastinal nodes >20 mm short axis i.e. high probability of malignancy

Central lesion where nodal status does not influence treatment

Mediastinal nodes

Neck nodes

Clinical/radiological features of advanced metastatic disease

Neck US + biopsy

Consider further imaging e.g. PET-CT or MRI

Pleural lesion

Not the subject of this update

Neural lesion

Biopsy most accessible site

Diagnosis and Stage

Early disease

(Treatment with curative intent)

Consider multi-modality treatment

Advanced disease

(Treatment with palliative intent)

Figure 2. Diagnosis and staging of lung cancer
**Figure 3. Mediastinal Diagnosis and Staging**
Effectiveness of Diagnostic and Staging Investigations

The place of diagnosis and staging investigations is determined by their accuracy in a given situation. In lung cancer, the initial clinical assessment and the information provided by the CT scan is able to classify patients into a limited number of groups that can suggest an appropriate preferred first test and sequence. Some diagnostic tests for lung cancer:

- Positron emission tomography (PET)
- PET with computed tomography (PET-CT)
- Magnetic resonance imaging (MRI)
- Single photon emission computed tomography (SPECT)
- Bronchoscopy ± biopsy
- Transthoracic needle aspiration (TTNA)
- Endoscopic ultrasound fine needle aspiration (EUS-FNA)
- Endobronchial ultrasound trans-bronchial needle aspiration (EBUS-TBNA)
- Non ultrasound-guided TBNA
- Cutting needle biopsy
- Mediastinoscopy
- Video-assisted thoracic surgery (VATS)

PET-CT

PET-CT is now widely used to assess whether a primary lesion is likely to be malignant, to look for evidence of regional lymph node involvement and to detect distant metastases. However, PET-CT cannot provide a pathological diagnosis so there is often the dilemma about whether to obtain tissue, especially given the now well documented limitations of PET-CT.

In SCLC, occult metastases may be detected by PET-CT, however it is not clear in what way these findings should influence decisions about offering treatment with curative intent.

Other Imaging Modalities

- MRI
  MRI is generally superior to CT in its ability to resolve soft tissue anatomy, which was the basis of the 2005 recommendation to use MRI to clarify the extent of superior sulcus tumors, where necessary. MRI is often used in other areas where clarification of anatomy is required, but this was not the subject of an evidence review.

- SPECT
  SPECT imaging can be used in the same way as PET in diagnosis and staging of lung cancer but is not in widespread use.

- Ultrasound
  Ultrasound is a useful modality to guide needle aspiration or biopsy of cervical lymphadenopathy, peripheral tumors in contact with the pleura, distant metastases and sampling of pleural tissue or fluid.

Minimally Invasive Procedures

- Fibreoptic bronchoscopy
  Fibreoptic bronchoscopy is a safe and effective way to diagnose and stage many patients with lung cancer. As well as obtaining samples from endobronchial tumor it can be routinely combined with non-ultrasound guided transbronchial needle aspiration (non US-guided TBNA) to sample tumours beneath the mucosa and hilar and mediastinal lymphadenopathy detected by CT.

- Endobronchial Ultrasound (EBUS) and Endoscopic (oesophageal) Ultrasound (EUS)
  EBUS and EUS offer real time ultrasound guided sampling. EBUS is able to access lymph node stations 2, 3P, 4, 7, 10 and 11. EUS is able to access lymph node stations 4L, 7, 8, 9, the left adrenal gland and the left lobe of the liver.
Diagnosis of Lung Cancer

- **Transthoracic needle biopsy**
  Transthoracic needle biopsy is used to obtain diagnostic samples from lesions that are not accessible via the bronchial tree and where there is no obvious lymph node involvement. This is usually where there are one or more peripheral lesions. CT is used to guide biopsy where lesions are in difficult to reach locations or where they are completely surrounded by aerated lung. Ultrasound is used where the lesion abuts the chest wall and is visible on ultrasound.

**Mediastinoscopy and surgical diagnostic and staging techniques**

- **Mediastinoscopy**
  Mediastinoscopy is a more invasive technique than EBUS or EUS, but provides much larger samples. There is currently debate about whether mediastinoscopy is warranted in patients who are suitable for treatment with curative intent who have had a negative EBUS or EUS. This is partly because such patients, even if found to have microscopic involvement of lymph nodes, may still benefit considerably from treatment with curative intent.

- **Anterior Mediastinotomy**
  Anterior (parasternal) mediastinotomy has developed primarily as a means of staging carcinoma of the lung located in the left upper lobe. It has also been advocated to establish the diagnosis of primary masses in the anterosuperior mediastinum, especially in the setting of superior vena caval obstruction when needle biopsy may be contraindicated.

- **Video-assisted thoracoscopic surgery (VATS)**
  Video-assisted thoracoscopic assessment may allow biopsies direct from the tumour mass and can often establish whether there is tumour invasion into the central mediastinal structures. Lymph node stations 7, 8 and 9 can be sampled. It may also be employed to establish the diagnosis in single pulmonary nodules, especially where the lesion is in a peripheral location.

**NICE Recommendations**

- Sputum cytology is rarely indicated and should be reserved for the investigation of patients who have centrally placed nodules or masses and are unable to tolerate, or unwilling to undergo, bronchoscopy or other invasive tests. [2005]

- Patients with known or suspected lung cancer should be offered a contrast enhanced chest CT scan to further the diagnosis and stage the disease. The scan should also include the liver and adrenals. [2005]

- In the assessment of mediastinal and chest wall invasion:
  - CT alone may not be reliable.
  - Other techniques such as ultrasound should be considered where there is doubt.
  - Surgical assessment may be necessary if there are no contraindications to resection. [2005]

- Ensure all patients potentially suitable for treatment with curative intent are offered PET-CT before treatment. [2011]

- Every cancer network should have a system of rapid access to PET-CT scanning for eligible patients. [2005]

- Magnetic resonance imaging (MRI) should not routinely be performed to assess the stage of the primary tumor (T-stage) in NSCLC. [2005]

- MRI should be performed, where necessary to assess the extent of disease, for patients with superior sulcus tumours. [2005]

- Offer EBUS-guided TBNA for biopsy of paratracheal and peri-bronchial intraparenchymal lung lesions. [2011]

- Every cancer network should have at least one center with EBUS and/or EUS to ensure timely access. [2011]

- The local test performance of non-ultrasound guided TBNA, EBUS and EUS-guided FNA should be the subject of audit. [2011]

- Ensure adequate samples are taken without unacceptable risk to the patient to permit pathological diagnosis including tumour sub-typing and measurement of predictive markers. [2011]
Sequence of Investigations

NICE Recommendations

- Choose investigations that give the most information about diagnosis and staging with the least risk to the patient. Think carefully before performing a test that gives only diagnostic pathology when information on staging is also needed to guide treatment. [2011]

- Chest CT should be performed before:
  - An intended fibreoptic bronchoscopy.
  - Any other biopsy procedure. [2005]

Peripheral primary tumour

- Offer CT- or ultrasound-guided transthoracic needle biopsy to patients with peripheral lung lesions when treatment can be planned on the basis of this test. [2011]

- Biopsy any enlarged mediastinal nodes (≥10 mm maximum short axis on CT) or other lesions in preference to the primary lesion if determination of stage affects treatment. [2011]

Central primary tumour

- Offer fibreoptic bronchoscopy to patients with central lesions on CT where nodal staging does not influence treatment. Enlarged lymph nodes (≥10 mm maximum short axis on CT) may be simultaneously sampled with TBNA (non-ultrasound guided) if required for diagnosis. [2011]

Mediastinal lymph node assessment

- Offer PET-CT as the preferred first test after CT showing a low probability of mediastinal malignancy (lymph nodes < 10 mm maximum short axis on CT) for patients who are potentially suitable for treatment with curative intent. [2011]

- Offer PET-CT, or EBUS-guided TBNA, or EUS-guided FNA, or non-ultrasound guided TBNA as the first test for patients with an intermediate probability of mediastinal malignancy (lymph nodes between 10 and 20 mm maximum short axis on CT) who are potentially suitable for treatment with curative intent. [2011]

- Offer neck ultrasound with sampling of visible lymph nodes, or non-ultrasound guided TBNA to patients with a high probability of mediastinal malignancy (lymph nodes > 20 mm maximum short axis on CT). If neck ultrasound is negative, follow with non-ultrasound-guided TBNA, EBUS-guided TBNA or EUS-guided FNA. If non-ultrasound-guided TBNA is negative follow with EBUS-guided TBNA or EUS-guided FNA. [2011]

- Offer neck ultrasound with biopsy of visible lymph nodes to patients that have neck nodes detected by initial CT. If negative, follow with non-ultrasound-guided TBNA or EBUS-guided TBNA or EUS-guided FNA. [2011]

- Evaluate PET-CT positive mediastinal nodes by mediastinal sampling (except where there is definite distant metastatic disease or a high probability that N2/N3 disease is metastatic [for example, if there is a chain of lymph nodes with high F-deoxyglucose uptake]). [2011]

- Consider combined EBUS and EUS for initial staging of the mediastinum as an alternative to surgical staging. [2011]

- Confirm negative results obtained by non-ultrasound-guided TBNA using EBUS guided TBNA, EUS-guided FNA or surgical staging. [2011]

- Confirm negative results obtained by EBUS-guided TBNA and/or EUS-guided FNA using surgical staging if clinical suspicion of mediastinal malignancy is high. [2011]

Stage M1b

- Confirm the presence of isolated distant metastases/synchronous tumours by biopsy or further imaging (for example, MRI or PET-CT) in patients being considered for treatment with curative intent. [2011]

- Consider MRI or CT of the head in patients selected for treatment with curative intent, especially in stage III disease. [2011]

- Offer patients with features suggestive of intracranial pathology, CT of the head followed by MRI if normal, or MRI as an initial test. [2011]
- An X-ray should be performed in the first instance for patients with localized signs or symptoms of bone metastasis. If the results are negative or inconclusive, either a bone scan or an MRI scan should be offered. [2005]

- Avoid bone scintigraphy when PET-CT has not shown bone metastases. [2011]

**When Should Molecular Testing For NSCLC Be Performed?**

**Epidermal growth factor receptor (EGFR)**

It is also called ErbB-1, is the member of a subfamily of closely related proteins. After ligand-binding, the intracellular tyrosine kinase domain of the EGFR receptor is activated and undertakes autophosphorylation, which initiates a cascade of intracellular events. A downstream signaling pathway involves the activation of p21-Ras and mitogen-activated protein kinases (MAPKs). EGFR signaling is critical for the normal cell proliferation, but its deregulation is crucial for cancer pathogenesis, neoangiogenesis, metastasis, and apoptosis inhibition.

EGFR is overexpressed in the advanced NSCLC, and is associated with the poor survival and resistance to chemotherapeutic agents, including cisplatin. The results of different studies investigating the prognostic value of EGFR expression in lung cancer are contradictory. However, since EGFR expression is clearly involved in the lung cancer pathogenesis, this molecule is an attractive target of different therapeutic approaches.

**Other driver mutation**

KRAS, EML4-ALK, ROS

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**Figure 4. Driver Mutations in NSCLC**

**Testing for EGFR Mutations and ALK Rearrangements**

**Recommendation:**

- EGFR molecular testing should be used to select patients for EGFR-targeted TKI therapy, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.

- ALK molecular testing should be used to select patients for ALK-targeted TKI therapy, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.

- In the setting of lung cancer resection specimens, EGFR and ALK testing is recommended for adenocarcinomas and mixed lung cancers with an adenocarcinoma component, regardless of histologic grade.

- In the setting of more limited lung cancer specimens (biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, EGFR and ALK testing may be performed in cases showing squamous or small cell histology but clinical criteria (eg, young age, lack of smoking history) may be useful in selecting a subset of these samples for testing.

- To determine EGFR and ALK status for initial treatment selection, primary tumors or metastatic lesions are equally suitable for testing.
**Figure 5.** Molecular Testing for NSCLC

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Biomolecular Testing in Non-Small Cell Lung Carcinoma

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EGFR and its family have important part in carcinogenesis from its role in cell proliferation, apoptosis, cell motility, and neovascularization. EGFR modification affecting the pathogenesis and development of different kind of cancer. Incidence rate of EGFR mutation in patient with histology of non-small cell lung carcinoma (NSCLC) is range from 10% to 50%, depending on patient’s ethnicity/population and detection methods conducted to mutation analysis.

Identification of sensitizing mutation from Tyrosine Kinase (TK) domain of EGFR has modified the management of NSCLC patients. Starting from initial study, two kinds of mutation which has been acknowledge as the most clinically common and significant are deletion of exon 19 and L858R mutation point.

Obtaining the tumor tissue become the main challenge for molecular analysis. First, biopsy sample often limited and the number of tumor cell obtained is too small for molecular analysis. Second, the biopsy might not represent the total number of cells that mutated, especially in metastasis patients. Third, genetical changes can occur during interval of biopsy and initial TKI therapy, particularly in patients receiving chemotherapy and radiotherapy. Study shows that EGFR mutation can be detected from patient’s serum or plasma, although the success rate for detecting EGFR in blood varies according to the technology used.

Biomolecular Testing in NSCLC:

- **EGFR mutation** – EGFR mutation in adenocarcinome is 15% in Caucasian population and often occurs in non-smoking patient, while in the Asian population is higher with EGFR mutation almost 62%
- **ALK translocation** – Translocation involving anaplastic lymphoma kinase (ALK) tyrosine kinase hover around 4% adenocarcinoma NSCLC in US and often occurs in non-smoking and young patients
- **ROS1 translocation** – ROS1 is tirosin kinase receptor from the insulin receptor family which act like oncogene driver in 1-2% NSCLC via genetic translocation between ROS1 and other gen, which most often is CD74. Translocation ROS1 often occurs in adenocarcinoma patients, young, and non-smoking patients
- **PD-L1 expression** – Programmed cell death ligand-1 (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) pathway are important checkpoint location which used by tumor cells to inhibit anti-tumor response
- **RAS mutation** – RAS oncogen family is identified from retroviral study, induced from rat sarcoma (ras) with KRAS, NRAS, and HRAS where each representing different huan gene homologue. The most common RAS mutation oncogenic are substitute from codon 12, 13, or 61, therefore causing constitutive activity RAS gen. KRAS mutation occurs about 20-25% of adenocarcinoma in US and often associated with smoker
- **HER2 mutation** – HER2 (ERBB2) includes in EGFR tirosin kinase receptor family. Mutation in HER2 is detected in 1-2% NSCLC. Mutation commonly occur are in-frame insertion in exon 20, and point mutation in exon 20. Tumor with this type of mutation is adenocarcinoma, and often occurs in non-smoking patients and woman. There is no association between HER2 amplification and HER2 mutation

Nowadays, examination for EGFR mutation can be conducted using sample liquid biopsy, namely circulating tumor DNA (ctDNA) plasma, which specifically is derivation from the tumor. In the bloodstream, there is cell-free DNA (cfDNA) which is distinguished from ctDNA by the presence of mutation, in which the mutation found in tumor cell but not in the normal cell. Cancer patients usually has higher level of cfDNA compare to healthy individual. Along with increasing tumor volume, tumor cell debris accumulated and released into circulation. In addition, the operational and careful handling of plasma sample become essential issues, as well as the type of technology used for examination of EGFR mutation plasma. Nowadays, ctDNA plasma applied either for diagnosis (1L setting) or relapse (2L setting), but analyzing different mutation.
Abstract
Palliative patients susceptible to infection, infections are the most common urinary tract infections and pulmonary infections. Besides the condition of the disease itself, as well as treatment of the underlying disease is a risk factor for the occurrence of infections in patients palliative. Mortality due to infection is quite high due to infection or advanced disease. Using antimicrobial in terminal patients with cancer should be carefully evaluated before signs of death appear. Microorganisms as etiology in pulmonary infections usually Gram negative and Gram positive bacteria. Antimicrobial treatment of infections in patients with palliative remains controversial, however antimicrobial administration may make the patient comfortable and longer life expectancy. Antimicrobial can be administered orally, intra-muscular, or parenteral. Oral administration more favorable. Nevertheless, antimicrobial administration is not without risk, a risk that must be considered is the possibility of infection Clostridium difficile, resistant microorganisms.

Introduction
Palliative treatment: to palliate a disease is to treat it partially and insofar as possible, but not cure it completely. Also sometimes called symptomatic treatment. Palliative patient generally had very advanced disease and multiple comorbid conditions. The majority of patients were very near the end of life (evidenced by 22.9% dying in the hospital, and another 44.3% discharged to hospice care) (1). The majority patients reasons for admission varied and included progression of disease and infectious complications as the 2 most common (2).

Acute complication experienced in terminally ill palliative patients often with infection and febrile episodes. Close to 90% hospitalized palliative patients administration antimicrobials during nearly to death, but often face challenging and making decision to their treatment approach a difficult one (3,4). Among patients treated with antimicrobials, the most common infectious diagnosis was pneumonia in 46.0%. The presence of pneumonia was established by clinical findings in 67.2%, and by sputum or bronchoscopic cultures in 32.8% (2).

Incidence
Palliative patients, especially cancer patients often susceptible to infections, approximately 42% in cancer patients. The true rate of infection remains uncertain, because in many cases the presence of fever alone led to a clinical diagnosis of infection. Other non-infectious causes of fever remain possible in these cases, including drug-induced fever and fever secondary to underlying malignancy. Its related with disease and therapy-induced factor. Two most common infections are urinary and respiratory tract. Infections is a serious complication and a leading cause of death in cancer patients (3). Female patients to be more susceptible to infection (5). Source of respiratory infection including pneumonia and bronchitis; others sources included, septicemia, wounds (1); intra-abdominal infections included peritonitis, cholangitis, and spontaneous bacterial peritonitis (2). Palliative patients infection not only in the wards hospitalized but entered an intensive care unit (5). Majority patients were diagnosed as having infection at the time of admission and other during hospitalization (2,6). Patients may have developed infection as a result of a longer length of hospice care (7).

Risk factors
Palliative patients as a terminal condition are susceptible to infections due to a variety of disease-related and therapy-induced factors (3,8). Many factors predispose to cancer-related infection including tumor necrosis, older age, impaired immunologic function, organ failure, malnutrition (common in cancer), and invasive device (5), other risk factors contributing to increased susceptibility to infection are asthenia, decreased level of consciousness, immobility, failure of host barriers (3), immunosuppression and neutropenia from chemotherapeutic agents, poor secretion clearance caused by deconditioning, and airway obstruction (8). Performance status, the fall risk assessment score, and central venous catheter were the factors that correlated with infection (9). These patients are at risk not only for the usual community-acquired pneumonia organisms but also for multidrug-resistant health care–associated organisms resulting from prior inpatient hospitalizations (8).
Pulmonary Infection in Palliative Treatment

Mortalities

A total mortality of suspected infection patients were 19% - 39%, and unfortunately frequent cause of death was untreated infection (3). In patients with solid tumor 47% mortality palliative care patients due to infection, 51% of these had pneumonia in postmortem examination. Infection related mortality increases to 63% in persons with hematological neoplasm (5). One study from Thompson and colleges (2) 44.1% patients died in the ICU and 40.7% underwent mechanical ventilation.

Approximately 32% mortality of patients suspected pneumonia episode without receive antimicrobial during 90-day and around 60.4 and 64.8% in patients with receive antimicrobial either oral or injections (10). Patients solid tumors received chemotheraphy- or radiation-induced neutropenia and infections were fatal in all patients. Death from infection during hospitalization was significantly associated with lung cancer (5).

Microorganism etiology

Palliative treatment-related bacterial infections showed that more than one bacterial. Gram negative and gram positive bacteria can causes infections (5). The most frequent was enterobacteriaceae, \textit{S. aureus} (3), \textit{E. coli} (5), especially \textit{S. aureus} induced-bacteremia.

Sign and symptoms

Symptoms of clinical picture suggestive of infection including fever, chills, cough. Fever suggestive infection was present in 54%, reverse was not result of infection. Infection symptoms may be absent, vague or atypical including malaise, anorexia, weakness, mental change, weight loss (5). Poor immune function may be result up to 80% of patients without fever present (6). Diagnosis of infection makes difficult due to it symptoms are common in cancer patients without infection. One best choice to prove patient experienced infection by positive body culture (5).

A significant correlation between patients managed for infection and psychological distress. Sedation and coma patients may be produce from serious infection, allowing the patient a peaceful death, and antimicrobial therapy can awaken the terminally ill patient and prolong the process of dying. Approximately 20% - 30% of infections were fatal. One study identified an association between mortality and poor condition or neutropenia. Another study found mortality was not significantly associated with the presence of bacterial infection in dying patients with cancer (3).

Diagnosis of pulmonary infection

Infection occurred frequently in palliative care patients with advanced cancer. Most studies defined infection as documentation of a clinical diagnosis of infection. Rates of suspected infection varied among the studies from 29% to 83%, with an overall rate among the evaluable studies of 41.6% (3). Should patients present to the hospital with a clinical and radiographic presentation consistent with pneumonia, an accurate history of their prior health care setting must be obtained to ensure appropriate antimicrobial agents are commenced (8). The term “suspected infection” is used because infections were presumed to be the cause of fever in many cases and the rate of actual infection is unknown. Only the study by Homsi and colleges (5) required a positive culture as a definition of infection, reflected by the lower frequency of infection of 29% (3). Among those residents who had a chest radiograph, pneumonia was radiographically confirmed in 84% of cases. (10).

Management of infection

Out of existing publications, there are differences in the palliative management of patients with infection: treatment palliative patients with infection are not aggressive to cure of goal, but only for improve quality of life or sustained of comfort. Pneumonia may well be managed with antipyretics and opioids for dyspnea rather than antibiotics (1). Givens and colleges (10) found that antimicrobial treatment for suspected pneumonia may be a double-edged sword, as it was associated with both survival and discomfort. In other publications, if indicated infections should treatment aggressively, usually intravenously antimicrobial result is successfully (5). Therefore, not possible to predict whether antimicrobial will produce a cure, or conversely whether withholding them will result in death. In life-threatening infections produce discomfort, antimicrobial might be considered part of a good palliative care plan (3). Existing research has not clarified the benefits of antimicrobial use for symptom improvement, symptomatic improvement for respiratory infection between 0% and 53% (11). Antimicrobial use for infection patients may produce prolonged survival and symptom relief, and motivate physicians to prescribe antimicrobial when treating terminally ill patients (4).

Prevalence of antimicrobial use in cancer palliative care patients around 19% and 84% and patients with documented infective episodes, closely to 100% receive an antimicrobial treatment (11). Antimicrobial
use, particularly broad-spectrum is not neutral due to drug toxicities and agents parenteral is health care cost, and antimicrobial use are at risk of Clostridium difficile (1). In a part of palliative patients (11.9%) for fever of unknown source treatment with empirical antimicrobial. Five point six percent of these developed Clostridium difficile infection, and demonstrated multi-drug resistant organism (2). To avoid unnecessary risks, when appear the sign of patient death antimicrobial can be terminated (6).

For patients with respiratory infections mostly given empirical antimicrobial therapy and the other based on microbiological culture (1). Regarding the symptoms of fever resolution, studies antimicrobial use reported fever resolution in 47.9% and 54.9% cases different with not treated with antimicrobial therapy only 7.1% cases fever resolution occurred (11).

Improvement related symptoms following antimicrobial use ranged from 21.4% and 56.7% of cases. Parenteral antimicrobial use more improvement than others route (11). The most common oral route of Antimicrobial are derivatives of macrolides, followed by fluoroquinolones, and the other miscellaneous. Seven days dying palliative patients, approximately 27% of patients who have an infection with more than one antimicrobial (7). To avoid unnecessary risks, when appear the sign of patient death antimicrobial can be terminated (6). Some studies have observed a longer survival time in patients receiving antibiotics, whereas others have noted no significant difference in survival time (7).

Most of (91%) palliative patients suspected pneumonia episodes given antimicrobial, agents of antimicrobial as follows: 55% oral, 16% intramuscular, and 20% intravenous or hospitalization. There is no difference in life expectancy between 3 routes antimicrobial therapy. Patients with pneumonia who are not hospitalized associated with greater mortality (10). Minimally invasive route of antimicrobial initiated therapeutic use for less patients discomfort and health care expenditure (4). Between parenteral and oral regimens of antimicrobial, parenteral administration may be appropriate for some cases and oral regimens were most preferred, but it is not always possible to predict whether antimicrobial therapy will produce favorable effect on symptom control (3). The most common antimicrobial given intravenously is Piperacillin / Tazobactam (37.1%), mostly empiric therapy, followed by vancomycin (32.9%) where 60% of patients who received vancomycin is combined with piperazillin / Tazobactam. Most of vancomycin is given empirically, 73% were given vancomycin with no apparent indication of microbiology (1).

The percentage of patients receiving antimicrobial administration is different, depend of length of hospitalization. Antimicrobial administration decreased from 78.0% at admission to 75.8% 1 week after admission, and 59.1% 2 days before death, respectively. Intravenous antimicrobial were the most frequent, followed by oral antimicrobial (6).

Preventive
Prevention of infectious diseases in patients with cancer who underwent palliative care is very important because the infection lowers the quality of life and can be a cause of death, infection therapy suite can help control symptoms in patients with cancer, and the use of drugs that are not effective in patients undergoing palliative care increases the risk of nosocomial infection (9). Vaccination with pneumococcus and influenza may can preventive for pneumonia pneumococcus and influenza.

Prognosis
Clinical symptoms in palliative care patients may indicate the possibility of a patient’s survival. Shortness of breath may be a poor predictor of survival for a palliative care patient. Dyspnea risk factor associated with imminent death or short-term life expectancies less than 2 weeks (12).

Summary
Palliative patients prone to infection, infections are the most common urinary tract infections and pulmonary infections. Besides the condition of the disease itself, as well as treatment of the underlying disease is a risk factor for the occurrence of infections in patients palliative. Mortality due to infection is quite high. Using antimicrobial in terminal patients with cancer should be carefully evaluated before signs of death appear. Antimicrobial treatment of infections in patients with palliative remains controversial, however antimicrobial administration may make the patient comfortable and longer life expectancy. Antimicrobial can be administered orally, intra-muscular, or parenteral. Oral administration more favorable. Nevertheless, antimicrobial administration is not without risk, a risk that must be considered is the possibility of infection Clostridium difficile, resistant microorganisms.
Pulmonary Infection in Palliative Treatment

References


Glutamine Supplementation in Critically Ill Patients

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Abstract

Glutamine (Gln) is an important energy source and has been used as a supplementary energy substrate. Furthermore, Gln is an essential component for numerous metabolic functions, including acid-base homeostasis, gluconeogenesis, nitrogen transport and synthesis of proteins and nucleic acids. Therefore, glutamine plays a significant role in cell homeostasis and organ metabolism. This article aims to review the mechanisms of glutamine action during severe illnesses. In critically ill patients, the increase in mortality was associated with a decreased plasma Gln concentration. During catabolic stress, Gln consumption rate exceeds the supply, and both plasma and skeletal muscle pools of free Gln are severely reduced. The dose and route of Gln administration clearly influence its effectiveness: high-dose parenteral appears to be more beneficial than low-dose enteral administration. Experimental studies reported that Gln may protect cells, tissues, and whole organisms from stress and injury through the following mechanisms: attenuation of NF (nuclear factor)-κB activation, a balance between pro- and anti-inflammatory cytokines, reduction in neutrophil accumulation, improvement in intestinal integrity and immune cell function, and enhanced of heat shock protein expression.

Key words: heat shock protein, apoptosis, cytokines, glutamine.

Introduction

Amino acid metabolism, particularly glutamine (Gln), increases in the critically ill patient. In catabolic states, large amounts of Gln are released from muscle tissue as part of the body's conserved evolutionary response to stress. Previous explanations for the release of Gln in periods of stress include: use as a fuel source for rapidly dividing cells, precursor for synthesis of nucleic acids, and role in renal acid buffering. Despite this massive release of Gln from muscle, it is well-described in the literature that Gln levels are significantly decreased in critical illness, ultimately leading to an increase in mortality in these patients. This indicates that humans only have 24–48 h of Gln stores to maintain Gln levels following injury.

While Gln is classified as a nonessential amino acid and can be synthesized de novo in states of health, it is now commonly described as a conditionally essential amino acid, particularly in catabolic and stress states. Recent data have revealed that following illness and injury, Gln plays a vital role in inducing cellular protection pathways, modulation of the inflammatory response, and prevention of organ injury. Recently, an editorial proposed four main hypotheses through which Gln exerts its protective effects in critical illness, while indicating that further research is needed to elucidate specific mechanisms. These mechanisms include improved tissue protection, immune regulation, preservation of glutathione and antioxidant capacity, and preservation of cellular metabolism after injury. Further, new data indicates that Gln activates intracellular signaling pathways and regulates the expression of genes related to signal transduction, apoptosis, and metabolism. This data indicates that the release of Gln from muscle is a 'stress signal' to turn on genes vital to cellular protection and immune regulation.

Metabolism and Catabolism of Glutamine in Normal Conditions

Glutamine is the most abundant free amino acid in the body and commonly known as a nonessential amino acid due to the ability of most cells to produce it. Glutamine is present in the plasma at levels around 0.6 mM and in the intracellular space at levels around 2 and 20 mM. It also serves as a metabolic intermediate, contributing carbon and nitrogen for the synthesis of other amino acids, nucleic acids, fatty acids, and proteins. Glutamine through glutamate is a glutathione precursor, a tripeptide consisting of glutamate, glycine, and cysteine, with intracellular antioxidant capacity. Thus, its functions within the cell are generally separated into four categories: 1) its role in nitrogen transport; 2) its importance in maintaining the cellular redox state; 3) its position as a metabolic intermediate; and 4) its role as an energy source. Although some tissues use glutamine for one pathway more than others, glutamine metabolism occurs in all cells.

Glutamine is synthesized by the cytosolic glutamine synthetase (GS) in many tissues, but degraded by mitochondrial glutaminase (GA) and utilized in high amounts by other tissues that do not synthesize it. Glutamine catabolism is initiated by the removal of an amine group to form glutamate. This can occur through a number of cytosolic transaminase enzymes that use the γ-amino nitrogen of glutamine in a variety of metabolic synthesis. However, the rate at which these reactions utilize Gln depends ultimately upon the metabolic demand for the reaction products and is, therefore, not appropriate for the control of glutamine homeostasis.
mitochondrial enzyme glutaminase catalyzes the hydrolysis of the γ-amino group of Gln to form glutamate and ammonia. Ammonia can be used to form carbamoyl phosphate or can diffuse from the mitochondria and the cell itself. Furthermore, glutamate can form α-ketoglutarate and, thus, enter into the citric acid cycle.

The synthesis of glutamine from glutamate is mediated by the enzyme glutamine synthetase. Thus, the regulated expression of this enzyme plays a key role in an organ’s overall glutamine production rate. In contrast to the many enzymes that utilize glutamine as a substrate, only glutamine synthetase is responsible for de novo synthesis of glutamine. In this line, glutamine synthetase catalyses the formation of Gln from glutamate and ammonia in the cytoplasm. Because both of these substrates are relatively abundant, the rate of glutamine formation is highly dependent upon the activity of glutamine synthetase.

Metabolism and Catabolism of Glutamine during Critical Illness

The expression of glutamine synthetase in mammalian systems is regulated mainly via two mechanisms: a) increased transcription in response to hormone action and b) regulation of protein stability in response to glutamine concentration. During physiologic stress, as sepsis, a rapid increase in plasma concentrations of cytokines and several classes of hormones, such as glucocorticoids, occurs. Glucocorticoids are vital multifaceted hormones with recognized effects on carbohydrate, protein and lipid metabolism, and they are part of the acute stress response. They are considered the primary mediators of glutamine synthetase expression during stress, and act on the lung and skeletal muscle in a rapid and direct glucocorticoid receptor-mediated manner. The transcriptional response of the rat glutamine synthetase gene to glucocorticoid has been characterized and shown to be attributable to two genetic regions. Each of these regions gives large glucocorticoid induction of transcription to the glutamine synthetase promoter, as well as heterologous promoter in a glucocorticoid-dependent.

Despite a large transcriptional response, glutamine synthetase protein levels do not always increase with GS mRNA levels, which suggests that the post-transcriptional control mechanism also regulates glutamine synthetase expression. Studies demonstrated that the presence of glutamine in the medium regulates glutamine synthetase expression via a post-transcriptional mechanism, where the rate of glutamine synthetase protein degradation is diminished and its activity is augmented in the presence of low glutamine concentration.

Although the skeletal muscle is the main source of Gln in normal conditions, skeletal muscles and lungs work together to maintain the circulating glutamine pool during critical illnesses. The concentration of glutamine, in the skeletal muscle tissue, affects glutamine synthetase expression differently during acute stress compared with chronic stress and/or caloric deprivation. During acute stress, glucocorticoids and glutamine depletion increase muscle GS mRNA levels rapidly, while glutamine synthetase protein levels are limited. During a chronic stress, Gln may directly impact glutamine synthetase gene expression or potentiate the effects of another mediator, such as glucocorticoids. Unlike in skeletal muscles, glutamine depletion increases glutamine synthetase protein stability in the lung, but without significant augment in GS mRNA. The combined effects of Gln depletion and glucocorticoids hormones can act synergistically to increase glutamine synthetase protein expression, allowing the lung to adjust GS activity to meet actual Gln demand.

Glutamine and the Expression of Heat Shock Proteins

Glutamine’s beneficial effects on critical illnesses may result from enhanced heat shock proteins (HSP) expression expressed by leucocytes, monocytes, and granulocytes. The heat shock proteins are a group of proteins essential to cellular survival under stressful conditions. These are a family of highly conserved proteins belonging to multigene families ranging in molecular size from 10 to 105 kDa – different weights are used for identification –, and found in all major cellular compartments.

The stress-inducible HSP70 and HSP72 are inducible forms of the stress protein, which may confer cellular protection. Treatment of sepsis-induced acute lung injury with an adenovirus overexpressing HSP72 limits nuclear factor (NF) kB (a crucial transcription factor regulating the expression of many pro-inflammatory cytokines and immunoregulatory molecules) activation and prevents lung injury. There is evidence that Gln can enhance HSP70 and 72 expression in lung macrophages and epithelial cells leading to marked protection against sepsis-induced injury. The cellular functions of intracellular HSP70 and HSP72 are responsible for limiting protein aggregation, facilitating protein refolding, and chaperoning proteins. These cellular functions serve to improve cell survival in the face of a broad array of cellular stressors.

It has been recognized that HSP72 is also found in extracellular space (eHSP72) where it exerts immunomodulatory function on innate and acquired immunity. In fact, during the early phase of ALI, there was an activation of the stress protein response (SPR) and a release of HSP72 into the alveolar spaces.
may serve as a marker of stress protein response activation in the distal air spaces of ALI patients, while SPR activation may protect the alveolar epithelium against oxidative stress.22 Initially, studies reported that eHSP72 was only released as a result of necrotic/lytic cell death, but it is now recognized that elevated eHSP72 may be found in the absence of necrosis.22 In this context, Ganter and colleagues (2006) showed a preserved alveolar fluid clearance and high levels of eHSP72 in pulmonary edema fluid of ALI patients, suggesting that the high level of eHSP72 is not related to cell injury in distal air spaces.22 It seems that, under physical or psychological acute stress, eHSP72 may exacerbate inflammatory process or stimulate the release of endogenous eHSP72 into the blood via an α1-adrenergic receptor-mediated mechanism facilitating the innate immunity.27,28

Glutamine starvation reduces the HSP70 expression since it decreases HSP70 mRNA expression.21 As plasma glutamine depletion occurs during systemic inflammation, the impaired HSP70 expression under these conditions is likely to have deleterious effects on the survival and function of leucocytes, and may contribute to the immunosuppression observed in these patients. However, Gln administration may restore the expression of HSP protecting tissues against injury, improving survival in animals with abdominal sepsis.18,19,24,25,29 Recently, Singleton and Wischmeyer (2007), using knockout mice, demonstrated that the beneficial effects of glutamine on survival, lung injury, and the inflammatory response following cecal ligation and puncture surgery depended on the expression of HSP70.25

The gene of HSP72 contains at least two regulatory elements that interact with heat shock transcription factors (HSFs).30 The induction of HSP72 requires HSF-1 binding to the heat shock element (HSE) in the promoter region of the HSP70 gene.31 Glutamine can initiate activation and lead to phosphorylation of HSF-1, yielding HSP expression and protecting cells against damage.18,28 Recently, it was demonstrated that the molecular mechanism of Gln mediated HSP70 expression appears to be dependent on O-GlcNac pathway activation and subsequent O-glycosylation and phosphorylation of key transcription factors, HSF-1 and Sp1, required for HSP70 induction.32

Modulation of Immune System

Glutamine is known to modulate immune cell function and production of cytokines. It may be mediated via attenuation of multiple pathways of inflammation, such as NF-κB, kinases proteins, inhibition of increases in iNOS expression, attenuating the interactions between polymorphonuclear lymphocytes and endothelium, and decreasing neutrophil infiltration into tissues.7,19,33 Two pathways that can explain Gln’s effects are: a) enhancement of MAPK phosphatase (MKP-1) expression, responsible for halting the production of pro-inflammatory cytokines, acting as an important negative regulator to inflammatory stimuli, b) inhibition of phosphorylation and degradation of IkB-α, an inhibitory protein that is bound to NF-κB, avoiding its translating to the nucleus.23,34

Glutamine infusion can result in enhanced tissue glutathione levels, partly responsible in avoiding the activation of NF-κB, and increase antioxidant capacity.35 Whereas HSP70 protects cells against oxidative stress by the repair or removal of damage proteins, the second major protection factor of mammalian cells, the antioxidant glutathione, reacts directly with ROS in order to prevent oxidative damage. A significant correlation between reduced glutamine supply and diminished intracellular glutathione was observed in cultured peripheral blood mononuclear cells and in critically patients.36,37 Doruk and colleagues (2005) showed reduced glutathione levels in the diaphragm of rats submitted to cecal ligation and puncture surgery, which was reversed with Gln administration.33

Glutamine supplementation also promotes balanced Th1/Th2 response during sepsis, decreasing IL-6 secretion in non-hepatic organs, while reducing intra-lymphocyte IL-4 and enhancing IFN-α expressions.7 O’Leary and colleagues (2007) showed in rats with abdominal sepsis that parenteral nutrition with glutamine recovered serum levels of IL-6 and IL-10.38

It is known that glutamine is an important fuel for lymphocytes and macrophages.39 Macrophages and neutrophils are involved in the early, non-specific host defense responses, and play an important role in the pathophysiology and/or protection against sepsis. In fact, this amino acid is required for the expression of lymphocyte cell surface markers, such as CD25, CD45RO, and CD17.36 Additionally, septic rats pretreated with glutamine showed reduced neutrophil infiltration in diaphragm muscle, preventing biochemical and histopathological changes.33 It has been demonstrated that Gln supplementation benefits the human leukocyte antigen-DR expression, essential molecule for antigen presentation, on monocytes in trauma and surgery patients.40

Another interesting question is the intestinal permeability. As glutamine is an important fuel for the enterocyte, intestinal consumption is important for maintaining the integrity of the intestinal barrier with
subsequent prevention of bacterial translocation and, through stimulation of the gut-associated immune system, prevention of gut barrier atrophy. It is proposed that a derangement of the gut mucosal barrier function, which occurs during critical illnesses, results in an amplification of the general inflammatory response predisposing patients to multiple organ failure. The intestinal mucosa provides a barrier between bacteria and bacterial products in the intestinal lumen and body’s circulation and organs. Prophylactic treatment with glutamine may minimize changes in intestinal permeability and bacteria translocation caused by endotoxemia in rats receiving total parenteral nutrition. In summary, there is evidence that glutamine-starving cells show an increased susceptibility to cell stress and apoptosis, as well as a reduced responsiveness to pro-inflammatory stimuli. The maintenance of plasma glutamine levels is essential for cells energy status, as well as for their functions and inflammatory response.

Apoptosis

Apoptosis can be induced by a range of environmental, physical or chemical stress. Studies have established that the survival-promoting effects of HSP70 can be partly attributed to the suppression of apoptosis. The reduced HSP70 expression in glutamine-starved cells, together with their impaired antioxidant capacity, is thus likely to make them more sensitive to the induction of apoptosis.

Evidence showed that cells in the presence of glutamine are not sensitive to Fas ligand. JNK/SAPK pathway is involved in the apoptosis process increased by Fas stimulation. JNK/SAPK induced by Fas ligand is mediated by ASK1 (a critical protein kinase in apoptosis), which is activated after Fas ligand treatment only in the absence of Gln. Thus, Gln may suppress apoptosis signal-regulating kinase (ASK-1) and JNK/SAPK activation by Fas ligand. Furthermore, L-glutamine potentiation of HSP72 is associated with increased gut epithelial resistance to apoptotic injury, and reduced HSP72 may be associated with increased caspase activity in glutamine-deficient. In fact, Gln induces autophagy under stressed conditions, and prevents apoptosis under heat stress through its regulation of the mTOR and p38 MAP kinase pathways.

Glutathione (GSH) metabolism is also closely related to apoptotic processes of immune cells. The increase of intracellular GSH is sufficient to reduce Fas-triggered increase in apoptotic cells. An overexpression of Bcl-2, an anti-apoptotic protein, causes redistribution of glutathione to the nucleus, thereby altering nuclear redox and blocking caspase activity.

Glutamine and the Development of Acute Lung Injury / Acute Respiratory Distress Syndrome

Critically ill patients are at high risk of glutamine depletion and subsequent complications, such as the developing of acute lung injury/acute respiratory distress syndrome (ARDS). Therapeutic interventions to improve outcomes from ALI/ARDS have met with limited success. There are many experimental studies investigating the effects and the mechanisms responsible for glutamine’s beneficial effects in ALI. However, in these studies, glutamine was administered before or few hours after the induction of lung injury. In this context, Gln could prevent neutrophil recruitment and infiltration, protect the alveolar barrier, and attenuate inflammatory lung injury, leading to survival improvement. The mechanisms underlying the majority of these findings may be related to Gln’s ability to induce heat shock protein (HSP) expression, which is known to enhance cell survival in the face of injury and attenuate the systemic inflammatory response, besides attenuating NF-κB pathway, buffering oxidative stress via glutathione generation, protecting gut barrier, and providing substrate for the appropriate division of immune cells. Related to clinical trials, the studies have not investigated the development of ALI/ARDS as an end-point.

Conclusions

Several controlled studies suggest that glutamine supplementation has beneficial effects on the clinical outcome of critically ill patients. These results may be explained by the glutamine’s influences on the inflammatory response, oxidative stress, apoptosis modulation, and the integrity of gut barrier. Additional studies should be performed to determine whether the outcomes are derived from the parenteral or enteral route, or if any specific group of patients could benefit from this therapy.
References


Nutrition in Palliative Care

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Abstract

Introduction

Palliative care is an approach aimed at improving quality of life of patients and families facing problems associated with a life-threatening illness. Improving quality of life involves prevention and relief of suffering by means of early identification and treatment of problems, seamless assessment, treatment of pain, and the provision of physical, psychosocial and spiritual care. Nutritional support is an important element of palliative care, since inadequate hydration and malnutrition results in skin and muscle wasting, vulnerability to the development of pressure ulcers, infection and respiratory problems.

Methods

Review of literature

Results

Three strategies can be used by health professionals to provide palliative care patients with nutritional support: 1) Dietary advice and counseling, 2) Oral nutrition intake, and 3) Artificial methods of providing nutrition and hydration.

Conclusion

Nutritional interventions offered as part of palliative care contribute to the goal of optimizing comfort, managing adverse effects of treatment, controlling symptoms, and maintaining psychological wellbeing. These goals are consistent with the concept of quality of life, however it is defined.

Keywords: Nutrition, palliative care, end of life care

Introduction


Palliative care is requisite when an individual has a life-threatening illness that is not responsive to curative treatment, such as chronic heart failure, respiratory disease, a neurological disorder or cancer. Palliative care is differentiated from end-of-life care, which is more concerned with the final days and hours of a person’s life (Department of Health, 2008; Marie Curie Liverpool Care Pathway, 2008).

Nutritional support is an important element of palliative care, since inadequate hydration and malnutrition results in skin and muscle wasting, vulnerability to the development of pressure ulcers, infection and respiratory problems (Kutner et al, 2005). The criterion for nutritional intervention is:

- A body mass index (BMI) of less than 18.5 kg/m2
- Unintentional weight loss greater than 10% within the last 3—6 months
- A BMI of less than 20 kg/m2 and unintentional weight loss greater than 5% within the last 3—6 months (National Institute for Health and Clinical Excellence (NICE), 2006).

However, NICE also stated that the provision of nutrition support is not always appropriate. Decisions on withholding or withdrawing of nutrition support require a consideration of both ethical and legal principles (both at common law and statute, including the Human Rights Act 1998).

An example of a commonly used nutritional screening instrument is the Malnutrition Universal Screening Tool (MUST) which was developed by the Malnutrition Advisory Group, a Standing Committee of the British Association for Parenteral and Enteral Nutrition (Elia, 2003). This tool can be used to determine the nutritional status of patients.
status of patients. If the patient is identified as malnourished or at risk of malnutrition, referral is made to a dietitian for an assessment.1

Categories of Nutritional Support2

Three strategies can be used by health professionals to provide palliative care patients with nutritional support.

1. **Dietary advice and counselling**

   Dietary advice and counselling should be offered to patients receiving palliative care and their careers or relatives. The aim is to encourage appropriate, individualized and useful eating habits, with dietary guidance tailored to meet the patient’s individualized needs (NICE, 2006).

2. **Oral Nutrition Intake**

   The aim of this type of intervention is to ensure appropriate amounts of required nutrients are consumed by the patient. Recent recommendations for the preservation of oral nutritional intake in patients receiving end-of-life care include guidelines on administering the modification of oral nutrition in order to achieve this key aim (Royal College of Physicians and British Society of Gastroenterology, 2010). These guidelines include recommendations relating to the texture and fortification of food and fluids, sensory techniques such as thermal stimulation and manipulation of the oral musculature, positioning and posture strategies, career education and behavioral and cognitive strategies (Figure 1).

   A range of prescribed oral nutritional supplements (ONS) may be administered to supplement and fortify diet. Holmes (2010) acknowledged the risks of diarrhea, abdominal cramps, pain and dehydration, associated with the high osmotic loads associated with some nutritional supplements where they are used as the only source of nutrients and the supplements are of a high calorific density. It is therefore recommended that supplements should be diluted with water to overcome these potential problems. Mechanical aids can also be used to facilitate chewing and swallowing to help with the digestion of food (NICE, 2006).

3. **Artificial methods of providing nutrition and hydration**

   **Enteral route:** This route is considered where the patient’s nutritional intake is insufficient to meet their nutritional need, and where there are problems with swallowing but gastrointestinal functioning is normal (Holmes, 2010). Nutrition is administered through a nasogastric tube or directly via a percutaneous endoscopic gastrostomy (PEG) tube passed through the mouth into the stomach and exiting through a hole in the abdominal wall. A patient can be fed for 2 years or more through a PEG.

   Bolus feeding provides nutrition with feeding taking place every 4-6 hours for those that can tolerate a large amount of food at one time. There can be an increased risk of pulmonary aspiration, nausea, vomiting and diarrhea with uncontrolled feeding. Nutrition can be administered either by intermittent bolus or continuously over 16-20 hours, which can increase tolerance and absorption. Feeding by bolus is easier to manage, can be self-administered, and is seen as convenient for those living at home (Holmes, 2010).

   **Parenteral route:** This process delivers nutrients through an intravenous catheter inserted into the internal jugular or subclavian vein. It is used where the patient is malnourished, at risk of becoming malnourished, where the gastrointestinal tract is not functioning and/or where there is unsafe or inadequate oral or enteral intake (NICE, 2006).

   Nutritional elements that satisfy the patients’ energy requirements are delivered through the parenteral route (intravenously in the form of either partial or parenteral nutrition), where essential nutrients are injected so as to supplement other forms of nutrition and provides part of the daily nutritional requirements, or total parenteral nutrition which provides all the patient’s nutritional requirements. The amount and type of nutritional mixture is individualized to meet the nutritional deficits and needs of the patient. Amino acids, essential fatty acids, vitamins and other nutrients can be delivered through a peripheral vein for no more than 14 days (NICE, 2006). Hypertonic solutions such as dextrose with concentrations of 10% or above can cause irritation and damage to the inner walls of peripheral veins increasing vulnerability to phlebitis and so these solutions are administered into the vascular system through larger high flow vessels such as the subclavian vein (Smeltzer et al, 2008).

   Solutions administered through the smaller peripheral veins are hypotonic to avoid complications such as phlebitis. There are risks with this method of administration such as thrombophlebitis, and there is a need to replace the peripheral cannula every 24-48 hours. The potential discomfort caused by the complications of delivery of this form of nutrition in patients receiving palliative care raises ethical issues. The value and
benefits of providing nutrition to a patient who is nearing the end of their life must be balanced against the potential pain. Decisions about the provision of nutrition in these circumstances require collaborative decisions to be made by the patient, family and multidisciplinary team. Where the patient has the capacity to contribute to the decision, his or her wishes should be considered paramount. This can be difficult if the patient decides to refuse nutrition as this will lead to more weight loss and hasten death, which can be distressing for family members.

The aim of nutritional support is to help patients cope with the metabolic demands of their illness and treatment, reduce the risk of infection and promote wound healing (Holmes, 2010). It is an integral strategy for maintaining wellbeing and quality of life when a patient has a chronic illness.

The effects of malnutrition uncomfortable, with nutritional support justified on the grounds that it maintains quality of life, although some patients may not consider being attached to a feeding pump for 16 hours a day an improvement to their quality of life. Maintaining quality of life is important, as evidenced by Somogyi-Zalud et al (2002), who found that comfort and care rather than life-sustaining treatments are perceived as preferable by 70% of patients aged over 80 years with cancer. Studies exploring palliative care in children have supported the important benefits obtained by patients receiving nutritional interventions (Heath et al, 2010). Studies often focus on the quality of life as measured by the parents rather than children, and the findings from these studies have demonstrated the prevalence of anxiety-related symptoms during the end-of-life period and its association with distress. Other distressing symptoms were fatigue, pain and loss of appetite (Hechler et al, 2008).

**Dietary modification strategies**

The guidelines acknowledge the range in texture of food and drink and recommend that practitioners should consider both the effect of modifications on nutritional value and the need for fortification of foods and energy dense drinks as well as portion and bolus size.

**Oral feeding strategies**

**a. Oral feeding manoeuvres**

Swallowing manoeuvres include clearing swallows, effortfull and supraglottic swallows.

**b. Sensory techniques**

Reduced sensation may be helped by:

- Thermal stimulation, with ice or chilled material applied to the oropharyngeal musculature
- Stretching/manipulation of the oral musculature to mimic oral movements of teeth cleaning, eating and clearing the mouth of food

**c. Positioning strategies**

Postural techniques for changing the direction of the bolus and reducing oesophageal reflux include chin tuck, head rotation to the affected side, head tilt, side lying or remaining upright.

**Communication strategies**

**a. Verbal**

In order to overcome communication and/or cognitive disabilities of some patients, nurses need to engage and communicate clearly with patients. The guidelines being familiar with any communication and cognitive impairments, and how the patient communicates, using communication aids, interpreters, drawing and pictorial information, ensuring there is sufficient time, that a family member is present, and using a quiet and private environment at an appropriate time of day. The process should include written and verbal information, limit information given in one session, allow time for questions and repair detail. Being in close proximity and letting the patient know you are close demonstrating and respect expresses reassurance.

**b. Non Verbal**

Carers can be encourage, trained and supported to be an active participant in providing nutritional support. Nurse can provide information and training to ensure carers use the correct techniques that supplements their knowledge of the patient’s dietary preferences.

**Carer support strategies**

Stress-reduction techniques, reducing external stimuli, environmental cues, use of snacks for those unable to eat at mealtimes, education of the patient and family regarding safety/nutritional issues and feeding guidelines can all support oral feeding.

In terms of the efficacy of nutritional interventions in palliative care, the evidence has suggested that weight stabilization can help alleviate some of the adverse effects of the metabolic, such as the acceleration of proteolysis and the depression of protein synthesis, as well as side effects of chemotherapy associated with cancer treatment and can influence not only physical but also social and psychological wellbeing in patients and length of survival with cancer (Bozzetti et al, 2002; Davidson et al, 20041; Tian and Chen, 2005). Where
individually tailored interventions are delivered using dietary advice, oral nutritional supplements, enteral and parenteral feeding dependent on need, this relationship is further confirmed (Marin Caro et al, 2007).

Two systematic reviews suggested that there is a positive effect from dietary advice on quality of life as a standalone intervention (Halfdanarson et al, 12008). Where advice is integrated with oral nutritional supplements, the benefits in reducing malnutrition are further enhanced (Baldwin and Weekees, 2011). Intervention strategies aimed at improving eating may also have a positive effect on quality of life (Hickson and Frost, 2004). However, these studies only included cancer patients, and only a small number of studies sampled patients receiving palliative care. More research is needed to confirm the relationship between nutrition and quality of life.

In addition, the metabolic processes and treatment effects such as muscle wasting and becoming malnourished, associated with many of the illnesses treated within palliative care, provide a clinical and ethical rationale for nurses to deliver and evaluate nutritional interventions to increase and maintain weight (Nursing and Midwifery Council, 2008; Royal College of Physicians and British Society of Gastroenterology, 2010). Nurses have the intimate knowledge of the patients and the clinical knowledge of illness effects and functioning, which allows them to effectively regulate the delivery and evaluation of nutritional interventions. Aspects of quality of use can be used to guide planning and deliver nutritional interventions.

Evidence for nutritional interventions in palliative care

When patients are identified as being malnourished or at risk of malnutrition, the initial nutritional approach is usually the provision of dietary advice. This may take the form of written or verbal advice aimed at improving dietary intake and include information on meal pattern, food choice and fortification of food (Durrieu et al, 2011). Symptoms affecting food intake and contributing to malnutrition are very common in the palliative setting; these include loss of appetite, fatigue, changes in bowel habits, nausea and vomiting, taste changes, oral pain and dysphagia (Labori et al, 2006). Such symptoms, particularly loss of appetite, have been identified as the main causes of distress in patients, contributing to poor quality of life. If dietary advice alone is insufficient or people have particular needs such as in dysphagia, then oral nutritional supplements may be considered as a means of improving dietary intake. As products vary in nutritional composition, it is necessary to consult the manufacturer’s product literature for a detailed analysis. Many manufacturers provide recipes and information on how the supplements may be used to maximize palatability. Often the strategies to improve oral intake through dietary advice have not been tested in the palliative setting, although there is some emerging evidence in the cancer treatment setting. A study of patients receiving radiotherapy treatment for colorectal cancer demonstrated that individualized dietary advice provided by a registered dietitian was superior to oral nutritional supplements and standard care, with respect to maintaining nutritional status, quality of life, radiotherapy toxicity and mortality (Ravasco et al, 2012). This study provided intensive advice and support for the duration of radio-therapy treatment with a long-term follow-up of a median of 6.5 years to assess the longer term outcomes. However, the evidence that dietary counselling can improve similar outcomes in palliative care patients is lacking.

Studies in palliative care have generally been of a much shorter duration, often with outcomes of nutritional status, dietary intake or quality of life. Some studies have addressed a number of strategies and interventions at the same time. For example, a study undertaken by Herrmann et al (2012) assessed the influence of a multi-professional team approach to providing dietary advice, oral supplementation, enteral tube feeding or parenteral nutrition to meet the nutritional needs of palliative patients with solid tumors (Herrmann et al, 2012). Such support with regular monitoring, review and amendments to the method of support resulted in an improvement of hand-grip strength and quality of life with a stabilization of nutritional status. While this study demonstrated good use of the methods of nutritional support available, there is variation in the use of the more invasive methods of artificial nutrition support in different countries. The UK is more likely to use parenteral nutrition only in cases of intestinal failure, whereas other countries may use it as a supplement to oral nutrition or enteral tube feeding (National Collaborating Centre for Acute Care, 2006; Bozzetti et al, 2009). However, this raises interesting questions about the appropriate use of these methods, especially if studies continue to demonstrate that sup- port, such as parenteral nutrition, may contribute to improved quality of life. Such support is expensive and requires specialist teams to man- age its use safely, support patients and caregivers and ensure it is effective (Penner et al, 2012). Future research should include cost-benefit analysis as an integral part of any outcome measures.

A randomized study of patients receiving palliative chemotherapy combined with dietary advice and/or oral nutritional supplements was under- taken for a period of 6 weeks, commencing as early as possible before the start of chemotherapy (Baldwin et al, 2011). Follow-up data was collected at 3, 6 and 12 months but failed to
demonstrate that this period of nutritional intervention influenced survival or quality of life. Nutritional status at 26 weeks post-chemotherapy was comparable between the groups although a difference in nutritional status was seen at 1 year, with those who had received dietary advice having a significantly heavier body weight. The numbers at this time were small so the results should be interpreted with caution.

The use of oral nutritional supplements has increased in recent years and has been supported by an increased availability of flavors and the introduction of more energy-dense liquids, which enable people to take smaller volumes of liquid. They may be purchased by patients or, in some countries, can be prescribed by doctors, potentially reducing the cost to the patient. Supplements may also be used extensively in health-care organizations including hospitals, nursing homes and hospices. Some oral nutritional supplements but not all, are categorized as ‘nutritionally complete’, indicating that if sufficient volume was consumed they would provide an adequate dietary intake. However, the majority are used in conjunction with an oral diet to supplement intake, either to meet nutritional requirements or promote weight gain. Use of these supplements is controversial as they can be expensive and use financial resources in both the community and hospital setting.

Malnourished patients are most likely to benefit from oral nutritional supplements. A randomized intervention study using dietary advice or oral nutritional supplements in malnourished care-home residents suggested that overall health-care costs were not significantly different between the two groups (Parsons et al, 2012). The oral nutritional supplements were effective at improving the quality-adjusted life years of malnourished patients, although it is difficult to extrapolate these results to palliative care patients.

A systematic review of nutritional interventions in malnourished patients with cancer looked at studies where nutritional interventions had been compared with standard practice (Baldwin et al, 2012). From these, six studies compared dietary advice with routine care, three compared oral nutritional supplements with routine care and seven compared dietary advice plus supplements if required, with routine care. All studies aimed to improve nutritional status in the participating patients and the follow-up periods varied, although the majority were less than 6 months. The review showed that there was no influence of nutritional interventions on mortality although there was a beneficial effect on global quality of life measures, assessed primarily via the questionnaire from the European Organization for Research and Treatment of Cancer (EORTC) which was the outcome measure used in the majority of studies (EORTC, 2014). In addition, the questionnaire indicated that nutritional supplements had a beneficial effect, particularly on ‘physical functioning’ and ‘emotional functioning’. Nutritional interventions were reported as improving energy intake when compared to those receiving routine care although there was heterogeneity between the studies examined. When this was accounted for, the difference diminished and was deemed to be not statistically significant. These highlights that measuring nutritional parameters alone may not be the most relevant outcome measure.

Nutrition Therapy End-of-Life Situations

**Question:** What is the role of artificial nutrition and hydration (ANH) in end-of-life situations?

*Based on expert consensus, we suggest that ANH is not obligatory in cases of futile care or end-of-life situations. The decision to provide ANH should be based on evidence, best practices, clinical experience and judgment; effective communication with the patient, family, and/or authorized surrogate decision maker; and respect for patient autonomy and dignity.*

**Rationale:** Neither EN nor PN has been defined to include basic IV hydration, but in the ethics literature, it is often considered part of the same treatment type, referred to as ANH. The anxiety should be anticipated and accurately addressed by the caregiver to help dispel misperceptions and decrease emotional distress. Cultural, ethnic, religious, or individual patient issues may supersede scientific evidence, in some circumstances necessitating the delivery of ANH. In this unfortunate situation, there have been little data to clearly define the benefits and harm of ANH in terminally ill patients. ANH does not improve outcomes in terminally ill patients and may at times increase patient distress. Though high-quality studies in terminally ill patients are difficult to perform, Bruera et al published a well-designed multicenter double-blind RCT concluding that IV hydration, 1 L per day, did not improve quality of life, symptoms, or survival, compared with placebo. Scientific, ethical, and legal perspectives indicate that there is no differentiation between withholding and withdrawing ANH. Numerous professional organizations have published guidelines or position statements to help guide healthcare providers on the ethical considerations involved in deciding whether to initiate, continue, or forgo ANH. Several themes remain constant: clear communication between providers and patients, family, or surrogate decision makers; respect for dignity and
patient autonomy; setting realistic goals of therapy; involvement of an interdisciplinary ethics committee or panel consultation when issues cannot be resolved; continuing care until any conflict around ANH is resolved; transferring care to equally qualified, willing practitioners if conflict cannot be resolved; and at no time should patients or families feel abandoned.

**Conclusion**

Nutritional interventions offered as part of palliative care contribute to the goal of optimizing comfort, managing adverse effects of treatment, controlling symptoms, and maintaining psychological wellbeing. These goals are consistent with the concept of quality of life.

**Reference**

Therapeutic Pediatric Flexible Airway Endoscopy

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Abstract

Application of flexible airway endoscopy (FAE) in children and small infants has much been limited for various reasons. One of the most critical to successfully performing a therapeutic FAE (TFAE) is keeping patient safety and ensure operator confidence throughout the whole procedure. Especially when applying in risky children who already have and vulnerable to significant cardiopulmonary compromise. The ability to maintain appropriate oxygenation, airway, ventilation, circulation and clear scope vision are prerequisites and crucial for achieving successful procedures. For more than two decades, different to the traditional using of rigid endoscopy or open surgical interventions, we have employed a convenient and less invasive modality of TFAE in our pediatric patients immediately after their diagnostic FAE. This comprises preferred use of short working-length FAE, a novel non-invasive ventilation (NIV) support technique with no ventilation bag, mask, or artificial airway and performed in the ICU setting. Many patients who are transferred from both domestic and foreign tertiary medical centers for weaning PPV, extubation, life-saving; and avoid more invasive surgical operations of tracheostomy, laryngotraqueal reconstruction, sternotomy or tracheobronchial plasty under general anesthesia, or extracorporeal life support. Now, we have accumulated 2800+ TFAE of upper and lower airways complicated procedures such as laser ablation, balloon dilatation, foreign body retrieval, stent implantation, stent-plast, etc. Some of them are unique and even have never been reported before in English literatures.

Conclusions

TFAE modality of using short working-length TFAE with NIV support in the ICU setting is safe, timely and effective in critically ill children. It could result in the successful extubation, weaning off mechanical ventilation, averted recommended surgical procedures and save-life.

Reference

Update in Pulmonary Fungal Infection

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Fungal infection has emerged as a worldwide health-care problem. The prevalence and prognosis of pulmonary fungal infection has been difficult to evaluate since diagnoses were seldom confirmed. Epidemiology of fungal infection varying according to geographical region. The SENTRY Antimicrobial Surveillance Program and the EPIC II study showed that Candida sp. is the most frequently isolated fungus worldwide, followed by Aspergillus sp.

Fungal infections can occur in either immunocompetent or immunosuppressed individuals. A clinician should be aware of clinical signs that may suggest the presence of fungal infections, such as persistent lung infiltrates, with or without mediastinal lymphadenopathy (Table 1).

Table 1. Clinical features of fungal infections

- Nonresolving pulmonary infiltration with fever that fails to resolve with standard antibiotic therapies directed at bacteria
- Patients with significant neutropenia (absolute neutrophil count < 500/microliter for > 21 d, hematologic malignancy or hematopoietic cell transplant or solid organ transplantation, patients with malignancies receiving chemotherapies
- Patient with emerging immunocompromising conditions (chronic corticosteroid use, novel immune suppression, renal insufficiency, COPD, diabetes mellitus, cirrhosis)
- Exposure or recent travel to endemic geographic regions
- Hilar and/or mediastinal adenopathy (may or may not be present)
- Associated skin lesions (erythema nodosum, morbiliform or toxic rash), arthritis, bone lesions, CNS disseminantion

The main problem in dealing with pulmonary fungal infection is in distinguishing simple colonization from invasive or disseminated infection. A diagnosis of invasive disease requires the presence of the fungus in normally sterile tissues, while dissemination is defined as invasion of noncontiguous organs secondary to hemogenous spread. Prompt diagnosis of fungal infections remains a challenge because there are no specific signs and symptoms, yet early diagnosis is essential to allow timely treatment, as delay in starting appropriate therapy has been associated with greater hospital mortality in critically ill patients. Newer methods of detecting fungal infections include non-culture techniques relying on detecting components of the fungal cells. The measurement of serum concentration of glucans (components of the cell wall of most fungi except Zygomycetes and Cryptococcus) can be used to rule out invasive fungal infections because of the high negative predictive value of this test. The use of BG detection has provided acceptable diagnostic values to screen invasive candidemia in oncohematological patients with neutropenia and in high-risk ICU patients. A meta analysis of studies evaluating assays for detection of BG in serum yielded a pooled sensitivity rate of 76.8% and a specificity rate of 85.3% for detection of invasive candidiasis. Other method is measurement of Galactomannan. The galactomannan is a component of the cell wall of Aspergillus that is released during tissue invasion and is detected in serum, BAL, or cerebrospinal fluid. Positivity of serum galactomannan is considered when the index is >0.7 in a single sample. Validity of serum test for diagnosis depends on the type of patient, being the highest in the neutropenic patient with 85% sensitivity and 95% specificity.

Several scoring system has been developed to predict fungal infection and the need for treatment. Pittet and colleagues developed “colonization index”, defined as the ratio of the number of body sites colonized with the same strain to the total number of sites cultured, to predict subsequent Candida infection. A colonization index of N0.5 had a specificity of 69% for Candida infection and a positive and negative predictive value of 66% and 100% respectively. When the colonization index was corrected for heavy colonization (ratio of heavily colonized sites to all colonized sites), values ≥0.4 gave positive and negative predictive values of 100%. Another strategy is the Candida score, which evaluates the presence of severe sepsis, multifocal colonization, total parenteral nutrition, and surgery; a score greater than 2.5 is predictive of invasive candidiasis with 81% sensitivity and 74% specificity.
Risk Factors and Different Step of Treatment Strategies in Fungal Infections

Currently, there are three classes of antifungal agents (Table 2) available. Treatment strategies (Figure 1) can be separated into prophylactic, pre-emptive, presumptive, empirical and definitive (or targeted) by considering risk factors (Table 3) and clinical features in the patients.

Table 2. Types of antifungal agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Relevant Medication</th>
<th>Mechanism of Action</th>
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<tbody>
<tr>
<td>Polyenes</td>
<td>Amphotericin B deoxycholate, lipid formulations of amphotericin B</td>
<td>Binds to ergosterol, leading to pore formation in the fungal cell membrane</td>
</tr>
<tr>
<td>Triazoles</td>
<td>Fluconazole</td>
<td>Inhibits fungal membrane ergosterol synthesis by inhibiting C-14-α-demethylase</td>
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<tr>
<td></td>
<td>Itraconazole</td>
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<td></td>
<td>Voriconazole</td>
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<td></td>
<td>Posaconazole</td>
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<tr>
<td>Echinocandins</td>
<td>Caspofungin</td>
<td>Inhibits fungal cell wall β-1,3-D-glucan synthesis</td>
</tr>
<tr>
<td></td>
<td>Anidulafungin</td>
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<td></td>
<td>Micafungin</td>
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Table 3. Risk factors of fungal infections

<table>
<thead>
<tr>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>o Chemotherapy (agent, dose, duration)</td>
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<tr>
<td>o Radiotherapy</td>
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<tr>
<td>o Corticosteroid</td>
</tr>
<tr>
<td>o Immunosuppression</td>
</tr>
<tr>
<td>o Prolonged ICU stay</td>
</tr>
<tr>
<td>o Surgery</td>
</tr>
<tr>
<td>o Renal replacement therapy</td>
</tr>
<tr>
<td>o Total parenteral nutrition</td>
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<td>o Mucositis</td>
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</tbody>
</table>

Figure 1. Treatment strategies in Fungal Infection

Prophylactic antifungal treatment is used when a patient presents a high risk of fungal infection because of underlying conditions (eg, bone marrow or solid organ transplantation or gastrointestinal tract perforation). Pre-emptive treatment is initiated based on positive results from the various available biomarkers or suggested scores. Empirical antifungal treatment starts when compatible signs and symptoms are present but the incriminated organism is unknown. Definitive treatment relies on overt invasive fungal infection with microbiological evidence that allows for specific, targeted therapy.
### Summary of IDSA Guidelines Recommendation

#### A. Management of Candidiasis

<table>
<thead>
<tr>
<th>Condition or treatment group</th>
<th>Therapy</th>
<th>Alternative</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Candidemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonneutropenic Adults</td>
<td>Fluconazole 800 mg (12 mg/kg) oral* loading dose, then 400 mg (6 mg/kg) orally* daily or an echinocandin*. For special conditions, see text.</td>
<td>A lipid formulation of amphotericin B 3 to 5 mg/kg IV daily; or fluconazole 800 mg (12 mg/kg) oral* loading dose, then 400 mg (6 mg/kg) orally* daily; or voriconazole 400 mg orally (or 6 mg/kg IV) twice daily for two doses, then 200 mg orally (or 3 mg/kg IV) twice daily</td>
<td>Choose an echinocandin for moderately severe to severe illness and for patients with recent azole exposure. Transition to fluconazole after initial echinocandin is appropriate in many cases. Remove all intravascular catheters, if possible. Treat 14 days after first negative blood culture result and resolution of signs and symptoms associated with candidemia. Ophthalmic examination recommended for all patients.</td>
</tr>
<tr>
<td>Neutropenic patients</td>
<td>An echinocandin* or a lipid formulation of amphotericin B 3 to 5 mg/kg IV daily. For specific recommendations, see text.</td>
<td>Fluconazole 800 mg (12 mg/kg) oral* loading dose, then 400 mg (6 mg/kg) orally* daily; or voriconazole 400 mg orally (or 6 mg/kg IV) twice daily for two doses, then 200 mg orally (or 3 mg/kg IV) twice daily</td>
<td>An echinocandin or a lipid formulation of amphotericin B is preferred for most patients. Fluconazole is recommended for patients without recent azole exposure and who are not critically ill. Voriconazole is recommended when additional coverage for molds is desired. Intravascular catheter removal is advised but is controversial.</td>
</tr>
</tbody>
</table>

#### Suspected candidiasis treated with empiric antifungal therapy

<table>
<thead>
<tr>
<th>Condition or treatment group</th>
<th>Therapy</th>
<th>Alternative</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonneutropenic Adults</td>
<td>Treat as above for candidemia. Fluconazole is preferred.</td>
<td>A lipid formulation of amphotericin B 3 to 5 mg/kg IV daily or amphotericin B deoxycholate 0.5 to 1 mg/kg IV daily</td>
<td>For patients with moderately severe illness and/or recent azole exposure, an echinocandin is preferred. The selection of appropriate patients should be based on clinical risk factors, serologic test and culture data. Duration of therapy is uncertain, but should be discontinued if cultures and/or serodiagnostic test have negative results.</td>
</tr>
<tr>
<td>Neutropenic patients</td>
<td>A lipid formulation of amphotericin B 3 to 5 mg/kg IV daily, caspofungin 70 mg IV loading dose, then 50 mg IV daily, or voriconazole 400 mg orally (or 6 mg/kg IV) twice daily for two doses, then 200 mg orally (or 3 mg/kg IV) twice daily</td>
<td>Fluconazole 800 mg (12 mg/kg) oral* loading dose, then 400 mg (6 mg/kg) orally* daily; or voriconazole 200 mg (3 mg/kg) orally* twice daily</td>
<td>In most neutropenic patients, it is appropriate to initiate empiric antifungal therapy after four hours. Serodiagnostic test and computed tomography imaging may be helpful. Do not use an azole in patients who received azole prophylaxis previously. (See topic reviews on treatment of neutropenic fever).</td>
</tr>
</tbody>
</table>

#### B. Management of Aspergillosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive syndrome of Aspergillus</strong></td>
<td></td>
</tr>
<tr>
<td>IPA</td>
<td>Voriconazole (16 mg/kg IV every 12 hours for 1 day, followed by 4 mg/kg IV every 12 hours; Oral therapy can be used at 200-300 mg every 12 hours or weight based dosing on a mg/kg; see text for pediatric dosing)</td>
</tr>
<tr>
<td>Invasive sinus aspergilllosis</td>
<td>Similar to IPA</td>
</tr>
<tr>
<td>Tracheobronchial aspergillosis</td>
<td>Similar to IPA</td>
</tr>
<tr>
<td>Aspergillosis of the CNS</td>
<td>Similar to IPA</td>
</tr>
</tbody>
</table>

This infection is associated with the highest among all of the different patterns of IA; drug interactions with anticonvulsant therapy.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspergillus infections of the heart (endocarditis, pericarditis and myocarditis)</strong></td>
<td>Similar to IPA</td>
<td>Endocardial lesions caused by Aspergillus species requires pericardiectomy</td>
</tr>
<tr>
<td><strong>Aspergillus osteomyelitis and septic arthritis</strong></td>
<td>Similar to IPA</td>
<td>Surgical resection of devitalized bone and cartilage is important for curative intent</td>
</tr>
<tr>
<td><strong>Aspergillus infections of the eye (endophthalmitis and keratitis)</strong></td>
<td>Sistemic IV or oral voriconazole plus intravitreal AmB or voriconazole indicated with partial vitrectomy</td>
<td>Systemic therapy may be beneficial in management of Aspergillus endophthalmitis; ophthalmologic intervention and management is recommended for all forms of ocular infections; topical therapy for keratitis is indicated</td>
</tr>
<tr>
<td><strong>Cutaneous aspergillosis</strong></td>
<td>Similar to IPA</td>
<td>Surgical resection is indicated where feasible</td>
</tr>
<tr>
<td><strong>Aspergillus peritonitis</strong></td>
<td>Similar to IPA</td>
<td>Removal of peritoneal catheter is essential</td>
</tr>
<tr>
<td><strong>Empiric preemptive antifungal therapy</strong></td>
<td>For empiric antifungal therapy, liposomal AmB (3 mg/kg/day IV) Caspofungin (70 mg day iIV and 50 mg/day IV thereafter), micafungin (100 mg day) voriconazole (6 mg/kg IV every 12 hours for 1 day), followed by 4 mg/kg IV every 12 hours or 3-4 mg/kg α 12 hours)</td>
<td>Preemptive therapy is logical of empiric antifungal therapy in defining a high-risk population with evidence of invasive fungal infection (eg. pulmonary infiltrate or positive GM assay result)</td>
</tr>
<tr>
<td><strong>Prophylaxis against IA</strong></td>
<td>Posaconazole; Oral suspension: 200 mg TID Tablet 300 mg BID on day 1, then 300 mg daily IV; 300 mg BID on day 1, then 300 mg daily</td>
<td>Efficacy of posaconazole prophylaxis demonstrated in high-risk patients (patients with GVHD and neutrophilic patients with AML or MOS)</td>
</tr>
<tr>
<td><strong>Saprophytic or colonizing syndromes of Aspergillus</strong></td>
<td>Aspergiloma</td>
<td>The role of medical therapy in treatment of aspergiloma is uncertain; penetration into preexisting cavities may be minimal for AmB</td>
</tr>
<tr>
<td><strong>Chronic cavitary pulmonary aspergillosis</strong></td>
<td>Similar to IPA</td>
<td>Innate immune defects demonstrated in most of those patients; long term therapy may be needed; surgical resection may lead to significant complications; anecdotal response to Inf-γ; Tranexamic acid may be helpful in management of hemotysis</td>
</tr>
<tr>
<td><strong>Allergic syndromes of Aspergillus</strong></td>
<td>ABPA</td>
<td>Corticosteroids are a cornerstone of therapy for exacerbations; itraconazole has a demonstrable corticosteroid-sparing effect</td>
</tr>
<tr>
<td><strong>Allergic rhinosinusitis caused Aspergillus</strong></td>
<td>Polyectomy sinus washout with intranasal corticosteroids</td>
<td>Antifungal therapy reserved for refractory or relapsing cases</td>
</tr>
</tbody>
</table>

Abbreviations: ABL, Amphotericin B lipid complex; ABPA, allergic bronchopulmonary aspergillosis; AmB, amphotericin B; AML, acute myelogenous leukemia; BID twice daily; CNS, galactomannan; GVHD, graft-vs-host disease; IA, invasive pulmonary aspergillosis; Inf-γ, interferon gamma; IPA, invasive pulmonary aspergillosis; IV, intravenous; MDS, myelodysplastic syndrome; PO, oral; TID, 3 times daily

References
4. Limper AH. Clinical approach and management for selected fungal infection in pulmonary and critical care patients.
Diagnosis and Management of Cytomegalovirus Pneumonia

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Abstract

Cytomegalovirus [CMV], a member of the human β herpes virus with high seroprevalence in adults, is one of the important causes of morbidity and mortality in immunosuppressed patients. The infection usually latent but can reactivate in critically ill immunocompetent patients causing prolonged ICU stay and increased mortality. Reactivation occurs when cell mediated immunity is disturbed. CMV infection oftentimes asymptomatic and remain unrecognized. The incidence of CMV infection falls between 0 to 36% in critically ill population. Infection usually occurs between 4 to 12 days after hospitalization in ICU with sepsis, mechanical ventilation more than 21 days, and multiple blood transfusions as potential risk factors for CMV reactivation. In order to achieve better outcome, rapid and accurate diagnosis of the etiology of pneumonia is needed especially in critically ill patients. Detection of CMV infection can be done using tissue biopsy and rapid PCR CMV cultures using urine and bronchoalveolar [BAL] fluid with shell vial method.

Introduction

Cytomegalovirus infection is common with a high seroprevalence rate. Cytomegalovirus becomes latent in multiple organs after primary infection, and asymptomatic viral shedding can be detected in saliva and urine. Severe dysregulation of the immune system can promote reactivation due to the release of immunomodulatory cytokines. Some studies have reported several cases of CMV reactivation in “non-immunosuppressed patients” (0-35%) such as in septic shock, trauma, and other critical cases. Pneumonia is one of the direct effects of CMV infection. CMV Pneumonia can develop in all populations of critically ill patients. CMV pneumonia is considered to be a form of reactivation than primary infection. Longer ICU stay and prolonged use of ventilator (median 18 days) were the risk factors observed in those with positive BAL for CMV. Unfortunately, CMV pneumonia usually suspected in later stage of disease and most probably was forgotten as a possible cause of pneumonia.

Risk factors for reactivation CMV infection varied in different studies. Several risk factors have been described in Table 1.

Table 1. Factors Previously Investigated as Potential Risk Factor for the CMV Reactivation and Clinical Variables Associated with CMV or HSV Active Infection in Critically Ill Patients

<table>
<thead>
<tr>
<th>Potential Risk Factor for Reactivation CMV</th>
<th>Clinical Variables Associated with CMV Active Infection</th>
<th>Clinical Variables Associated with HSV Active Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Increased mortality</td>
<td>Increased mortality</td>
</tr>
<tr>
<td>Mechanical ventilation at ICU admission</td>
<td>Increased morbidity</td>
<td>Prolonged length of ICU stay</td>
</tr>
<tr>
<td>Presence of bacterial or fungal infection</td>
<td>Prolonged length of ICU stay</td>
<td>Prolonged length of hospital stay</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Prolonged length of hospital stay</td>
<td>Prolonged duration of mechanical ventilation</td>
</tr>
<tr>
<td>History of corticosteroid use</td>
<td>Increased CD3 count</td>
<td>VAP</td>
</tr>
<tr>
<td>Burn injuries</td>
<td>Presence of end organ dysfunction</td>
<td>ARDS</td>
</tr>
<tr>
<td>Enteral feeding</td>
<td>Increased development nosocomial bacterial infections</td>
<td>Acute lung injury</td>
</tr>
<tr>
<td>Prior admission to other hospital ward</td>
<td></td>
<td>Severity of disease</td>
</tr>
<tr>
<td>Prolonged pre-treatment&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Secondary bacterial infection</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>Corticosteroid treatment</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease severity score&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconsistent data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion &lt;24 h of ICU admittance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Patients treated at a hospital ward >1 week before admittance to the ICU. <sup>b</sup>Different studies have used: Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sepsis-related Organ Failure Assessment (SOFA) score or Simplified Acute Physiology Score (SAPS) II.


Diagnostic Method

The tests frequently used for detecting CMV infection are the detection of antigens (the pp65 antigenemia assay), DNA, and mRNA. Examination using Quantitative DNA detection techniques has high sensitivity in providing prognostic information, therefore it is more frequently used. On the other hand, the negative predictive value of PCR is high and can be used to rule out disease. In the appropriate clinical context, a high viral load (VL) in BAL and tissue correlates best with a disease, but one important issue is that CMV reactivates silently in seropositive patients with no disease.3 A study by Chemaly et al compared CMV VL examination using BAL and blood specimens from lung transplant specimens. It shows higher CMV VL in the BAL specimens, suggesting stronger association and predictive value with CMV pneumonitis than blood VL.10 Another study reported that immunohistochemistry and CMV VL in BAL is predictive for the development of invasive CMV disease.11 Examination using CMV VL in BAL is rapid and more useful to establish CMV diagnosis than conventional cultures which need 1-4 weeks.7 The study by Rasmussen reported a direct correlation between PCR VL and risk of CMV disease. Cytomegalovirus infection can be detected as early as two weeks with PCR and has the advantage for early preemptive therapy.12

Antiviral treatment

Drug of choice for the treatment of CMV disease is Ganciclovir or Foscarnet for intravenous (IV) route, and Valganciclovir for oral route. Recommended dose for Ganciclovir is 5mg/BW/day IV as an induction dose for 2-3 weeks, followed by another 3-4 weeks maintenance dose via the oral route.3 For critically ill patients with renal problems, the drug dose needs to be adjusted. Intravenous immunoglobulin is recommended for the treatment of CMV pneumonia. Experimental studies using mice models showed the benefit of prophylactic therapy, which can prevent reactivation and CMV associated pulmonary fibrosis, than delayed treatment.1

References

The Role of Serology and Polymerase Chain Reaction in Diagnosing Cytomegalovirus

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Dr Cipto Mangunkusumo General Hospital

Abstract

Cytomegalovirus infection occurs in almost everyone. Most of CMV infection is asymptomatic. Clinical symptoms range widely, not typical and diverse, so the diagnosis is based on clinical symptoms can not be determined. CMV infection can occur various forms, as a primary infection, latency and reactivation or secondary infections. Virus can be found in various fluids and tissues of the body. Laboratory tests are needed to determine the exact diagnosis of CMV infection and prove that the symptoms that occur associated with CMV infection. Various methods have been developed for the detection of CMV infection include electron microscopy, histopathology, serology, virus isolation and molecular detection such as PCR and so on. Serological and molecular detection test is an examination which is widely used for the detection of CMV infection. Measurement of IgM and IgG conducted for detection of primary infection or recent infections. IgM detection methods have some constraints in terms of technical, but in a secondary or reactivation of CMV infection IgM can also be detected, that it can not distinguish between primary or secondary infection. IgG avidity examination can be a solution to overcome the limitations of IgM examination. High avidity IgG may indicate past infection or low avidity IgG is a marker for new infections. Molecular detection is another alternative for detection of CMV infection especially for those having problems in the use of serological test. Polymerase Chain Reaction is a method that is often used for the detection of CMV infection. Qualitative PCR can be used for the detection of primary infection or reactivation, the interpretation depends on the type of specimen and the time taken. Quantitative PCR can be used to monitor the course of infection CMV since before it happened, the primary infection or reactivation and evaluation of treatment outcomes. A definitive diagnosis of CMV diseases is very important for the management and prevention of infection because it has provided the antiviral drug ganciclovir which is an antiviral drug of choice. For the management and treatment of CMV diseases, Selection of laboratory tests and specimens for the detection of CMV infection should be adjusted to the availability of test and examination purposes as it would affect the interpretation of results

Keywords: CMV infection, latent, reactivation, IgM detection, IgG avidity examination, PCR
Mechanical Ventilation in Acute Asthma

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Abstract

In most patients with acute severe asthma intensive therapy with inhaled beta-agonist, systemic corticosteroids and oxygen is usually sufficient to improve pulmonary function and ameliorate symptoms. However, despite maximal medical therapy some patients develop life-threatening features and require ventilatory support. Fewer than five percent of patients admitted with an acute asthmatic attack require intubation and ventilation. Mechanical ventilation in status asthmaticus is a life support system associated with substantial morbidity and should be instituted only when it becomes evident that maximal therapy will not be efficacious. To avoid excess morbidity and mortality however, one must be precise in management of these patients.

Respiratory failure from severe asthma is a potentially reversible, life-threatening condition. Poor outcome in this setting is frequently a result of the development of gas-trapping. This condition can arise in any mechanically ventilated patient, but those with severe airflow limitation have a predisposition. It is important that clinicians managing these types of patients understand that the use of mechanical ventilation can lead to or worsen gas-trapping. In this review we discuss the development of this complication during mechanical ventilation, techniques to measure it and strategies to limit its severity. We hope that by understanding such concepts clinicians will be able to reduce further the poor outcomes occasionally related to severe asthma.

When a patient with severe asthma does not respond adequately to medical therapy, prompt intervention in an effort to provide adequate oxygenation and ventilation by means of noninvasive positive pressure ventilation (NPPV) or invasive positive pressure mechanical ventilation is frequently lifesaving. Given that these patients have a propensity to develop severe airflow limitation, making it difficult to exhale all of their inspired gas, gas-trapping (which leads to dynamic hyperinflation and is also referred to as intrinsic positive end expiratory pressure [PEEP] and auto-PEEP) frequently occurs. As a result, one of the most important principles of mechanical ventilation in this setting is to utilize a strategy aimed at reducing the likelihood that this complication will occur.

While the prevalence of asthma has increased, outcomes of severe asthma appear to be improving, with lower complication rates and fewer in-hospital deaths. Nonetheless, it is estimated that about 10% of individuals admitted to hospital for asthma go to the intensive care unit, with 2% of all admitted patients being intubated. Not surprisingly, admission to the intensive care unit and need for mechanical ventilation are associated with mortality. When death does occur it is most commonly a result of one of the complications of severe gas-trapping. These complications include barotrauma, hypotension and refractory respiratory acidosis. If the morbidity and mortality associated with severe asthma is to continue to decrease, then it is imperative that clinicians caring for such patients have a clear understanding of how gas-trapping can occur and of how it may be recognized/measured and limited.

Introduction

One of the most challenging aspects of respiratory care is the management of the patient with status asthmaticus who requires ventilatory support. Although the incidence and prevalence of acute severe asthma episodes that require ventilatory support are relatively unknown, the asthma hospitalization and death rates have declined in recent years, which suggests a concurrent decline in the need for mechanical ventilation of patients with asthma. That decline, despite an increased prevalence of asthma, probably reflects our improved ability to manage asthma on a long-term basis and early during exacerbations. However, patients continue to present with severe exacerbations that require mechanical ventilation, and mortality may approach 10% in these patients.

There are very few comprehensive data regarding the rate of severe asthma episodes and the incidence of asthma respiratory failure that requires mechanical ventilation. According to the most recent United States Surveillance for Asthma, for the 3-year period 2001-2003, an average annual 20 million persons in the United States had asthma. Among those persons, asthma caused an average annual 1.8 million emergency-department visits, 504,000 hospital discharges, and 4,210 deaths. Thus, using the number of emergency room visits and hospitalizations as a surrogate for asthma exacerbations, around 5–10% of asthmatics. Of those patients, a small but important percentage require mechanical ventilation.
Recent reports of asthma-related intensive-care-unit morbidity and mortality reported an intubation rate of 2–20 patients per year and a death rate of 1–26.7% of intubated patients. Thus, asthma-induced respiratory failure that requires mechanical ventilation remains a noteworthy problem in the care of asthma. Unfortunately, we have little in the way of randomized trials to guide the care of these patients, and they can be extremely difficult to manage.

**Asthma**

**Definition**

Asthma is a heterogeneous disease, usually marked by an airway chronic inflammatory. It is defined by the acts of symptoms in respiration such as wheezing, shortness of breath, the congestion in the chest and coughing varies from time to time and in the intensity, along with limited airflow expiration.

This definition is reached by the consensus, based on characteristic consideration that is peculiar of asthma and which distinguishes them from other respiratory conditions.

**Asthma Phenotype**

Asthma is a heterogeneous disease, with different underlying disease processes. Demographic characteristics, clinical and/or pathophysiology groups are often known as phenotype of asthma. In patients with more severe asthma, there are a number of therapies guided by phenotype which is available. However, until this moment, there is no strong relationship that has been found among the particular pathological display and certain clinical patterns or response of therapy. Therefore, more research is needed to understand the clinical utility of classification on phenotypic of asthma.

Many of the phenotype has been identified. Some of the most common including:

- **Allergic Asthma:** this is the most easily recognized asthma phenotype, which often begin in infancy and associated with the acts of the past and/or family of allergic disease such as eczema, allergic rhinitis, or allergic to food or medicine. The examination of patient sputum before therapy often expresses the inflammatory of eosinophilic airway. Patients with asthma phenotype usually have a good respond with corticosteroid inhalation therapy (ICS).

- **Non-alergical asthma:** a number of adults do have asthma which is not associated with allergy. Cellular profile of the sputum of these patients maybe neutrophilic, eosinophilic or just containing little inflammatory cells (paucigranulocytic). Patients with non-alergical asthma often have less responds to ICS.

- **Slow onset asthma:** In some adults, particularly women, are known to have asthma for the first time during thier adult life. This leads patients to develop non-alergical asthma, and often need higher doses of ics or relatively refractory therapy of corticosteroid.

- **Asthma with limited flow of fixed air:** Some patients with asthma that has been going on long duration of compiled limited flow of fixed air is also considered because of remodelling of the walls on the channel of breath.

- **Asthma with obesity:** Some of obesity patients with asthma have prominent respiratory symptoms and a little inflammatory in the eosinophilic airway.

**Pathophysiology**

Life-threatening asthma resulting from heavy exacerbation puts patients at risk of asphyxia. The worsening of exacerbation increases the risk of death. Unfortunately, it is difficult to classify the severity of exacerbation. According to the consensus guidelines, asthma exacerbation considered heavy when the patient satisfies certain criteria (Table 1).

**Table 1. Definition of heavy asthma exacerbation**

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>Accesory muscle activity</td>
</tr>
<tr>
<td>Paradoxical pulse &gt;25 mm Hg</td>
</tr>
<tr>
<td>Heart Beat &gt; 110 x/minute</td>
</tr>
<tr>
<td>Respiratory Rate &gt;25-30 x/minute</td>
</tr>
<tr>
<td>Limited ability to speak</td>
</tr>
<tr>
<td>PEF or FEV1 &lt; 50% of predicted</td>
</tr>
<tr>
<td>Arterial Oxygen Saturation &lt; 91.92%</td>
</tr>
</tbody>
</table>
In addition, patients with certain historical patterns of asthma are more likely to have a severe exacerbation (Table 2). However, it is important to note that over 50% of patients who have a life-threatening asthma episode may not have suggestive histories or disease patterns. Thus, any patient with asthma can present with a life-threatening exacerbation at any time.\(^3\)

**Table 2. Risk Factors for Severe Asthma Exacerbation\(^3\)**

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior mechanical ventilation</td>
</tr>
<tr>
<td>Prior intensive care unit admission</td>
</tr>
<tr>
<td>Recent hospitalization</td>
</tr>
<tr>
<td>American Thoracic Society definition of severe asthma</td>
</tr>
<tr>
<td>Poor adherence to therapy</td>
</tr>
<tr>
<td>High allergen exposure</td>
</tr>
</tbody>
</table>

The major physiologic changes associated with a severe exacerbation are airflow limitation, bronchial hyperresponsiveness, airway closure, loss of elastic recoil, and hyperinflation (or air trapping). These all result from airway narrowing, largely due to bronchoconstriction, although edema and mucus production in the airways also probably contribute to the reduction in airway caliber. In fact, autopsy studies of patients who died of asthma indicate a high incidence of airway obstruction from mucus impaction, which suggests that edema and mucus production may play a more prominent role in severe exacerbations\(^3\).

It is important to note that research shows that the basis of the edema, mucus production, and bronchoconstriction in asthma is airway inflammation. In general, the airway inflammation characteristic of asthma results from an immune reaction to an inhaled antigen or infectious agent from the environment. In allergic asthma, the airways develop predominantly eosinophilic inflammation. In non-allergic asthma, neutrophilic and pauci-immune forms have been described, but it is unclear if these represent distinct clinical phenotypes, as they often respond to conventional asthma therapy.\(^9\) Some data suggest that neutrophilic forms are more often associated with severe or refractory asthma and thus may be more common in those presenting with severe exacerbations. In response to the airway inflammation, airway smooth-muscle cells become hyperreactive, leading to reversible bronchoconstriction in response to various stimuli. Based on this understanding of asthma pathogenesis, the current approach to therapy for asthma exacerbation includes bronchodilators to relieve bronchoconstriction and anti-inflammatory therapy (i.e., corticosteroids), which is critical for the ultimate resolution of an exacerbation.\(^3\)

The airway narrowing increases the resistance to airflow and requires the patient to work harder to breathe. The increased resistance lengthens the exhalation time required to empty the lung, which leads to air trapping (hyperinflation). In addition, factors such as low pulmonary elastance and persistent activation of the inspiratory muscles contribute to the tendency for air trapping. Hyperinflation stimulates the feeling of dyspnea, impairs gas exchange by increasing dead space, increases the work of breathing, and in extreme cases leads to hemodynamic compromise and barotrauma. Unfortunately, mechanical ventilation, when improperly managed, can exacerbate hyperinflation by increasing the minute ventilation. Thus, it is not surprising that mechanical ventilation of a patient with asthma can be associated with increased dead-space ventilation, barotrauma, and hemodynamic collapse (caused by effects on venous return).\(^3\)
Mechanical Ventilation in Acute Asthma

**Figure 1.** A: Positron emission tomogram of residual intrapulmonary tracer gas in a lung cross-section from a patient with asthma. The tracer concentration increases according to the following color scale: black (no tracer), red, yellow, and white (most tracer). The insoluble tracer is washed out during breathing or is retained inside large ventilation defects. After deep inhalations (lower panel), tracer clearance is enhanced from parts of these defects (circle). B: Volumetric rendering of ventilation defects (red) and the external surface of the lungs (blue). The image orientation is as if the subject were standing facing the reader. These images demonstrate the heterogeneity of ventilation in asthmatic lungs.3

Recent research suggests that the pattern of airway narrowing is heterogeneous, leading to lung areas with relatively preserved ventilation near areas with high-grade obstruction (Fig. 1). Indeed, some airways may be completely obstructed by severe constriction and mucus impaction and thus may trap gas in the lung at high pressure. The implication is that routine measurements of end-inspiratory and end-expiratory pressure, used to judge the safety of ventilation, may underestimate the amount of trapped gas in the patient, as has been described clinically. Thus, this heterogeneity contributes to the complexity of ventilation and makes it more likely to have unrecognized hyperinflated regions that lead to poor ventilation perfusion matching, hemodynamic compromise, and increased susceptibility to barotrauma.3

**Mechanical Ventilation in asthmatic patient**

**Indication of Intubation**

The decision to intubate is based essentially on clinical judgment. Progressive exhaustion and patient fatigue despite maximal therapy together with altered level of consciousness are indications for intubation. In the absence of respiratory arrest maintaining adequate oxygenation (and oxygen transport) with supplemental oxygen is seldom a problem even in very severe asthma and is a relatively uncommon reason for intubation. If the patient is cooperative, hypercapnia and fatigue do not necessarily mandate intubation because noninvasive ventilation may be an option.11

**Purposes of Mechanical Ventilation in Asthma**

Once the patient is intubated, the primary focus of mechanical ventilation should be achieving adequate oxygenation (oxygen saturation 88–92%) and ventilation, while minimizing hyperinflation. To achieve those goals it is often necessary to hypoventilate the patient. Important considerations are determining exactly what a “safe” amount of hyperinflation and what are the minimal ventilatory requirements (i.e., arterial blood pH > 7.20). Unfortunately, there have been few randomized controlled trials to guide us. Case series have suggested that hypoventilation and moderate respiratory acidosis can be well tolerated in these patients, although the exact cut-off of a “safe” pH has not been determined. In addition, Tuxen et al found that the incidence of complications can be reduced by limiting hyperinflation below a critical value (assessed by measuring the exhaled tidal volume [VT] after a 40–60 s prolonged expiratory pause maneuver). Others have recommended pressure or volume limits (plateau pressure < 30 cm H₂O, VT 8–10 mL/kg) based on normal physiology, but the safety of that type of approach has not been validated.3

It thus appears prudent to take an approach of “controlled hypoventilation” or “permissive hypercapnia” with a minute ventilation that maximizes expiratory time (thus minimizing hyperinflation), but provides enough ventilation to keep the arterial CO₂ and pH in a reasonable range.11 The safe range of these values depends in part on certain characteristics of the patient’s condition (e.g., hemodynamic stability, arrhythmias) and the clinical judgment of the care team.3
**Ventilator Settings**

Table 3 shows a recommended set of initial ventilator settings for the intubated asthmatic patient.

<table>
<thead>
<tr>
<th>Table 3. Initial Ventilator Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure or volume ventilation per individual or institutional preference and patient characteristics</td>
</tr>
<tr>
<td>Avoid air-trapping</td>
</tr>
<tr>
<td>$T_i$ 0.8–1.2 s (high flow, constant rather than descending-ramp flow)</td>
</tr>
<tr>
<td>$f$ 10–15 breaths/min</td>
</tr>
<tr>
<td>$V_T$ 6–8 mL/kg</td>
</tr>
<tr>
<td>$P_{plat}$ &lt; 30 cm H$_2$O</td>
</tr>
<tr>
<td>PEEP 0 cm H$_2$O</td>
</tr>
<tr>
<td>$F_{I_{O_2}}$, adequate to provide $S_{O_2}$ 88–92%</td>
</tr>
</tbody>
</table>

1. **Mode**

The first decision to be made is the ventilation mode. This choice may be influenced by institutional preference, but there are clear advantages and disadvantages to both pressure-targeted and volume-targeted strategies. In a pressure-targeted mode the peak inspiratory pressure is limited and the lungs will not be inflated to a pressure above the set peak pressure. This has the advantage of always limiting the amount of hyperinflation. For example, if pressure control is used with an inspiratory pressure of 30 cm H$_2$O, the pressure in the lung will not exceed 30 cm H$_2$O, even if there are occluded airways with trapped gas. Another advantage of a pressure-targeted mode is that if the airway resistance suddenly increases, the patient will not hyper inflate; however, the VT will drop. The problem with a pressure-targeted mode is that if the airway resistance is very high, it will be difficult to deliver an effective VT.

In Medoff experiences, he found it very difficult to provide adequate ventilation (arterial pH - 7.20) to severely obstructed patients with pressure control. This is largely due to the mechanics of delivering a VT against a high resistance with a low pressure limit. The smaller VT also makes it more difficult to deliver aerosolized bronchodilator-aerosol. Thus, a pressure-targeted mode will provide the safest form of ventilation, but at the expense of decreased CO$_2$ clearance, a lower pH, and less effective aerosol delivery. It should also be noted that as the patient’s airflow obstruction improves, a high pressure setting with a pressure-targeted mode could lead to a large VT. Thus, as the patient improves, the pressure setting should be reduced accordingly.

A volume-targeted approach will better provide a minimal VT by delivering very high flow and pressure that overcome the high airway resistance. This provides better ventilation and aerosol delivery but increases the risk of hyperinflation. Often we monitor plateau pressure after a volume-targeted breath as a surrogate for end-inspiratory lung volume (which should best track with the risk of barotrauma). However, the plateau pressure is an average pressure and will reflect only the pressure in open lung units. Lung areas that have high pressure in the initial part of the inspiratory cycle, and lung segments that become occluded at the end of inspiration, may still be at risk of barotrauma despite a “safe” plateau pressure. Thus, a volume-targeted ventilation mode will better ensure adequate ventilation in severe cases or with abrupt increases in airways resistance, but probably increases the risk of hyperinflation in the asthmatic patient. Medoff strategy is to use pressure control when possible, but in most cases I need to start with a volume-targeted approach and carefully monitor for signs of hyperinflation.

2. **Minute Ventilation, Tidal Volume, and Respiratory Rate**

The risk of hyperinflation will track directly with the minute ventilation. Most experts recommend limiting VT in ventilated asthmatic patients to 6–10 mL/kg. I usually use small VT (6–8 mL/kg), based in
part on the experience in patients with acute lung injury. Although asthmatic patients may not have the same risk of ventilator-induced lung injury as do patients with acute lung injury, some data suggest that reducing VT in all patients with respiratory failure may reduce the risk of ventilator-induced lung injury.14

3. Inspiratory Time and Inspiratory Flow

In the end, the most critical determinant of hyperinflation in a mechanically ventilated asthmatic patient is the expiration time. The longer a patient exhales, the less gas will be trapped in the lung at end-expiration, which reduces the risk of hyperinflation during inspiration. One can maximize expiratory time for a given minute ventilation by shortening the inspiratory time. In volume-targeted modes this is accomplished by increasing the inspiratory flow rate and using a constant-flow pattern. In pressure-targeted modes the flow rate is determined in part by the patient’s inspiratory drive, so there is much less ability to control the flow rate in a pressure-targeted mode. It is important to note that recent research suggests that there is a plateau in expiratory flow after a certain point, so increasing the expiratory time above a certain value has limited benefit. In general, after about 4 seconds of expiration there is nominal gain in reducing hyperinflation.15

One must also consider the consequences of a high constant-flow rate. Higher airway pressure and a more heterogeneous distribution of ventilation will result when inspiratory flow is high, which can increase the risk of focal areas of hyperinflation and make ventilation less effective by increasing dead space. Based on this, I favor a moderately high flow rate (60–80 L/min) with a descending flow pattern, targeting an inspiratory time of 0.8–1.2 seconds.3

4. Fraction of Inspired Oxygen

Oxygen-enriched gas should be administered to all ventilated asthmatic patients, but the fraction of inspired oxygen needs to be only enough to provide a blood oxygen saturation greater than 88%. It is important to note that bronchodilators can decrease oxygen saturation by dilating the pulmonary vasculature and reducing ventilation-perfusion matching.3

5. Positive End-Expiratory Pressure

The application of PEEP in status asthmatics is controversial. In patients with emphysema, PEEP can counterbalance the intrinsic PEEP (auto-PEEP) without affecting expiratory flow because of dynamic collapse of the airways and a "waterfall effect." This can be helpful in patients who are spontaneously breathing, because it improves ventilator triggering. However, in asthmatics the site of increased resistance is in central (less collapsible) airways. Furthermore, asthmatic airways are likely to be stiff (from inflammation) and more resistant to dynamic collapse, and thus will not have the same waterfall effect as in patients with emphysema.

If there is no dynamic collapse, then, in theory, the use of PEEP will increase the back-pressure to expiratory flow and result in more hyperinflation. Indeed, early physiology studies of asthmatics on ventilators demonstrated that the application of PEEP led to more hyperinflation. Thus, most review articles do not recommend the routine use of PEEP in patients with asthma.3,11
Figure 3. Three of the possible responses observed in plateau pressure (Pplat), total intrinsic positive end-expiratory pressure (auto-PEEP), and functional residual capacity (FRC) with the application of PEEP (represented as a percentage of auto-PEEP). The FRC measured at zero external PEEP was considered the reference. Changes were independent of ventilator settings. A: Paradoxical response with a decrease in lung volumes. B: Biphasic response: initially there is no change in lung volume, until the applied PEEP reaches about 80% of the auto-PEEP. C: Overinflation response: there is increased air trapping as PEEP increases.³

However, recent research suggests that physiology can be varied, so that some patients respond PEEP with increased trapped air, some patients without lung volume changes, and some with a paradoxical decrease of lung volume (Fig. 3). This would suggest that in some patients PEEP can be carefully used, although the practice is not currently using PEEP during controlled ventilation.³

6. Hyperinflation Monitoring

Once the patient is intubated and stabilized with the initial ventilator settings, care teams must frequently monitor hyperinflation, using one or more maneuvers. Assuming the patient is not breathing spontaneously and in harmony with the ventilator, the pressure end of inspiration (plateau) and expiratory (auto-PEEP) should be measured as soon as any changes in ventilator settings, and periodically when in stable settings. Pressure plateau is a substitute for lung volume at the end of inspiration, which is directly correlated with the risk of barotrauma. Auto-PEEP can be used as a measure of the degree of airway obstruction and to assess the risk of hemodynamic disturbances associated with hyperinflation. In general, we target auto-PEEP is less than 5 cmH₂O and plateau pressure less than 30 cmH₂O, but it is important to realize that these measurements represent the average pressure, so some areas of the lung may be exposed to pressures higher than those measured by plateau pressure and auto-PEEP. In addition, as mentioned earlier, auto-PEEP measurement standards do not reflect the pressure in the lung area behind the obstructed airway at the end of expiration. This is called an occult - an occult PEEP should be suspected in patients who have a measure of auto-PEEP is low but high plateau pressure and evidence of hyperinflation on chest X-rays. Thus, it can not be assumed that the patient is ventilated safely, even when the value of auto-PEEP is less than 5 cm H₂O and plateau pressure less than 30 cmH₂O.³

The most predictive measurement is the possibility of lung volume at the end of inspiration. For this measurement and left paralyzed patients breathe for 40-60 seconds, after a period of stable ventilator settings. Data shows that if diekskalasi volume of less than 20 mL / kg, a patient’s risk for experiencing barotrauma low and no further changes are required ventilator settings. However, frequent use of this maneuver for routine monitoring is not practical, because the paralytic therapy is relatively contraindicated in patients with asthma due to high risks of neuromuscular complications.¹⁷ In very severe cases where the risk of barotrauma is high (or if barotrauma is already there), occasionally usable lung volume at the end of inspiration to guide therapy. The real key is the assessment of patients who often voted with the development of the disease process, because the level of bronchoconstriction can change quickly, which often require changes in ventilator settings.
The Inspired Air Humidification

Heated humidification should be achieved with the cascade humidifier, not with the heat and humidity exchangers. This latter device is undesirable for two reasons: first, they add expiratory airway resistance, which hardly helps to reduce hyperinflation. Second, because inserted between the endotracheal tube and the Y-piece of the ventilator tubing, it can increase the dead space and therefore contribute to hypercapnia.

Termination Mechanical Ventilation

When exactly to begin the termination process of mechanical ventilation is a matter of clinical judgment. In practice, when hyperinflation dynamic has quite subsided (as assessed by the resolution substantially from wheezing on auscultation of the chest and auto-PEEP below 5 cmH2O), trial vents Supported pressure begins, followed by a lockout procedure mechanical ventilation standards if it is well tolerated. In contrast to chronic obstructive pulmonary disease, discontinuation of mechanical ventilation can usually be quickly achieved in patients with acute severe asthma. Difficulty discontinuation of mechanical ventilation in the absence of severe persistent airway obstruction should raise the suspicion of myopathy induced by administrating neuromuscular blocking agents and corticosteroids previously.

Pharmacology Therapy

1. Beta-Adrenergic Agent Used

As a first-line treatment of bronchoconstriction, β-adrenergic agents should be given as a dose repeated inhalation rather than as continuous intravenous infusion for a fast onset of action and incidence of adverse events were lower with the way that pertama. Aerosol Salbutamol can be delivered via metered-dose inhalers (MDI) or nebulizers. MDI, if possible with the addition of spacer device, preferably than nebulizers for easier manipulation, reproduction dose easier, achievement of maximum bronchodilation faster and the risk of bacterial contamination is lower. A common starting dosage in acute asthma for inhaled albuterol (salbutamol) is 2.5 mg by nebulization (0.5 ml of a 0.5 % solution in 2.5 ml of normal saline) every 20 min for three doses, then approximately hourly as dictated by the patient's clinical course. If severe airflow obstruction persists, albuterol (salbutamol) can be nebulized at higher doses (5 mg) and more frequently (even continuously), unless side effects, such as tachyarrhythmias or severe tremor, limit administration.

Recent reports indicate that for administration of inhaled/β2-agonists, metered-dose inhalers combined with a spacer are as effective as nebulized solutions in acute asthma of all degrees of severity. In severe asthma, four puffs (400 µg) of albuterol (salbutamol) is as effective as 2.5 mg via nebulization, and three puffs (1.95 µg) of metaproterenol ( orciprenaline) is as effective as 15 mg by nebulizer. With severe airflow obstruction, most providers still prefer administration via hand-held or mask nebulizer because less patient coordination and supervision are required.

<table>
<thead>
<tr>
<th>Examples</th>
<th>Dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line therapies</strong></td>
<td></td>
</tr>
<tr>
<td><strong>β2-Agonists</strong></td>
<td>Albuterol (salbutamol) 2.5 mg in normal saline via nebulizer or 4 puffs (400 µg) by MDI with a spacer q20 min × 3</td>
</tr>
<tr>
<td></td>
<td>Metaproterenol ( orciprenaline) 15 mg via nebulizer q20 min × 3 or 3 puffs (3.95 mg) by MDI with a spacer q20 min × 3</td>
</tr>
<tr>
<td></td>
<td>Epinephrine (adrenaline) 0.3 ml 1:1000 solution SC q20 min × 3</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>Prednisone 150–225 mg PO qd in divided doses 60–125 mg IV q6–8 h</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
</tr>
<tr>
<td><strong>Oxygen</strong></td>
<td>Titrator to keep SaO2 &gt; 90%</td>
</tr>
<tr>
<td><strong>Second-line therapies</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Methylxanthines</strong></td>
<td>Theophylline Load: 5–6 mg/kg IV over 20–30 min (reduced loading dose in patients already taking theophylline preparations) Maintenance: 0.6 mg/kg/h IV; titrate to serum theophylline concentration 8–15 µg/ml</td>
</tr>
<tr>
<td></td>
<td>Ipratropium 0.5 mg via nebulizer qh × 3</td>
</tr>
</tbody>
</table>

Figure 4. Medical treatment of status asthmaticus (MDI metereddose inhaler)
2. Corticosteroids

The best time to begin systemic corticosteroids is prior to the development of status asthmaticus, when the patients’ usual medications fail to control their deteriorating PEFR and increasing symptoms. Many patients and physicians remain reluctant to intervene with a course of corticosteroids early in worsening asthma because of fear of side effects. The consequence of delay is often progression to severe disease requiring emergency care. The time to onset of action of systemic corticosteroids is thought to be several hours; the resultant improvement in lung function evolves slowly as airway inflammation gradually resolves. As a result, in status asthmaticus the first dose should be given as soon as possible (in the physician’s office or emergency department). Significant improvement with systemic corticosteroids has been difficult to demonstrate during the few hours that the asthmatic patient spends in the emergency department.

3. Anticholinergics.

Anticholinergics (e.g., ipratropium bromide and glycopyrrolate) are not first-line agents. They are slower in onset and produce less bronchodilation at peak effect than β2-agonists. Recent large, prospective, double-blind trials in acute asthma among adults have failed to show a significantly better response to the combination of nebulized ipratropium and albuterol than to nebulized albuterol alone. Ipratropium bromide and glycopyrrolate may be useful adjuncts to β2-agonists and corticosteroids in patients whose asthma is not responding to therapy, but we do not favor their routine use in acute, severe asthma. Patients with bronchospasm induced by β-blockers and patients receiving therapy with monoamine oxidase inhibitors may particularly benefit from this class of bronchodilator. Ipratropium bromide can be given by metered-dose inhaler (18 µg/puff) or by nebulization (0.5 mg diluted in normal saline). Optimal dosing is uncertain. A useful strategy in acute severe asthma failing to respond to standard therapy is administration of ipratropium in combination with albuterol (combined in the same nebulizer cup) for three successive hourly treatments. If no benefit is evident, then the anticholinergic can be discontinued.

4. Anti-leukotriene agents

This new class of medications for control of asthma symptoms consists of agents that block either the synthesis or action of the sulfidopeptide leukotrienes, mediators that are potent bronchoconstrictors and also induce pulmonary vascular leakage and inflammatory cell infiltration of the airways. Although these medications have generated a great deal of excitement, they are only approved in the United States for use in chronic asthma management as disease controllers. Inhibition of pro-inflammatory mediators, such as leukotrienes, is likely to speed resolution of the acute exacerbation, but to date there is no evidence for their efficacy in the management of acute severe asthma in the intensive care unit.

5. Heliox

Heliox is a blend of helium and oxygen available in mixtures containing 60-80 % helium. Because this mixture is less dense than air, turbulent flow is rendered more laminar, resulting in decreased airway resistance to gas flow. In some patients this effect increases ventilation, decreases the work of breathing, and delays the onset of respiratory muscle fatigue, forestalling the development of respiratory failure. In others, in whom the predominant mechanism of airflow limitation involves laminar flow in small airways, heliox is of no benefit and may interfere with usual care. These properties suggest heliox to be ideally suited for patients with acute asphyxic asthma, but limited clinical data are available on its use in the adult intensive care unit. The role of heliox in acute asthma remains controversial, and it is generally limited to centers experienced in its administration.

6. Antibiotics

Respiratory infections that trigger asthmatic attacks are almost uniformly viral in etiology. The purulent-appearing sputum of acute asthma most often reflects an increase in airway eosinophils, not neutrophils, and even focal radiographic opacities may be the result of eosinophilic pneumonia or atelectasis secondary to mucus plugging rather than bacterial pneumonia. Therefore, unlike in exacerbations of chronic obstructive pulmonary disease, antibiotics are not a standard treatment in acute asthma. When compared to placebo in a randomized, double-blind study of patients hospitalized with status asthmaticus, amoxicillin neither improved spirometry nor shortened length of hospitalization. We recommend that use of antibiotics be restricted to those patients with fever, sputum that contains neutrophils, or clinical evidence of bacterial pneumonia or sinusitis.

Conclusion

Asthma is a common chronic respiratory disease characterized by symptoms that vary such as wheezing, shortness of breath, chest tightness, and / or coughing, and by the variations of expiratory air flow limitation.
Mechanical Ventilation in Acute Asthma

Life-threatening asthma is resulting from severe exacerbation leading patients at risk of asphyxia. The main physiological change associated with severe exacerbation is airflow limitation, bronchial hyper-responsiveness, airway closure, lost of elasticity, and hyperinflation (or air trapping). Although by giving maximum therapy, progressive exhaustion, patients fatigue, and the conscious level changing are the indication to do intubation.

Once the patients is intubated, the primary focus of mechanical ventilation should achieve oxygenation (oxygen saturation 88-92 %) and adequate ventilation that minimizes hyperinflation. It seems prudent to take a ‘controlled – hypoventilation’ or ‘permissive hypercapnia’, with ventilation per minute to maximize expiratory time (thus minimizing hyperinflation), but provides enough ventilation to keep CO₂ and arteries pH in a normal range. Pressure controlled can be used if possible, but in many cases, it should start with approaching targeted-volume and monitor carefully the sign of hyperinflation.

Most of experts recommend limiting VT in asthma patients with ventilation 6-10 ml per kilogram. In some patients PEEP could be carefully used, even though PEEP is not currently use practically for ventilation controlled.

Care team must also be intensively monitoring hyperinflation by using one or more maneuver. End of inspiration pressure (plateau) and the end of expiratory (auto-PEEP) have to be measured as soon as any adjustment or changes in the ventilator, and periodically when in a stable arrangement.

When the dynamic hyperinflation has subsided enough (assessed by the substantial resolution of wheezing in the chest auscultation and auto-PEEP below 5 cmH₂O), pressure supported ventilation trial begins, followed by mechanical ventilation standard termination procedures if well tolerated.

Reference
3. https://www.cdc.gov/mmwr/preview/mmwrhtml/ss5608a1.htm?utm_source=Master+Newsletter+Mailing+List&utm_campaign=ss5608a1&utm_medium=email&utm_term=0_b8c28de774-69272de8f-%5BUNIQID%5D


Endobronchial Ultrasound Transbronchial Needle Aspiration (EBUS-TBNA): The importance of adequate sampling

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Introduction

The increasing number of diseases caused by lung malignancies and infections necessitates medical practices to provide accurate diagnosis through diagnostic procedures. According to the WHO data in 2013, there is an anticipated increase in patients with lung malignancies by approximately 30%. These patients who visit medical facilities, especially national tertiary referral hospitals in Asia, have serious disease or are at advanced stages of the disease.

Delay in diagnosis occurs in part initially by the lack of information that the patients have regarding screening or the initial stages of lung cancer / infection. In addition, physicians play a significant role, primarily in obtaining adequate sample specimens required to determine the histopathological diagnosis. There are other issues that are often encountered, including limited advanced diagnostic tools available for further diagnosis, such as bronchoscopy/endobronchial ultrasound; yet again, there are other problems in the referral system and national healthcare insurance program that are not well-developed.

Bronchoscopy is a technique that has been proven to be able to provide accurate diagnosis and endoluminal therapy for patients with lung malignancies or infections. The involvement of structures outside the endoluminal mucosa such as the lymph nodes must be assessed as their condition has direct implications on the type of treatment given to the patient with suspected lung malignancy or infection. Other diagnostic modalities such as computed tomography (CT) scan / positive emitron tomography (PET) scans can also support the required diagnostic procedure. Frank Detterback et al (Diagnosis and Management of Lung Cancer, Chest Journal 2013), states that positive PET or CT should not be directly considered as metastasis.

Since the first time it was used for the diagnosis of lung cancer / infection, endobronchial ultrasound is proven to have higher sensitivity and specificity compared to CT and PET scan. Success in obtaining samples from the enlarged lymph nodes / masses based on CT / PET scans is based on three factors: the use of TBNA needles in obtaining the specimen for histopathology examination, the technique of sample collection, size of the lymph node > 0.5cm and the competence of the interventional pulmonology specialist. The ability to obtain adequate sample is related to targeted therapy, especially the current trend among oncologists that demands immunohistochemical examinations to identify possible mutations of the epidermal growth factor receptor gene to attain information regarding the suitability of tyrosine kinase enzyme inhibitor use which is hoped to increase progression-free survival.

Failure to obtain an adequate sample occurs often. This is believed to be caused by the needle caliber being too small, or the retrieval technique that lacks precision. A larger caliber needle is believed to be able to obtain larger specimens in the complete form. In additional, the approach technique employed including a combination of the jabbing method and slow pool is clinically proven to be effective and able to increase the diagnostic yield of lung malignancies and infections.
SECTION 2

Workshop
Inhalation Therapy

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Abstract

Inhalation therapy is a term which is used to describe a variety of treatment techniques, including the delivery of a variety of drugs that may be administered via inhalation, targeting lung tissue, airway secretion, central and/or peripheral airways. However, studies to date have typically been carried out on drugs targeting systemic effects which are administered through inhalation, aiming at deposition in the alveoli where the drug can be rapidly absorbed and distributed. There are three different kinds of inhalation device: pressurized metered dose inhaler (pMDI), dry powder inhaler (DPI) spray or nebulizer systems. A nebulizer system can be based on one of three different techniques; jet, ultrasonic and vibrating membrane; all are available as different models. Choosing the optimal device for a patient is essential to ensure the effectiveness of the therapy. However, the choice is dependent on several different factors and there is no single device that is best for all patients in all situations: individual solutions are necessary. Inhalation technique and handling of the device is essential for the effective treatment.

Introduction

Inhalation therapy is a term which is used to describe a variety of treatment techniques, including the delivery of a variety of drugs that may be administered via inhalation, targeting lung tissue, airway secretion, central and/or peripheral airways. Inhalation has been employed as a method for delivering medications for more than two thousand years, and the benefits of delivering medication directly to the affected site the lungs have been understood for more than two hundred years.

At the beginning of the Industrial Revolution, physicians were inventing therapies and experimenting with ideas for devices: it was a time of great creativity. However, by the end of the period the scientist and the regulated pharmaceutical industry had emerged and the role of the physician had been constrained. Few of the devices invented then remain in use today, but many of the principles used are still embodied in modern devices.

The word ‘inhaler’ was first used by the English physician, John Mudge. In his 1778 book, *A Radical and Expeditious Cure for a recent Catarrhous Cough*, aerosol therapy refers to the delivery of a drug to the body via the airways by delivering it in an aerosolized form. Whereas the aerosolized drug may be intended for systemic use utilizing the vast surface area for absorption provided by the respiratory tract, the overwhelming majority of the aerosols are meant for topical use. Evidence of use of aerosol therapy has been found during the days of Hippocrates, who utilized hot vapors for the management of respiratory diseases. However, the modern era of aerosol therapy began with the introduction of the Medihaler Epi in 1956. The last few years have seen a major evolution in our understanding of aerosol delivery to the human subjects. Modern technology along with increasing understanding of human pulmonary physiology has aided the development of improved systems of aerosol delivery. This form of therapy has revolutionized the management of patients with various pulmonary diseases. More and more bronchodilators and anti-inflammatory agents are becoming available for use as aerosol therapy.

Unlike oral or intravenous therapies, aerosolized therapy delivers drugs directly to the internal lumen of the airways and onto the therapeutic sites. For this reason, the systemic dose of most aerosolized drugs is reduced compared to oral and IV treatments. Direct delivery to the lungs also permits a more rapid bronchodilation in response to β2-adrenergic agonists and anticholinergics, and with some LABAs the duration of the effect is enhanced compared to oral treatments.

Basic Principles of Aerosol Therapy

The basic advantage of aerosol therapy lies in the delivery of high local concentrations of the drug directly to the site of action with minimized risks of systemic effects. This is achieved with a much lower dose compared to what may be required for systemic administration for equivalent therapeutic response. The commonest aerosolized drugs are the bronchodilators and anti-inflammatory agents used for obstructive airway diseases, such as asthma and chronic obstructive pulmonary disease (COPD). Their efficiency results from local effects in the airways.
High local concentration of these agents in the lung maximizes their intended effects and minimizes systemic absorption and the potential adverse reactions. Another advantage of this mode of drug delivery is the rapidity of onset of action after the drug is inhaled as compared to other modes of delivery.

An understanding of factors affecting delivery of aerosols is essential before using them. The pulmonary deposition of aerosol is achieved by way of three key mechanisms, namely inertial impaction, sedimentation and diffusion. These three mechanisms operate in different combinations for different aerosol drugs at different sites in the pulmonary tree. Whereas inertial impaction is the predominant process in the oropharynx and the larger airways for aerosols with relatively large particle size (>3μ), diffusion by way of Brownian motion is the dominant mechanism for the smaller sized aerosols (<0.5μ). Aerosols with the particle size in the range of 1-3 μ are subject to gravitational sedimentation in the small airways and the same tends to be enhanced by breath holding. The fraction of drug eventually delivered at the desired site of action also depends on the physical properties of the aerosol and also the host factors that include pattern of ventilation, status of the airways and lung mechanics.

Factors affecting delivery of aerosolized drugs to the lungs

1. Physical Characteristics of the Aerosol Particle
   - Size (mass median aerodynamic diameter)
   - Density
   - Electrical Charge
   - Hygroscopy
   - Shape
   - Velocity of the aerosol particles

2. Host Factors
   - Inspired volume
   - Inspiratory time
   - Inspiratory flow
   - Breath-hold duration
   - Timing of aerosol delivery during inspiration (with metered dose inhaler)

Inhalation may be used to administer several different classes of drugs with varying properties and indications. The effects of inhalation therapy in general are dependent on a variety of factors, which include:

1. Indication and target area, or tissue/substance.
2. Treatment strategy (if part of a ‘treatment package’).
3. Fraction of the nominal dosage delivered to the lungs, dependent on: (i) aerosol quality; (ii) characteristics of the inhaler device; (iii) patients’ ability to handle the device; and (iv) inspiratory manoeuvre(s) accomplished through the device.
4. Deposition pattern (especially regarding less absorbable drugs, or drugs targeting non-blood supplied substances), dependent on the factors noted above, and on ventilation distribution
5. Adherence with the treatment.

Particle and patient related factors that influence aerosol deposition

Drug delivery via the respiratory tract is more complex than oral therapy. Successful therapy requires a delivery system that generates drug particles of an appropriate size, such that they penetrate beyond the oropharynx and larynx and deposit in the lungs. Aerodynamic diameter is generally thought to be the most important particle-related factor that affects aerosol deposition. Upon entering the oral cavity, particles will deposit by impaction, sedimentation and Brownian motion depending on their size. Particles .5 mm are most likely to deposit by impaction in the oropharynx and be swallowed.

Important patient-related factors include the morphology of the oropharynx and larynx and the patient’s inspiratory volume and flow rate. The patient’s inspiratory flow rate generally determines the velocity of the airborne particle and this, in turn, also affects the probability of its impaction in the oropharynx and larynx. To minimize deposition in the upper airways and enhance delivery of the drug to the lungs when using a pMDI with or without a spacer, or a Breath Actuated-pMDI, patients should inhale slowly. “Slowly” translates into inhaling fully over 2–3 s in a child and 4–5 s in an adult after a deep exhalation. This ensures that flows are, 30 L.min-1,
which is the ideal flow when using a pMDI. With DPIs, the patient has to inhale as deeply and as hard as they can to overcome the internal resistance to flow and generate the aerosol for inhalation.

Many drugs are currently delivered directly to the lungs as an aerosol. These include short-acting β2-adrenergic agonists and long-acting β2-adrenergic agonists (LABA), anticholinergics, inhaled corticosteroids (ICSs), nonsteroid anti-inflammatories, mucolytics and new formulations for antibiotics. Other drugs are under development for aerosol delivery. Devices that are available to deliver these drugs include pressurized metered-dose inhalers (pMDIs), used either alone or attached to spacers or valved holding chambers (VHCs), breath actuated (BA)-pMDIs, dry powder inhalers (DPIs), nebulizers and soft mist inhalers.

**Pulmonary Drug Delivery Systems**

1. **Pressurized Metered-Dose Inhalers**

   The pMDI was first introduced in 1956 to provide a delivery system for inhaled bronchodilators with a multi-dose capability and reproducible dosing characteristics. pMDIs contain propellants, which are currently being changed from chlorofluorocarbons (CFCs) to hydrofluoroalkanes (HFAs) because the former damage the ozone layer in the stratosphere. The pMDI produces a rapid-moving plume of aerosol, the duration of which is typically 0.1–0.4s. The velocity of the aerosol plume may be 8 m.s⁻¹ at a distance of 10 cm from the actuator, and is even higher at distances closer to the nozzle. The plume often feels cold on the back of the throat as the propellants evaporate. Most pMDIs only deposit 10–20% of the dose in the lungs, even with good inhaler technique, and most of the dose is deposited in the oropharynx. Higher lung deposition and lower oropharyngeal deposition may be achieved with some recent formulations, where the drug is formulated as a solution in HFA propellant, rather than as a suspension of micronized particles.

   Correct pMDI technique involves firing the pMDI, while breathing in deeply and slowly, and then following inhalation with a breath-holding pause to allow particles to sediment on the airway surfaces. Most importantly, the pMDI must not be fired after the patient has completed inhalation, as there will then be no airstream to carry the aerosol into the lungs. Some aerosol will probably still reach the lungs if the pMDI is fired shortly before inhalation begins. Failure to correctly time firing with inhalation is sometimes termed “poor coordination”.

2. **Dry Powder Inhalers**

   Dry Powder Inhalers (DPIs) were first introduced in 1970, and the earliest models were single-dose devices containing the powder formulation in a gelatin capsule, which the patient loaded into the device prior to use. Since the late 1980s, multi-dose devices have been available, giving the same degree of convenience as a pMDI. The first of these was the Turbuhaler™ (AstraZeneca, Lund, Sweden).

   DPIs may be more expensive than pMDIs but this will vary according to pricing policies in different countries. All currently marketed DPIs are breath-actuated and no propellants are needed to generate the aerosol. The patient’s inhalation through the device is used to disperse the powder formulation and to deliver it into the lungs. However, patients can make crucial errors with a DPI; for instance, by failing to load a dose correctly or by exhaling into the DPI so that the dose is blown away. Unless clearly instructed, some patients might not know that they must firmly seal their lips around the mouthpiece, causing them to attempt an “open mouth” inhalation technique that will not deliver any dose.

   The Turbuhaler™ DPI, and possibly other DPIs in which doses are metered from a bulk powder reservoir, must be kept upright (held vertically) when loading a dose before inhalation, so that the dosing chamber will fill under gravity. Compared with a standard pMDI, fewer patients demonstrate errors in inhaler technique with a DPI. Many DPIs must be stored in a dry environment to prevent the drug formulation being degraded by moisture. DPIs tend to work better with rapid and forceful inhalation, since this disperses the powder formulation into small “respirable” particles as efficiently as possible. Delivery to the lungs may be reduced with slow inhalation and for each DPI it is necessary for patients to attain a minimum inhaled flow rate in order to ensure that some drug is delivered to the lungs. It is also desirable that the rate of increase of inhaled flow at the start of inhalation should be as high as possible. This is sometimes called high flow “acceleration” or high “early flow”.
3. **Nebulizers**

**Basic Components of Nebulizers**

A nebulizer consists of various parts which are assembled together for its working such as medication reservoir, baffle, compressor, mouthpiece and facemask. Nebulizer solutions are dilute water based solutions of drug with excipients added to achieve several pharmaceutically desirable goals. All current nebulizer solutions are sterile and most are packaged as unit dose form-fill vials to avoid the invasion of anti-microbial agents and the need for dilution by the patient.

**Advantages of Nebulizers**

- Large dose of drug can be administered over multiple breaths.
- Can be used at any age group.
- Require no propellants that can damage the atmosphere.
- Ensures more efficient intrabronchial drug deposition.
- In emergency medicine used to treat acute bronchial asthma and acute exacerbations of COPD, frequently in combination with positive pressure ventilation.
- Delivery of inhaled steroids.
- Easy to administer in a very simple manner.

Nevertheless, these devices possess a number of additional drawbacks that tend to favour the use of alternate delivery devices. Drawbacks of inhalation therapy with nebulizers are summarized in this section:

- Low deposition efficiency of the drug in the target areas.
- Higher cost and size complications.
- Time consuming.
- Noisy.
- High maintenance requirements i.e. the equipment must be cleaned and sterilized on regular basis and the air filtered.
- Dependent on outside power sources, electricity.

**Types of Nebulizers**

Traditional nebulizers can be broadly classified into two categories depending on their operating principle such as jet and ultrasonic nebulizers. The jet nebulizer uses compressed air to aerosolize the drug solutions, whereas the ultrasonic nebulizer uses energy from high frequency sound waves.

**Jet Nebulizers**

Jet nebulizers are widely used in pediatric and adult medical practice, for acute and domiciliary treatment of a variety of respiratory diseases. They are also known as ‘atomizers’ or ‘pneumatic nebulizers. Jet nebulizers operate on the Bernoulli principle: use high velocity air flow through nozzle to draw liquid containing the drug side feed tubes into the nozzle region as a consequence of suction arising from the expansion of the jet at the nozzle orifice. Owing to the large kinetic energy of the air jet, the liquid immediately breaks up into aerosol droplets as it emanates from feed tubes. Clinically important characteristics of nebulizer performance is respirable dose provided for the patient, determined by mass output of nebulizer and size of the droplet that are produced. Other important characteristics of nebulizer performance include nebulization time, cost ease of use and requirement for cleaning and sterilization. A short nebulization time that delivers an effective dose is desirable. Many nebulizers are low cost, mass produced, single patient-use devices.

**Ultrasonic Nebulizers**

Ultrasonic nebulizers work by applying an alternating electric field to a piezoelectric transducer, which converts the electrical signal into a periodic mechanical vibration, in contact with the liquid to be nebulized. Ultrasonic vibrations from the crystal are transmitted to the surface of drug solution where standing waves are formed. Droplets break free from the crests of these waves and are released as aerosol. The size of droplets produced is inversely proportional to two thirds of the power of acoustic frequency.

An ultrasonic nebulizer has three components: the power unit, the transducer and a fan. The power unit converts electrical energy to high-frequency ultrasonic waves at a frequency of 1.3-2.3 megahertz. The power unit also controls the amplitude of the ultrasonic waves. The transducer vibrates at the frequency of the ultrasonic waves applied to it (piezoelectric effect). The conversion of ultrasonic energy to mechanical...
energy by the transducer produces heat, which is absorbed by the solution over the transducer. A fan is used to
deliver the aerosol produced by ultrasonic nebulizer to the patient, or the aerosol is evacuated from the
nebulization chamber by inspiratory flow of the patient.

Ultrasonic nebulizer possesses a number of advantages and disadvantages which are described in the
subsequent section:

- **Advantages**
  - Little patient management required.
  - Aerosol accumulates during exhalation.
  - Small dead volume.
  - High dose output and fast drug delivery.
  - No propellants requirement.
  - Operate for several days on a single recharge.
  - Silent during operation.
  - Compact

- **Disadvantages**
  - Large particle size and less efficient.
  - Microbial contamination risk.
  - Poor portability and expensive.
  - Prerequisite of electric power supplier.
  - Drug preparation required.
  - Prone to electrical and mechanical breakdown.

**Summary**

Inhalation therapy is a preferred mode of drug delivery as it provides rapid onset of action, increased
bioavailability, low gastrointestinal side effects and user-friendly environment with better patient compliance.
A variety of drugs are in use and more drugs formulations are being investigated, consequently leading to
development of compatible inhalers, which necessitates good understanding of drug formulations and functioning
of inhalers. There is no significant difference between various inhaler devices in their efficacy outcome; however
most are drug specific depending on drug formulations.

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Disinfection and Sterilization of Bronchoscopy Endoscope Device

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Abstract

All invasive procedure always involves contact with mucous membrane or medical device patients. The main risk of all these procedures is the transmissions of microbial pathogens that cause infection.

Failure in disinfection or sterilization of equipment can cause transmission through contaminated medical equipment (such as; contaminated bronchoscopes Mycobacterium tuberculosis). Along with increasing risk of infections mainly associated with a bronchoscope, or disinfection techniques required adherence to a high level of disinfection procedures in the right way.

Disinfection is defined as the process of lowering the number of disease-causing microorganisms or pathogens that could potentially by way of physics or chemistry. This process is usually not included in destroying spores. Sterilization is a process of treatment of materials or goods which at the end of the process cannot be shown the existence of microorganisms living on such materials or goods (The Ministry of Health Indonesia, 2002).

In the process of disinfection methods should always be preceded by stages starting from the clean-up manually (enzymatic), flushing, leakage test, high level disinfection/sterilization, final rinsing, drying, storage and documentation. The purpose of disinfection and sterilization among others eliminate the presence of feces, blood, mucus, and the rest of the protein clot attached to the tool in good Bronchoscopy lumen as well as the outside lumen after the action, so that non of the microorganism. Not only clean but also able to kill bacteria, viruses/parasites and fungi, and microorganisms either chemically or mechanical.

In this case, the device (Scope Bronchoscopy) can be disinfected with high level disinfectant fluids namely disinfectant that has broad spectrum in its activity to kill bacteria and viruses in minutes.

Keywords: Disinfection, Sterilization, Bronchoscopy endoscope device.

Reference: 2002-2006

Disinfection

Disinfection is defined as the process to eliminate microorganisms which causes disease or had the potential to become a pathogen using chemical or physical means. This process usually does not eliminate spores. Disinfection process starts by eliminating most bacteria in the surface of the instruments while the rest is killed using disinfectant products.

Sterilization

Sterilization is a process given towards instruments or devices resulting no microorganism can live in those instruments or devices (Depkes RI, 2002).

Aim

The purpose of this process is to eliminate dirt, blood, sputum, and protein excess left in the surface and lumen of bronchoscopic devices after procedure, to prevent microorganism vegetation. The purpose of this action is not only to achieve cleanliness but also to kill bacteria, virus, fungi, parasites, and other organisms using chemical or mechanical devices.

Disinfectant

There are two kinds of disinfectant:

- Low potent disinfectant, which have no potency to kill HIV and hepatitis B virus
- High potent disinfectant, which have potency to kill HIV and hepatitis B virus
Bronchoscopy Device and Scope Bronchoscopy

Bronchoscopy is a device used to evaluate the condition of bronchiolus. This device is inserted from the nose or mouth. Bronchoscopy devices are disinfected using high potent disinfectant (broad-spectrum disinfectant to eliminate bacteria and virus in minutes).

Procedure of Disinfection and Sterilization
- Pre-cleaning
- Leackage Test
- Manual cleaning
- Flushing
- Disinfection/ sterilization (Strip test, DTT temperature)
- Final rinsing
- Drying
- Storing (room temperature)

Manual Cleaning

Before starting the procedure, prepare sterile gloves, self-protection equipment, two buckets of clean water and enzymatic detergent solution each. After bronchoscopy procedure is finished while the device still attached to the light source, carefully handle the scope and wash with gauze/ disposable cloth soaked in enzymatic detergent solution.

Start from top to bottom/ distal and remove the usable gauze/ cloth to medical waste bin. Place the distal scope into the bucket with enzymatic detergent solution, aspirate through suction channel for 30 seconds, remove the scope, then aspirate the air for 10 seconds, and then stop the suction machine.

Release the scope from the light source, do leakage test to check whether there is leakage on the scope to prevent further damage.

Place the scope in the trolley to prevent infection from spreading in the workplace. Put the scope in the new enzymatic solution, make sure every part is submerged, and then open the suction valve and biopsy valve.

Clean the scope with soft brush or channel cleaning brush through biopsy channel. Brush repeatedly to dislodge the dirt, and then wash the surface using cleaning cloth/ sponge. Make sure all the dirt is removed.

Place the suction cleaning adaptor to suction cylinder. Rinse using enzymatic detergent using spuit for minimal 150-200 ml.

Please remember to not let the scope dry before the washing to prevent the organic compound to become dry and hard to remove. Things taken into consideration:
- Push air through suction cleaning adaptor to remove excess enzymatic detergent solution
- Place the scope into the bucket filled with clean water
- Rinse the device with clean water through suction cleaning adapter each port minimal 150-200 ml
- Blow air to remove excess water, then dry the surface using soft clean cloth
- After thorough washing and cleaning, place the scope into disinfection solution. Make sure every part is submerged
- Insert disinfection solution into all suction cleaning adaptor until air bubbles emerge
- After submerging and before removing the scope from the solution, remove disinfectant solution from every channel by blowing air using spuit through suction cleaning adaptor
- Disinfection using machine is usually done after cleaning/ washing manually. In this final rinsing, its preferable to use filtrated water
- Place the scope into bucket filled with filtrated water. Rinse each port using filtrated water 150-200 ml minimal through suction cleaning adaptor using spuit
- After rinsing, blow air using spuit through each port, so that water could be expelled from the channel. Lift the scope, and then dry them. Make sure there are no water left in the scope
Disinfection and Sterilization of Bronchoscopy Endoscope Device

- Equip the scope to the light source, turn on the light source, and make sure that the air pump and the suction were on so that air from the air pump can dry the channel
- If there is a compressor, you can use them for drying; if not, use sterile section tube, connect the suction and the scope using suction connection part, so that the water in each channel can be dried off
- Rinse with alcohol 70%
- Dry the exterior part of the scope using clean cloth (for each scope used one clean cloth)
- The storage must be clean, dry, have good ventilation, and preferably air conditioned
- Room temperature is set to 22°C, with humidity no more than 50%. The scope must be stored with the body hanging straight in the specially designed cupboard complete with UV light

Bronchoscopy Accessories

All bronchoscopy accessories should be sterilized because almost all of them were associated with vascular and tissues. The principal to sterilized bronchoscopy accessories is the same with bronchoscopy scope, however after drying, sterilization is done in sterilization central with low temperature plasma 50°C-55°C.

Conclusion

Disinfection and sterilization are important in the prevention of nosocomial infection/ healthcare associated infection (HAIS).

References
**Peripherally Inserted Central Catheter**

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**RSUD Raden Mattahe/FKIK Universitas Negeri Jambi**

**Definition**

Peripherally Inserted Central Catheter (PICC) is described as a central line that is inserted into a peripheral vein in the upper arm and advanced along the vein until the tip resides in the lower 1/3 of the superior vena cava (SVC). The midline peripheral catheter is considered a peripheral venous catheter because it does not enter the central vein. The distal tip should dwell in the basilic or cephalic veins at or below the axillary level.

![Figure 1](image)

(a) Peripherally Inserted Central Catheter (PICC). (b) Midline peripheral catheter.

**Types of Central Catheters**

There are several kinds of central catheter. Some is a single lumen, others is a multilumen catheter, depends on manufacturer as shown below:

![Figure 2](image)

(a) Groshong catheter; (b) Cavafix catheter; (c) Power PICC catheter

**Catheter Insertion Site**

Generally PICCs are inserted into the basilic and cephalic veins of the antecubital space or brachial veins. The basilic vein is more preferred as it offers the largest diameter of upper extremity vessels and affords a non-tortuous entry into the subclavian vein. The cephalic vein (~6mm) is smaller than the basilic vein (~8mm) and angles 90 degrees to enter the terminal portion of the axillary vein, sometimes making catheter advancement difficult. Brachial veins lay deep in the center of the mid upper arm and cannot be outwardly visualized or palpated; ultrasound guidance is required for access. The most appropriate location for the tip of PICCs is the lower one-third of the superior vena cava (SVC), close to the junction of the SVC and the right atrium. PICCs are
not recommended in patients with renal failure and impending need for dialysis, in whom preservation of upper extremity veins is needed for fistula or graft implantation.

**Indication and Contraindication**

Indications for PICC insertion include 1) compromised/inadequate peripheral access, 2) infusion of hyperosmolar solutions or solutions with high acidity or alkalinity (e.g. Total Parenteral Nutrition), 3) continuous infusion of vesicant or irritant agents (inotropes, chemotherapy), 4) short or long term intravenous therapy (e.g. antibiotics)

Contraindications for PICC insertion including 1) inadequate vein 2) pre-existing skin surface or subsurface infections at or near the proposed catheter insertion site, 3) lympoedema, 4) anatomical deviation from surgery, injury or trauma, 5) anatomical irregularities that may compromise catheter insertions or catheter care procedures, 6) mastectomy surgery with axillary dissections +/- lympoedema on affected side, 7) crutch walking as this causes pressure on veins of the arm.

**Procedure and Monitoring For Inserting PICC Line**

Catheter is inserted under sterile technique using mask, gown and gloves. Increasing the size of the sterile field at insertion site reduces risk of sepsis. Skin cleansing at insertion site is one of the most important measures to prevent catheter related sepsis. Aqueous chlorhexidine 0.015% is applied to the insertion site and allowed to dry for 3 minutes. Insertion of PICC may be assisted by the use of transilluminator, which helps to locate the vein and to improve the accuracy in depth perception during venipuncture attempts. Insert the PICC line 2-3 cm beyond the anticipated length and ‘pull back’ into the correct position. Aspirate blood and then flush with heparin saline (50IU/5ml) 0.3 ml. This ensures the line is in a larger vessel and prevents line migration centrally. Avoid excessive pressure with syringe. Always use a ‘sharp-safe’ technique – place any sharp in a plastic receptable prior to disposing in a sharps bin. Ensure the catheter is fully inserted into the hub. Once inserted the remaining catheter is looped and secured to sterile skin using steristrips. The insertion site and hub are then covered with occlusive dressing.

Guidelines for physician notification after insertion PICC: excessive bleeding, new and/or different cardiac arrhythmias, sudden and unexplained onset of respiratory distress, chest pain, onset of pain and/or edema in the cannulated arm, numbness or tingling in the cannulated limb, swelling or decrease circulation to affected arm.

Confirmation of placement can be assessed by Chest X-ray, aspiration of blood from PICC line, ability to easily infuse solutions, measurement of PICC length from insertion site to catheter hub.
Complication
1. If PICC migrates more than 2 cm in or out, consult with physician and X-ray confirmation of placement may be required before reassess.

2. Redness, tenderness, swelling and heat may be signs and symptoms of thrombosis around the PICC.

3. The infection may be at the insertion site or in the vein. Redness, discharge, tenderness, swelling, heat, patient temperature and generally feeling unwell may be signs and symptoms of infection associated with the PICC.

4. Occlusion can be complete or partial. Signs of occlusion are resistance when flushing, sluggish flow, inability to infuse fluids, frequent occlusion alarm on infusion pump, infiltration or extravasion or swelling or leaking at insertion site, inability to withdraw blood, sluggish blood return. Complete occlusion can be mechanical, chemical or thrombotic.

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Indication and Insertion Technique
of Central Venous Catheter

Fauzar

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Introduction

Central Venous Catheter (CVC) is a catheter placed into a large vein in the neck (internal jugular vein or external jugular vein), chest (subclavian vein), the arm (basilica vein) or thighs (femoral vein). CVC also called a central line, the same as intravenous (IV) catheter but the access for IV catheter is a small size vein. CVC is a modality that is often used in health care, especially in the intensive care unit (ICU), as an intravenous access or a hemodynamic monitoring.

CVC insertion is an invasive procedure, thus the insertion of CVC on the aforementioned veins has its advantages and disadvantages such as in the difficulty level of installation, the risk of infection and patient comfort. CVC requires precision in the insertion procedure which are including to determine the techniques for insertion and choosing the proper insertion site.

Indication for the use of CVC

Indications for the use of CVC include:
- The need for intravenous fluid substitution in large quantities and quickly.
- Intravenous access for medicines with a high concentration (high osmolarity) and aggressive.
- Parenteral Nutrition
- Hemofiltration in surgery and emergency.
- Long-term infusion therapy (chemotherapy, dialysis)
- Measurement of central venous pressure (CVP) in the intensive therapy

Contraindications

Relative contraindications for the use of CVC:
- The presence of lesions (tumor or inflammation) in the puncture area
- Stenosis of the carotid artery (in the insertion site of internal jugular vein)
- Pneumothorax without WSD and the contralateral thoracic trauma
- Anatomical defects (tumor mediastinum, chest wall deformation, fracture)
- Obesity or cachexia
- Emphysema
- Absolute contraindications:
  - Clotting disorders

Location for insertion

There are several locations for CVC insertion (figure 1) such as jugular vein, subclavian vein, femoral vein and cephalic vein. The insertion location depends on the patient’s situation, for example; the condition of the patient, the operator experience, insertion techniques and tools availability. The internal jugular vein is the most frequent site for CVC insertion, this is because the internal jugular is a large vein with a lower risk of pneumothorax than the subclavian vein. While the subclavian vein is a preferred site location for patients with suspected cervical spine trauma, because the position of the head does not need to be exalted in the installation of CVC in the subclavian vein, however it has a higher risk of pneumothorax, about 2-3%.
Cannula insertion technique on internal jugular venous

The skin at the insertion area cleaned with a chlorhexidine 2% in 70% isopropyl alcohol. A meta-analysis study found that there is a decrease in the incidence of infection associated with the installation of CVC with aseptic procedure using chlorhexidine than using povidone iodine. The insertion of CVC should be with guidance of USG, because it can reduce the number of insertion failure, decrease complications, and the insertion procedure is faster than not using USG.

Seldinger's technique is one of the standard approach for catheter insertion on central venous. This technique uses a guidance through the needle access (figure 2), where this guidance will facilitate the entry of a catheter into the vein. The selection site CVC insertion is one of the factors that could reduce the risk of mechanical complications during the insertion procedure. The locations that must be avoided are the sites which have been tried and failed, or have bone deformity, surgical wounds, radiation or scar tissue. A meta-analysis comparing the installation of CVC in the internal jugular vein and subclavian showed that the insertion on internal jugular vein often puncture the arteries, but fewer problems related to catheter malposition.

After a local anesthetic on the insertion site, the needles inserted gently consistent with the anatomical reference, while maintaining negative pressure. The presence of aspirated blood is a sign that the needle puncture the vein. Guidance is inserted through the needle up to a maximum length of 20 cm (corresponding to the border atriocaval). The needle is slowly removed, leaving the guidance in place. ± 0.5 cm incision was made with a knife in the guidance entrance, followed by a dilator, to widen the insertion site. The catheter is inserted into a vein through a guidance (guidewire) and then the guidance is removed. The length of the inserted catheter should be sufficient so the catheter tip is on the border of atriocaval (figure 3). Aspiration is done at each end of the catheter to ensure the position of the catheter in the vein after that each catheter should be rinsed with pure saline or containing heparin. The catheter is fixed to the skin with sutures and covered with sterile to avoid infection.
Complication

1. **Infection**
   
   A CVC infections study in the UK in 2011 showed the data of the occurrence of infections of 1000 cases per day, and found that 40% infections in the blood flow associated with the use of CVC.

2. **Thrombosis**
   
   Patients who carried out the insertion of CVC can cause thrombosis. A study obtained catheter related thrombosis occurred in 21.5% of patients with the installation of CVC in the femoral vein, while in subclavian vein the incidence rates about 1.9%.

Another complication based on the route of catheter insertion was described in table 1.

**Table 1.** The frequency of occurrence of mechanical complications based on the route of catheter insertion

<table>
<thead>
<tr>
<th>Complication</th>
<th>Internal Jugular</th>
<th>Subclavian</th>
<th>Femoral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial puncture</td>
<td>6.3–9.4</td>
<td>3.1–4.9</td>
<td>9.0–15.0</td>
</tr>
<tr>
<td>Hematoma</td>
<td>&lt;0.1–2.2</td>
<td>1.2–2.1</td>
<td>3.8–4.4</td>
</tr>
<tr>
<td>Hemothorax</td>
<td>NA</td>
<td>0.4–0.6</td>
<td>NA</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>&lt;0.1–0.2</td>
<td>1.5–3.1</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>6.3–11.8</td>
<td>6.2–10.7</td>
<td>12.8–19.4</td>
</tr>
</tbody>
</table>

*Data are from Merrer et al., Sznaier et al., Mansfield et al., Martin et al., Durbec et al., and Timsit et al.* NA denotes not applicable.

**Reference**

Thoracic Ultrasound

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Acute respiratory failure is one of the most distress situations for the patient in emergency department. The patient does not always present in a condition that are ideal for immediate diagnosis, even sometimes compromises the outcome. Lung ultrasound is becoming a standard diagnostic and therapeutic tool in the management of patients because it helps the clinician to rapidly evaluate thoracic pathologies and guide many bedside procedures. Accurate bedside detection of thoracic disorder should help diagnose the acute respiratory failure and assess the most possible cause based on lung ultrasound finding. Before performing the lung ultrasound examination the physician should be trained intensively so they can operate the ultrasonography properly and have the basic knowledge about the abnormality of ultrasound finding. There are six ultrasonography pattern frequently found in patients with acute dyspnea, namely sliding lung, A-lines, B-lines, C-lines, pleural effusion and lung point.1,2,3,4

**Sliding Lung.** The pleura appear as a moving bright line on lung ultrasonography. When using a high-frequency transducer the visceral and parietal pleura can be visualized as separate linear structures that closely apposed. These thin pleural surface is lubricated with a small amount of serous fluid. Lung sliding is a movement of the pleural line against a fixed chest wall in association with respiration. Visualization of lung sliding implies that the two pleural surfaces are mobile and in apposition with each other and that no air is opposed between them at the point of the transducer. An alternative method of assessing lung sliding is M-mode. Pleural sliding gives a characteristic seashore sign (Figure 1). The near field of the image displays the static appearance of the chest wall layers (the “sea”), and the far field displays the motion pattern of dynamic pleural sliding (the “shore”). The presence of lung sliding implies with 100% certainty that no pneumothorax is present at the point of the probe. Abolition of sliding lung occurs when the visceral pleura does not slide against parietal pleura due to inflammatory adherences, chronic symphysis or separated of these layer as it happens in pneumothorax.5,6

**Figure 1. Seashore sign**

**A-lines.** Air underlying the visceral pleura serves as an acoustic barrier to penetration of ultrasound waves, in the opposite fluid can facilitates its transmission. In normal healthy patients, the pleural surface is readily imaged but underlying lung cannot be seen. Normally aerated lung produces an artifact due to pleural line reverberations called A-lines. A-lines are hyperechoic horizontal lines appear at regular interval deep to the pleural line and between the rib shadows (figure 2). At the other extreme, when the lung becomes airless, as in a massive consolidation or atelectasis, it can be visualized like any other solid organ. The A profile designates anterior predominant bilateral A lines associated with lung sliding. The A’ profile is an A profile with abolished lung sliding.6,7,8,9
Thoracic Ultrasound

**Figure 2.** A-lines are seen as horizontal, curvilinear hyperechoic lines

**B-lines.** Various air/fluid ratios lead to generation of other artifacts, as fluid composition of the lungs varies in different pathologic states, known as B-lines. B-lines also called "lung rocket" or "comet tail", appear as hyperechoic vertical sonographic artifact arises from the inferior aspect of the pleural line and extend to the edge of the screen without fading. Its obscure A-lines and move with lung sliding (Figure 3). The B profile designates anterior predominant bilateral B-lines presenting with lung sliding. The B' profile is a B profile with abolished lung sliding. The A/B profile designates anterior predominant B-lines on one side and predominant A-lines on the other.7,9

**Figure 3.** B-lines pattern seen when interstitium is widened with fluid

**C-profile and pleural effusion.** C profile designates alveolar consolidation pattern where ultrasonography show an area of hyperechoic echotexture with punctiform elements or hepatization, with presence of static or dynamic air bronchogram. Hepatization is applied when the lung density and pattern resemble that of the liver. Pleural effusion is easily detects as fluid collections throughout the body with anechoic or hypoechoic structures. A free-flowing pleural effusion usually accumulates in the most dependent areas of the chest, and its position can change with changes in the patient’s posture or positioning in the bed (figure 4). It is important to study the entire chest to detect pleural effusions that may be loculated and will not collect independent areas of the chest. The term of PLAPS is represents of posterior and/or lateral alveolar and/or pleural syndrome. All these definitions are based on the patient being supine or semi-recumbent.7,8,9
Figure 4. C-profile or alveolar consolidation pattern (A) and pleural effusion (B)

**Lung Point.** Lung point designates as the margin of pneumothorax. A partially collapsed lung resulting from pneumothorax usually exhibits a chest point where the lung adheres again to the parietal pleura. This finding represent a pneumothorax juxtaposed to aerated lung (lung sliding, A lines/B lines) and moving with each respiratory cycle. A lung point can be viewed in M-mode, with the screen over time between the seashore and barcode (stratosphere) pattern with the transducer stationary. Barcode sign reveal a static pattern in both the near and the far field, signifying the absence of any motion deep to the parietal pleura consistent with the absence of lung sliding. This sign is known as the “lung point” and is 100% specific for the diagnosis of pneumothorax (Figure 5). Although highly specific, the lung point has low sensitivity because it cannot be visualized in totally collapsed lungs.9,10

Figure 5. Seashore sign (A), Barcode / Stratosphere sign (B) and Lung Point (C)

**BLUE Protocol (Bedside Lung Ultrasound in Emergency Protocol)**

The BLUE protocol is procedure that assist the clinician in evaluation of acute dyspnea with a microconvex 4- to 8-MHz frequency transducer for evaluation of the lung and the pleural space. This protocol is not designed to replace the standard procedure for making the diagnosis consisting of history taking, physical examination and supporting examination such as ECG and chest X-ray, but as a complementary.

**BLUE protocol - Exam points.** The four hemithorax exam points in the BLUE protocol are determined by placing the hands horizontally over the anterior chest with the upper fifth finger abutting the clavicle, the digits of both hands together, and the nails at mid-chest (Figure 6). Point 1 is located between the third and fourth finger of the upper hand. Point 2 is located in the middle of the palm of the lower hand. The lower fifth finger approximates the lower anterior border of the lung (phrenic line). The wrists cross over the anterior axillary line.
The location of point 1 and point 2 and its ultrasound finding are shown in figure 7. Either point 1 or point 2 visualize the lung parenchyma of the upper lobe and middle lobe.9,10

Point 3 requires the user to slide the transducer along the lateral chest wall from the anterior to mid-axillary line at the level of the phrenic line made by the lower fifth finger. Point 4, also called the posterolateral alveolar pleural syndrome (PLAPS) point, is found at the intersection of the posterior axillary line and the transverse phrenic line (Figure 8). Its visualize the costophrenic pleural recesses and lung parenchyma of the lower lobe.9,10
Practically this examination is performed as follows (Figure 9): 

1. Start the examination at point 1 with placing the transducer on mid-clavicular line at the second intercostal space, with the ultrasound marker pointing toward the head of the patient.

2. Continue the examination by sliding the ultrasound transducer to the point 2 located on the anterior axillary line at the fifth intercostal space, usually just lateral to the nipple in men. Visualization is performed in each intercostal space, concentrating on the image between the two rib shadows, and should last for at least one complete respiratory cycle.

3. Repeat the process at point 3 located along the diaphragm in mid-axillary line and also at point 4 located at the most posterior point along the diaphragm. At this point the transducer face is pointing to the sky with patient back rotated off the bed.

4. The following lung findings are evaluated: A-lines, B-lines, slidding lung, lung point, pleural effusions and consolidation.

5. In addition to lung findings, the following can be evaluated to supplement the examination:
   a. Left ventricular function and size
   b. Right ventricular function and size
   c. Lower extremity vasculature to detect the presenting of thrombosis
The 5th Jakarta International Chest and Critical Care Internal Medicine (JICCCIM) 2017

The use of the BLUE protocol provided an accurate diagnosis in 90.5% of cases of acute respiratory failure. The following signs and findings are organized for evaluating a patient with acute dyspnea (figure 10)\(^9,10,11\):

1. Firstly look for the presence or absence of lung sliding. Abolished lung sliding with the presence of A-line (A’ profile) are indicative of pneumothorax if accompanied by the "lung point sign." In another condition if abolished lung sliding is accompanied by B-lines (B’ profile) then pneumonia is suspected.

2. In the presence of lung sliding, then look for the A-lines which indicate presence of air (A profile). Venous ultrasonography in the lower extremity should be performed for further analysis. The interpretation of the findings can be as follows:
   a. Presence of A-lines and a thrombosed vein suggest pulmonary embolism.
   b. Presence of A-lines and the absence of deep vein thrombosis suggest pneumonia in the presence of PLAPS or COPD/asthma in the absence of PLAPS.

3. The presence of sliding lung accompanied by diffuse, bilateral B-lines (at least in four points of the anterior chest wall) may indicate cardiogenic or non-cardiogenic pulmonary edema (ARDS). Echocardiography should be performed to conform the diagnosis.

4. Lung ultrasound in pneumonia may yields various signs. The frequent abolition of lung sliding (B’ profile) is explainable by inflammatory adherence due to exudate. Pneumonia can also be found in a wide variety of locations, which explains the asymmetric consolidation (C profile).\(^12\)

---

**Figure 10. The BLUE protocol using lung ultrasonography to guide diagnosis of severe dyspnea**

**The Role of Lung Ultrasound to Differentiate the cause of Pulmonary Edema**

Pulmonary edema can be caused by acute cardiogenic pulmonary edema (ACPE) or acute respiratory distress syndrome (ARDS). In ACPE the lung ultrasound finding reveal a homogeneous pattern due to hydrostatic edema with interstitial thickness and subsequent extravasations of fluid in the alveoli in the absence of impaired alveolar-capillary membrane. Hence a homogenous white lung pattern which is usually observed in both anterior and posterior lung fields along with evidence of pleural effusion, is predominant in ACPE. However, in ARDS the
integrity of alveolar-capillary membrane is compromised, and its causes an early, diffuse, heterogenous alveolar flooding. In ARDS therefore the white lung pattern is rather heterogenous in the anterior fields of lung (spared area), whereas it tends to appear more homogenous with bilateral pleural line modification and consolidated area in the posterior lung fields, depend on severity of ARDS (Figure 11).

![Figure 11. Spared area in ARDS (A) and White Lung in ACPE (B).](image)

In ACPE the pleural surface membrane is usually regular and smooth without accompanied by subpleural consolidation. In the opposite with ARDS where the pleural surface is irregular and subpleural consolidation are usually found (figure 12).10,13

![Figure 12. Pleural line in ARDS (A) and ACPE (B).](image)

In conclusion, lung ultrasound is becoming a standard procedure in managing patient with acute dyspnea. This procedure is noninvasive, easily repeatable at bedside, and provide an accurate evaluation of respiratory disorder of patient with acute dyspnea. Nevertheless this protocol can not replace the general standard procedure in handling patient consisting of taking the history of the present illness, performing the physical examination and getting the supporting data from chest X-ray and ECG. Bedside lung ultrasound is therefore an essential tool as a complementary for diagnosis and management of acute respiratory failure.
Thoracic Ultrasound

References

Cryotherapy is an old method used in different fields of medicine taking advantage of the properties of cold. In pulmonary medicine, especially in endoscopic application, cryotherapy allows tissue destruction by applying cycles of freezing and thawing, producing tissue necrosis by local cytotoxic effect.

The success of freeze injury, which is the main mechanism of cryotherapy, may be influenced by many factors; the survival of cells is dependent on the cooling rate, the thawing rate, the lowest temperature achieved, and repeated freeze-thaw cycles.

**Cooling Agent**

Nitrous Oxide (N\textsubscript{2}O) is the commonest cooling agent used. The vapor haze of N\textsubscript{2}O occurs at the metal tip of the cryoprobe where it expands from a high pressure to atmospheric pressure (the Joule-Thompson effect). The core temperature needed for a lesion to be destroyed is between -20°C and -40°C. Freezing to -40°C or below the rapid rate of −100°C per minute will cause more than 90% cell deaths.

**Equipment**

The cryoprobes are rigid, semirigid or flexible. Rigid and semirigid cryoprobes can only be used through a rigid bronchoscope, but flexible can be used through the channel of the fiberoptic bronchoscope.
The cryoprobe/forceps is used to freeze the target tissue. The transfer line connects the cryoprobe/forceps to both the cooling agent storage container (e.g., gas cylinder) and the console. The console controls the flow of cooling agent through the transfer line.

Indication and Contraindication of Cryotherapy

**Advantage**

Cryotherapy is a safe and low cost method and can be used as a single therapeutic method or as a palliative method or in conjunction with other treatment modalities such as laser and brachytherapy.

Cryotherapy is safe, with no danger of bronchial wall perforation, no radiation danger, no risk of electrical accidents or fires, and does not require much special training. Patients tolerate the procedure well and show a significant improvement in symptoms.

One advantage of cryotherapy is safety: the operator and other members of the team need no optical protection and no specialized training for rigid bronchoscopy or laser safety. Similarly for the patient, there is no danger of bronchial wall perforation, endobronchial fires or "popcorn effect," danger of electrical accidents, radiation emission, and the possibility of danger using high oxygen during the procedure.

**Disadvantage**

A disadvantage of cryotherapy is that the destruction of the tumor often requires two or more endoscopies due to the delayed effect.

Disadvantages include delayed results and the requirement for multiple bronchoscopies to remove debris or to retreat, which is a serious issue for cryotherapy in a patient with impending respiratory failure due to an obstructive airway lesion.
Basic Flexible Bronchoscopy in Children

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Introduction

Flexible bronchoscopy for pediatric respiratory disease is a routine procedure to investigate respiratory problems/diseases. Flexible bronchoscopy (FB) is indicated when the benefits outweigh its risks and when it is a best way to obtain diagnostic information. The decision to perform FB in children should always be made on an individual basis after consideration of the patient’s history, physical examination, and the results of previous diagnostic test. Understanding of indication, contraindication and patient management before and after procedure are the key factors to optimize the benefit of bronchoscopy and to ensure patient safety.

Indication and Contraindication

Flexible bronchoscopy can be performed for diagnostic and therapeutic purposes. Indication for bronchoscopy varies with age of patient. FB is not indicated to attempt to remove a foreign body. Although it has been suggested that flexible bronchoscopy should precede a rigid bronchoscopy to localize the foreign body and guide the surgeon with the rigid bronchoscope. The indications of FB are described in table 1. The only absolute contraindication is that the procedure will elicit no information of value. Relative contraindications include pulmonary hypertension, baseline hypoxia and uncorrected bleeding diathesis.

Table 1. Indications of flexible bronchoscopy

<table>
<thead>
<tr>
<th>1. Exploration of the airway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent stridor</td>
</tr>
<tr>
<td>Persistent wheezing</td>
</tr>
<tr>
<td>Hemoptysis</td>
</tr>
<tr>
<td>Suspicion of a foreign body</td>
</tr>
<tr>
<td>Persistent or recurring atelectasis</td>
</tr>
<tr>
<td>Persistent or recurring pneumonia</td>
</tr>
<tr>
<td>Localized pulmonary hyperlucency</td>
</tr>
<tr>
<td>Problems related with the artificial airways</td>
</tr>
<tr>
<td>Miscellaneous (large burns, phonatory anomalies)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. Obtaining biological samples (bronchoalveolar lavage, bronchial biopsy, bronchial brushing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia in immunosuppressed patients</td>
</tr>
<tr>
<td>Chronic Interstitial pneumonia</td>
</tr>
<tr>
<td>Pneumonia due to hypersensitivity</td>
</tr>
<tr>
<td>Pulmonary hemosiderosis</td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
</tr>
<tr>
<td>Other (sarcoidosis, alveolar proteinosis, histiocytosis)</td>
</tr>
<tr>
<td>Endoluminal obstructive pathology</td>
</tr>
<tr>
<td>Aspiration lung syndromes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Therapeutic applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration of endobronchial secretions</td>
</tr>
<tr>
<td>Instillation of medication</td>
</tr>
<tr>
<td>Difficult or selective intubations</td>
</tr>
<tr>
<td>Management of the foreign body combined with rigid bronchoscope</td>
</tr>
</tbody>
</table>

Patient Management

A. Prebronchoscopic procedures

The child may be admitted either as a day case or as an inpatient depending on the likelihood of complications or if other investigations need to be performed. The family should be given full information about the procedure prior to admission, including the risks and postbronchoscopic care. Fasting prior to the procedure is usually 4-6 h for milk and solids, or 3 h for water.

B. Selection of anesthetic or sedation technique

Appropriate anesthetic or sedation technique is determined by the indications for the procedure. The available techniques are: 1) sedation (spontaneously breathing); 2) general anesthesia (child may or may not be spontaneously ventilating). Topical anesthesia is of a particular importance when conscious sedation is used. Lidocaine 2-5% is applied on the nose and the larynx and 0.5-1% below the larynx. Lidocaine may...
be instilled directly, sprayed or nebulized (3-5 ml 2-4% lidoca ine). The total dose should not exceed 5-7 mg/kg. FB may induce anxiety, fear and pain. As no single agent adequately provide anxiolysis, analgesia and amnesia, a combination of drugs is most often used. The main drugs which are commonly used for FB procedure is described in table 2.

**Table 2. Main Drugs Used as Sedation for Pediatric Flexible Bronchoscopy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Dose</th>
<th>Onset of action (min)</th>
<th>Duration (min)</th>
<th>Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>Anxiolysis Amnesia</td>
<td>IV : 75-300 mcg/kg</td>
<td>1-5</td>
<td>90</td>
<td>Flumazenil 0.01 mg/kg</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Analgesia</td>
<td>IV : 0.5-2 mg/kg-1</td>
<td>5</td>
<td>180-240</td>
<td>Naloxone 0.01 mg/kg</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Analgesia Amnesia</td>
<td>0.25-0.5 mg/kg intermittent IV bolus</td>
<td>2-4</td>
<td>10-20</td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>Deep sedation (to suppress cough)</td>
<td>Intermittent bolus dose 0.5-1 mg/kg Continuous infusion: 100 mcg/kg/min</td>
<td>&lt;1</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Remifentanl</td>
<td>Deep sedation</td>
<td>IV 0.1-0.25 mcg/kg/min Continuous infusion 0.05 mcg/kg/min</td>
<td>2-5</td>
<td>2-3</td>
<td></td>
</tr>
</tbody>
</table>

**Technique for adequate ventilation during procedure**

Oxygen supplementation during the procedure is mandatory in young infants and children especially those with poor respiratory status. Supplementation oxygen can be delivered with a naso-pharyngeal prong through one nostril with the bronchoscope passed down the other or by a facemask over the nose and mouth. During general anesthesia, the airway and ventilation should be maintained by one of the following methods (table 3).

**Table 3. Techniques to Ensure Adequate Ventilation during Anesthesia**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facemask</td>
<td>Inspect entire airway</td>
<td>Probably the most technically challenging for the anesthetist</td>
</tr>
<tr>
<td></td>
<td>Assess airway dynamics/malacia</td>
<td>Laryngospasm may be a problem</td>
</tr>
<tr>
<td></td>
<td>Does not limit size of bronchoscope</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngeal prong</td>
<td>Easy to pass tube</td>
<td>Possibly less good upper airway access</td>
</tr>
<tr>
<td></td>
<td>Inspect most of upper airway</td>
<td>Laryngospasm in spontaneously ventilating child</td>
</tr>
<tr>
<td></td>
<td>Assess airway dynamics/malacia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Does not limit size of bronchoscope</td>
<td></td>
</tr>
<tr>
<td>Laryngeal mask</td>
<td>Easy to position mask</td>
<td>Airway control suboptimal</td>
</tr>
<tr>
<td></td>
<td>Secure airway</td>
<td>Cannot assess upper airway</td>
</tr>
<tr>
<td>Endotracheal intubation</td>
<td>Deep anesthesia safe</td>
<td>Cannot assess vocal cord movement</td>
</tr>
<tr>
<td></td>
<td>Easy and quick to re-pass bronchoscope if necessary</td>
<td>May limit size of bronchoscope</td>
</tr>
</tbody>
</table>

**Flexible bronchoscopy equipment**

Children are not small adult. It is also applied to choose appropriate flexible bronchoscope size before starting the procedure. Good understanding of anatomical structure of pediatric airway will ensure the appropriate choice of bronchoscope size. Epiglottis in children is floppier than in adult and usually U-shaped. The larynx in children is funnel shape which is different with the cylinder shape in adults. Airway in children is also more anterior and higher. Trachea is more flexible and cricoid is the narrowest part of the airway in children. The appropriate size of bronchoscope based on airway diameter is shown in table 4.
**Table 4. Cricoid Diameter Based on Age and Suggested ETT Size**

<table>
<thead>
<tr>
<th>Age</th>
<th>Cricoid airway diameter (mm)</th>
<th>Tracheal tube</th>
<th>Bronchoscope size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Size ID</td>
<td>ED (mm)</td>
</tr>
<tr>
<td>Premature</td>
<td>4.0</td>
<td>2.5-3.0</td>
<td>3.5-4.0</td>
</tr>
<tr>
<td>Team newborn</td>
<td>4.5</td>
<td>3.0-3.5</td>
<td>4.0-4.9</td>
</tr>
<tr>
<td>6 months</td>
<td>5.0</td>
<td>3.5-4.0</td>
<td>4.9-5.4</td>
</tr>
<tr>
<td>1 year</td>
<td>5.5</td>
<td>4.0-4.5</td>
<td>5.4-6.2</td>
</tr>
<tr>
<td>2 year</td>
<td>6.0</td>
<td>4.5-5.0</td>
<td>6.2-6.9</td>
</tr>
<tr>
<td>3 year</td>
<td>7.0</td>
<td>5.0-5.5</td>
<td>6.9-7.4</td>
</tr>
<tr>
<td>5 year</td>
<td>8.0</td>
<td>5.5-6.0</td>
<td>7.4-7.9</td>
</tr>
<tr>
<td>10 year</td>
<td>9.0</td>
<td>6.5 cuffed</td>
<td></td>
</tr>
<tr>
<td>14 year</td>
<td>11.0</td>
<td>6.5 cuffed</td>
<td></td>
</tr>
</tbody>
</table>

* A larger bronchoscope may be helpful, if there is a large air leak and IPPV is being used.

**ETT**: endotracheal tube, **ED**: external diameter, **IPPV**: Intermittent positive pressure ventilation

**Complications**

Complication is rare in children. Most of the life-threatening adverse events involve drug overdose, inadequate monitoring, or inappropriate sedation. Upper airway pathology, persistent radiographic changes, oxygen dependency and a weigh <10 kg are major risk factors associated with adverse events. Type of complications that are commonly found in FB procedure is depicted in table 5.

**Table 5. Complications of flexible bronchoscopy**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Clinical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Mechanical</td>
<td>Epistaxis, laryngospasm, trauma (avulsion, tear), stridor, airway hemorrhage, lower airway obstruction (hypoxemia, hypercapnia, increased intracranial pressure), air leak (pneumothorax, pneumomediastinum), bronchospasm, atelectasis</td>
</tr>
<tr>
<td>B. Microbiological</td>
<td>Nosocomial infection from contaminated equipment, intrapulmonary spread of infection</td>
</tr>
<tr>
<td>C. Anesthetic</td>
<td>Apneu, hypoxemia, hypercapnia, hypotension, nausea, vomiting, aspiration, adverse drug reaction</td>
</tr>
<tr>
<td>D. Multifactorial</td>
<td>Aspiration, fever, cardiac arrhythmias, death</td>
</tr>
</tbody>
</table>

**Special Procedures**

Several special procedures can be performed even in small preterm infant. This article will only describe some of the procedures which are bronchoalveolar lavage (BAL) and biopsy.

**A. Bronchoalveolar lavage (BAL)**

BAL is a diagnostic procedure used for recovering cellular and non-cellular components of the epithelial lining fluid of the alveolar and bronchial airspaces. An ERS task force report regarding technical aspects for performing BAL with normal value has been published. Parameters that are measured in BAL consist of percentage of instilled NS that is recovered and various BAL fluid (BALF) cellular and non-cellular components. Specimen examination in BAL consists of microbiology test using culture or molecular biology testing, citology and supernatant to examine proteins and inflammatory mediators. There are different reported methods for determining BAL instillation volume in children (table 6). Location of BAL will be focused in the most affected area that is identified radiologically and/or endoscopically. However, BAL location for diffuse lung disease will be in the right middle lobe because this area offers better fluid recovery or right lower lobe that is easier to be performed especially in infants.

BAL has been used in pulmonary infections of immunodeficient or immunosuppressed children not improving with standard treatment. BAL may be give useful diagnostic information in some cases of chronic interstitial lung disease (ILD), histiocytosis, alveolar proteinosis and haemosiderosis. BAL can be used to monitor disease activity in allergic alveolitis and sarcoidosis.
### Table 6. Methods for Determining BAL Instillation Volume in Children

<table>
<thead>
<tr>
<th>Alliquot Size</th>
<th>Patient Size Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4 fractions of 10-20 mL</td>
<td>N/A</td>
</tr>
<tr>
<td>5 to 20-mL fractions</td>
<td>Adjusted by FRC</td>
</tr>
<tr>
<td>5 mL for infants</td>
<td>N/A</td>
</tr>
<tr>
<td>10 mL for small child</td>
<td>3 mL/kg Divided into 3 aliquots for children &lt;20kg</td>
</tr>
<tr>
<td>15 mL for large child</td>
<td>Divided into 20-mL aliquots for children &gt;20kg</td>
</tr>
</tbody>
</table>

FRC: functional residual capacity, N/A: not applicable

### B. Biopsies

#### Endobronchial biopsy

Endobronchial biopsy is a safe procedure for diagnosis of tuberculosis, other infectious or granulomatous disorders and obtaining ciliated cells for the diagnosis of primary ciliary dyskinesia. Endobronchial biopsy aims to obtain sample of superficial airway structure that can be performed with a brush or forceps. Biopsies should be taken from segmental subcarinas, which are sharper and thus allow a better grip by the forceps. A routine chest radiograph is not necessary after endobronchial biopsy.

#### Transbrachial biopsy

Transbrachial biopsy (TBB) is a technique to obtain peripheral lung tissue for diagnostic studies including histopathological examination and for microbial cultures. The procedure is carried out under deep sedation or general anaesthesia. Fluoroscopy is mandatory for accurate positioning of the biopsy forceps in order to get the maximum yield from sites of radiographic abnormality and to minimise the risk of pneumothorax. The forceps are introduced through the bronchoscope and advanced under fluoroscopic screening until resistance is felt. Then the forceps are withdrawn 1-2 cm, the jaws of the forceps are opened and wedged into the lung tissue after rapidly advancing. Subsequently, the forceps are closed and briskly withdrawn. After completion, a small saline lavage and visualisation of the bronchial tree should be performed to ensure haemostasis. A chest radiograph 2-4 h later is mandatory to rule out a slowly developing pneumothorax. Only one lung should be sampled on a same occasion and the middle lobe and lingula are avoided to reduce risk of pneumothorax. At least three biopsies should be obtained for microbiological and histological studies.

The major complication of TBB is a pneumothorax. Other complications include small haemorrhages, transient pyrexia, and transient dyspnoea. Thus, it is recommended that patients should be observed overnight following the procedure.

### References

Introduction

Bronchoscopy is a diagnostic and therapeutic procedure that permits direct visualization of normal and pathological alterations of the upper and lower airways. Expert knowledge of airway anatomy is a prerequisite for successful performance of the procedure.1 To become competent in performing bronchoscopies entails proper training and dedicated practice, as well as accurate interpretation of endoscopic findings to incorporate into differential diagnosis and management strategies.2 Interventional pulmonology can be defined as "the art and science of medicine as related to the performance of diagnostic and invasive therapeutic procedures that require additional training and expertise beyond that required in a standard pulmonary medicine training programme".3

Bronchoscopy Approach

The procedure can be performed with the patient sitting upright in a semi-recumbent position being approached from the front (Fig. 1). This has the advantage of allowing it to be carried out in sicker patients who desaturate upon lying flat. For this setup the bronchoscope image obtained is such that the posterior aspect is visible at the top, the anterior aspect is below, the right is on the left part of the image and the left is on the right part of the image (Fig. 1).4

![Figure 1. Room setup with the semi-recumbent patient being approached from the front. (Left) Bronchoscopic image obtained with the semi-recumbent patient approached from the front. (Right)](image1)

The posterior approach with the patient lying flat is also widely used (Fig. 2). This approach is also required in a number of procedures such as endobronchial ultrasound and also the superdimension procedure. With this approach the image obtained is such that the anterior aspect is at the top, the posterior aspect is the inferior aspect of the image and the left side of the patient is the left sided image and the right side of the patient is the right side of the image (Fig. 2).4

![Figure 2. Room setup with patient being approached from the back in a supine position. (Left) Bronchoscopic image obtained with the supine patient approached from the back. (Right)](image2)
Upper Airway

Nasopharynx

The upper airway examination begins with a quick assessment of nasal and oral cavities. Nasal anatomy is complex; relevant structures include the nasal septum that divides the nose into two cavities and lateral nasal walls that are largely defined by the maxilla. Each of the walls is divided by three structures: the superior, middle, and inferior turbinates. When the flexible bronchoscopy is introduced through the nose, the inferior turbinate is seen laterally and the nasal septum is seen medially. The bronchoscope is then directed posteriorly into the pharynx. When viewing the nasal cavity, the bronchoscopist should assess for septal deviation, hypertrophy of turbinates, presence of polyps, and integrity of mucosa.

Oropharynx and hypopharynx

When the flexible bronchoscope is introduced orally, it passes through the oropharynx and larynx and into the trachea. Beyond the base of the tongue, the bronchoscope is passed through the curvature of the oropharynx, which is bordered superiorly by the soft palate and extends to the tip of the epiglottis. The flexible bronchoscope is then directed posterior to the tip of the epiglottis. The three major structures in the hypopharynx are the pyriform recess, the postcricoid region, and the posterior pharyngeal wall. Tongue size, tooth integrity, and temporomandibular joint mobility are important factors affecting the ease of introduction into the oropharynx. The space between the base of the tongue and the anterior surface of the epiglottis on either side constitutes the vallecula. The valleculae are separated by the median glossoepiglottic fold and bordered laterally on either side by the lateral glossoepiglottic folds. Valleculae are often locations for foreign body entrapment and upper airway obstruction.

Larynx

The larynx is composed of a series of cartilages, ligaments and fibrous membranes. At bronchoscopy the epiglottis is the more proximal structure. It is a broad leaflike structure. The sides are attached by the arytenoid cartilages. The cuneiform and corniculate can be seen at the end of the arytenoid cartilage. The cuneiform cartilage is more anterior and superior to the corniculate cartilage. The vocal folds consist of the false cords or vestibular folds and the true vocal folds. They stretch back from the thyroid angle to the vocal processes of the arytenoids. The vocal folds are involved in the production of sound.

Lower Airway

Trachea

The lower airway (trachea to conductive bronchi) begins at the cricoid cartilage (at about the level of the sixth cervical vertebra, C6). The adult trachea ranges from 16 to 20 mm in internal diameter and has 18–22 cartilage rings. The trachea tapers slightly and aims posteriorly as it divides at the carina, at the level of fifth thoracic spine to the left and right main stem bronchi. The horseshoe-shaped tracheal cartilage shapes the anterior part of the trachea, whereas the posterior part of the trachea consists of smooth muscles that joins the ends of the tracheal cartilage. Starting at the upper trachea, mucosal integrity should be examined, even when there are no gross endobronchial lesions. The presence of extrinsic tracheal deviation and compression due to paratracheal masses should be noted. The distal trachea and main carina are important sites for examination because malignant diseases often metastasize to the surrounding mediastinal lymph nodes. If a lesion is identified, both sides of the lungs should be examined completely before biopsies are taken. The importance of complete surveillance is that unexpected satellite airway pathologies can occur in up to 10% of primary bronchogenic carcinomas. After main pathology is visualized or diagnostic procedures are started, the bronchoscopist can become too distracted to return to a thorough and careful examination of the remainder of the airways.

Main Carina

The carina is a concave spur of cartilage located where the distal trachea divides into the right and left main bronchi. The carina normally appears as a sharp structure and forms the medial borders of the origin of the right and left main bronchi. The sharp angle is maintained as it is primarily composed of cartilage (carinal) and ligaments (interbronchial). Enlargement of the subcarinal structures, such as the subcarinal lymph nodes or the left atrium, may lead to blunting or widening of the carina.

Right Bronchial Tree

The right main bronchus is approximately 1.5cm in length and has an internal diameter of 10–12 mm. The first branch, the right upper lobe (RUL) bronchus, arises just below the carina, and courses laterally for a distance of 1–2 cm before branching into apical, anterior, and posterior segments. Beyond the RUL bronchus, the right main bronchus becomes the bronchus intermedius, extends approximately 2–2.5 cm, and divides into right middle lobe and lower lobe bronchi. The right middle lobe bronchus arises from the anterolateral wall of
the bronchus intermedius and extends anteriorly and laterally for about 1–2 cm before dividing into medial and lateral segments. The lateral segmental bronchus is visualized over a greater distance, and the medial segment has a more oblique course. Beyond the origin of the superior segment, the right lower lobe divides into anterior, posterior, medial, and lateral segments.\textsuperscript{1,2}

**Left Bronchial Tree**

The left main bronchus is approximately 4–4.5 cm in length and tends to progress posteriorly, inferiorly, and laterally. It divides into left upper and lower lobe bronchi. The left main bronchus is much longer than the right and is radiologically seen in three to four contiguous sections below the carina. The upper lobe bronchus is 2- to 3-cm long and divides into upper lobe and lingular divisions. The upper division divides into apicoposterior and anterior segmental bronchi. The lingular bronchus is about 2–3 cm in length and divides into superior and inferior segmental bronchi. The superior segment of the left lower lobe bronchus arises immediately on entering into the left lower lobe. Beyond this, the left lower lobe bronchi is approximately 1 cm in length and divides into anteromedial, lateral, and posterior basilar segments.\textsuperscript{1,2}

**Reference**

Medical Thoracoscopy

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Introduction

Based on European Respiratory Journal, the definition of medical thoracoscopy is thoracoscopy performed under local anaesthesia in the endoscopy suite with the use of nondisposable instruments, and is generally for diagnostic purposes. It is an important technique for assessment of undiagnosed exudative pleural effusion. Medical thoracoscopy also known as medical pleuroscopy.

Medical thoracoscopy is the branch of interventional pulmonology to help diagnosed pleural diseases. It is similar with video-assisted thoracoscopy surgery (VATS). The differences between medical thoracoscopy and VATS are mentioned in table 1.

Table 1. The differences between medical thoracoscopy and VATS

<table>
<thead>
<tr>
<th></th>
<th>Medical Thoracoscopy</th>
<th>Video-Assisted Thoracoscopy Surgery (VATS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Procedural room</td>
<td>Operation theatre</td>
</tr>
<tr>
<td>Sedation</td>
<td>Local anesthesia + mild-medium sedation</td>
<td>General anesthesia</td>
</tr>
<tr>
<td>Ventilation</td>
<td>Spontaneous ventilation</td>
<td>One-lung ventilation</td>
</tr>
<tr>
<td>Purpose</td>
<td>Diagnostic – biopsy, Therapeutic – pleurodesis, adeolysis</td>
<td>Minimal invasive surgery: lobectomy, pneumonectomy</td>
</tr>
<tr>
<td>Performer</td>
<td>Respirology consultant/ Pulmonologist/ Pediatrician</td>
<td>Thoracic surgery</td>
</tr>
<tr>
<td>Process</td>
<td>Less invasive Less expensive</td>
<td>More invasive</td>
</tr>
</tbody>
</table>

Indication

Thoracoscopy can be done to achieve diagnostic or therapeutic purpose. Diagnostic thoracoscopy indicated in pleural effusion and spontaneous pneumothorax. The most common indication for therapeutic thoracoscopy is pleurodesis to prevent recurrent pleural effusion and pneumothorax. Other indications are diffuse lung disease, localized lung lesions, chest wall lesions, mediastinal tumors, and postoperative cavities.

Contraindication

Absolute contraindication for medical thoracoscopy are:
- No pleural cavity / minimal pleural effusion
- Uncontrolled bleeding / severe haemosthatic disorder

Relative contraindication for medical thoracoscopy are:
- Mild haemostatic disorder
- Respiratory failure / need ventilator
- Unstable cardiovascular condition
- Frequent cough

Preparation

Medical history, physical examination, radiology examination (posteroanterior, lateral, decubitus chest x-ray), ultrasonography, and CT scan may assist in appointing the insertion site for thoracoscopy. Laboratory examination, such as complete blood count, coagulation, electrocardiogram, blood gas analysis, percutaneous oxymeter, and lung dunction test, are conducted to evaluate systemic and respiratory condition of the patients. For this procedure, patient was put under mild sedation, therefore patients with severe hypoxemia not associated with pleural effusion are prohibited to undergo thoracoscopy procedure.

Medical thoracoscopy is using disposable instrument, which was inserted to one or two point towards pleural cavity. This procedure helps the operator to achieve internal visualization of the pleural cavity. Afterwards,
the operator insert accessories instrument through rigid-flexion pleuroscopy channel or with double puncture technique. In double puncture technique, small incision was made along intercostals cavity, in order to insert another pleural trochar for additional instrument. This technique usually conducted to prevent bleeding, severe adhesion, suctioning large amount of pleural effusion, or conduction biopsy.

![Figure 1. Thoracoscopy instruments](image)

**Complication**

Medical thoracoscopy is a safe procedure. Complication of oxygen desaturation under local anesthesia while thoracoscopy is rarely happens. Another fact is, this procedure is safe to be conducted for massive pleural effusion. Pleural fluid evacuated as soon as inserting the trochar, in order to improve breathing. Other complications for medical thoracoscopy are bleeding, pleural cavity infection, intrathoracal trauma, atelektasis, and respiratory failure. To prevent complication, it is important to:

- Delay thoracoscopy procedure for a few days if the patient has a cough
- Observe patient’s vital sign and peripheral oxygen saturation while conducting the procedure
- Give oxygen to the patient while undergoing procedure
- Avoid taking biopsy sample from internal fissure or mediastinum
- If the bleeding exceeds 20 ml, stop the bleeding and maintain haemostasis
- Insert chest tube (until the lung expand) to prevent emphysema subcutaneous
- Start physiotherapy from the day the thoracoscopy was conducted, to train the diaphragm and to prevent accumulation of secretion and obstruction
- Give radiation therapy 7 Gy/day for 3 days in the scar area from day-10 post-thoracoscopy to prevent the invasion in mesothelioma cases

**References**

SECTION 3

Poster
Clinical Scores for Diagnosing Occupational Asthma in Workers Exposed to Sensitizers

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Introduction
Specific inhalation challenge (SIC) as the reference test for occupational asthma (OA) is not widely accessible.

Methodology
This retrospective diagnostic study aimed to evaluate current diagnostic tools, and, to develop diagnostic model for OA (defined as positive SIC). Data from workers with suspected OA who were exposed to high-molecular-weight (HMW) (n=142) and low-molecular-weight (LMW) agents (n=285) and still working at least one month before the SIC were evaluated. Logistic regression models were developed in each exposure group. The added values of different objective tests to clinical and exposure characteristics were evaluated. The models were tested for accuracy, and, internally validated. The final models were translated into clinical score and the sum scores were stratified into risk groups.

Results
In workers exposed to LMW agents, the predictive model did not perform better diagnostically than the methacholine challenge test alone. In the HMW group, the final model included sex, age >40 years, symptom duration ≥1 year, rhinoconjunctivitis, inhaled corticosteroid use, the methacholine challenge test, and specific skin-prick test. It had a good discriminative ability (the corrected area under the characteristic curve was 0.909, 95% CI 0.88-0.93), calibration (Hosmer-Lemeshow p-value 0.129), and internal validation (a correction factor of 0.99 from the bootstrapping procedure). The high probability category of the diagnostic model had good diagnostic properties (positive predictive value of 88.7%, positive likelihood ratio of 7.4) and was superior to the combination of methacholine challenge test and specific skin-prick test in detecting OA.

Conclusions
Our model quantifies an individual’s probability of OA with better diagnostic parameters than the combination of the methacholine challenge test and specific skin-prick test in workers exposed to HMW agents. Our model may be of benefit in diagnosing OA in centers where access to SIC is difficult or impossible. Nevertheless, external validation of the model is necessary.

Keywords: clinical scores, diagnostic study, occupational asthma
Characteristics of Multidrug-Resistant Tuberculosis Patients in Prof. Dr. R. D. Kandou Hospital, Manado

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Introduction

The emergence of MDR-TB has become a major global health problem. Drug resistance TB results from inadequate treatment of active TB. A number of factors may play a role in the development of this condition. This study was aimed to evaluate the characteristics of MDR-TB patients in Prof. Dr. R. D. Kandou Hospital.

Methods

A cross-sectional study was conducted to patients who received treatment for MDR-TB in Prof. Dr. R. D. Kandou Hospital between July 2016 and January 2017. Characteristics examined were baseline characteristics, previous TB treatment, previous BCG vaccination, the presence of co-morbidities, nutritional status, and psychological status.

Results

Of 196 suspected patients, 35 (17.9%) were definitely diagnosed as MDR-TB. Most subjects were male (65.7%), aged 45-54 years (31.4%), married (82.9%), had various jobs (57.1%). Fifty-one percent had senior high school as level of education. All subjects had been treated with anti-tuberculosis drug (ATD) for >30 days. Forty-five percent was relapse case. Most subjects had two-cycles of ATD (48.6%), and poor compliance to treatment (71.4%). Chronic cough was the most common complain (51.4%). Forty-eight percent had high level of M.TB bacilli in direct sputum examination. Most subjects had received BCG vaccination (51.4%). Diabetes was the most common co-morbidity (42.9%). Most subjects were underweight (57.1%). Forty-five percent had mild depression.

Conclusion

17.9% of the suspected patients were definitely diagnosed as MDR-TB. Male, married, various jobs, previously treated with ATD, relapse case, poor compliance to treatment, received BCG vaccination, and underweight were the main characteristics.

Keywords: tuberculosis, multidrug-resistant, characteristics
Tyrosine Kinase Inhibitor Resistance in Non Small Cell Lung Carcinoma Subtype Adenocarcinoma Patient with Positive Epidermal Growth Factor Receptor

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Introduction

The found of Epidermal Growth Factor Receptor (EGFR) mutation in patient with Non Small Cell Lung Carcinoma (NSCLC) began the personalized therapy in treatment management of NSCLC. Since discovered 10 years ago, EGFR mutation which was response to Tyrosine Kinase Inhibitor (TKI) such like gefitinib, there was also found that the condition in which that therapy was resisted. Mutation in exon 20 insertion that leads to poor signaling of EGFR inhibition is associate with oncogenic transformation which is resistance to TKI. This case will be discussed to know if there is any resistance to TKI that need to treat by other strategy.

Case Report

A 42 year old woman diagnosed with NSCLC with Adenocarcinoma subtype, metastation process in vertebrae, hospital acquired pneumonia, suspect of MESCC, pleural effusion due to malignancy, and antral erosive gastritis. Diagnose of NSCLC with adenocarcinoma subtype based on cytology examination of pleural effusion which found a malignant cell refer to NSCLC with adenocarcinoma subtype. Result from EGFR examination at December 7, 2016, found that there was a mutation in exon 19 (deletion) and 20 (insertion). Patient then treated with Iressa 250 mg per oral once a day. There was no any positive progression of diseases until she died.

Conclusion

Ninety percent of patient diagnosed with NSCLC with adenocarcinoma subtype which was EGFR positive had a mutation in exon 19-21. Study showed that insertion in exon 20 which led to oncogenic transformation was associated with TKI resistance due to poor signaling EGFR inhibition which was proof on in vitro study. This problem need to be solved with other treatment strategy like chemotherapy, EGFR therapy with TKI 3rd generation, comprehensive genetic analysis to know the mutation (deletion) in exon 20 and substitution of T790M and new therapy modalities that work in pathway which is activated by EGFR.

Keywords: Lung Cancer, Non Small Cell Lung Carcinoma, Adenocarcinoma, Epidermal Growth Factor Receptor, Tyrosine Kinase Inhibitor, Gefitinib, Iressa
Albumin and Endothelin-1 Level Were Associated with Pulmonary Dysfunction in Liver Cirrhosis

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Introduction

Pulmonary dysfunction (PD) is a common and serious problem in patients with advanced liver disease. Studies which evaluate PD in liver cirrhosis were still limited. The aim of this study was to evaluate PD (without intrinsic cardiopulmonary disease) in liver cirrhosis patients and its association with laboratory parameters.

Methods

The present study was a cross sectional study on 80 consecutive liver cirrhosis patients admitted to Adam Malik General Hospital, Medan, Indonesia in July – December 2016. Inclusion criteria were inpatients and outpatients with liver cirrhosis, age >18 years. Patients with coexisting primary pulmonary pathology, coexisting intrinsic heart disease, active smokers, and those who declined to participate were excluded. Pulmonary dysfunction was diagnosed by evidence of liver cirrhosis, abnormal arterial oxygenation (PaO2 ≤ 70 mmHg) while breathing room air. All data were analyzed with statistical software, using univariate and bivariate analysis with 95% confidence interval. Bivariate analysis was carried out using Chi Square, Fisher Exact, independent t test, Mann Whitney U test with significance level set at p<0.05.

Results

There were 80 subjects, consisted of 45 males (56.3%) and 35 females (43.8%). Mean age was 51.36 ± 12.6 years old. There were 63 patients (73.8%) without PD, 17 (21.2%) with PD. There were significant associations between PD with ascites, hepatic encephalopathy, and child pugh score (p<0.05). There were significant lower level of albumin and higher level of endothelin-1 in patients with PD compared than without PD (p<0.05).

Conclusion

Liver cirrhosis patients with PD had a higher endothelin-1 levels and lower albumin level compared than without PD, raising the possibility of using Endothelin-1 and albumin levels as a predictor for PD in liver cirrhosis.

Keywords: Pulmonary dysfunction, liver cirrhosis, endothelin-1, albumin
Epididymis Tuberculosis: A Case Report

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Introduction

Epididymis Tuberculosis (TB) is a rare condition. Tuberculosis is an infection of the epididymis-specific chronic granulomatous the genitourinary tracts are extremely rare, even in endemic countries where the incidence of pulmonary and extrapulmonary TB has a very high prevalence.

Case Report

A man aged 43 years with complaints of a lump in pubic left, slowly swelling without pain since 6 months ago. There is no history of fever or pulmonary disease. Histopathology showed epididymal tissue looked fibrosis and tubercles with epithelioid cells and lymphocytes with lagerhans Datia conclusion tuberculous inflammatory process. Patients do antituberculosis treatment.

Conclusion

Epididyminis TB is not easy to diagnose because there was generally no systemically active TB occur together. Although epididymis TB is a manifestation of TB is very rare, it is important to recognize its existence, especially when the patient comes from endemic areas such as in Indonesia.

Keywords: Tuberculosis, epididymis, histopathology.
Spontaneous Pneumothorax in B20 Patient with Pulmonary Tuberculosis and Lung Abscess

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Background
Although it is a rare complication, spontaneous pneumothorax is a complication of pulmonary tuberculosis. Literatures reported were minimal. Spontaneous pneumothorax occurs without trauma in the chest wall. This may be a primary or secondary pneumothorax. The primary pneumothorax occurs in the absence of lung disease, whereas secondary pneumothorax caused by lung disease. Pulmonary tuberculosis are the main cause incidence of secondary pneumothorax. This case was reported because the incidence of secondary pneumothorax in patients with pulmonary tuberculosis mostly in developing countries.

Case Report
A 25 years old man with spontaneous pneumothorax pulmonary dextra, pulmonary tuberculosis, lung abscess, and B20 was admitted to hospital with a chief complaint shortness of breath increasingly for 2 weeks, pleuritic chest pain, productive purulent cough, intermittent fever, and the change in body weight ± 15 kg for 3 years. He was a survivor of B20 and pulmonary tuberculosis since January 2013, but the treatment stop until the patient was hospitalized. During the treatment, spontaneous pneumothorax occurred in the right lung, the patient was installed water seal drainage and re-start therapy with 1st category tuberculosis drugs, the clinical responses were good during therapy.

Discussion
The incidence of secondary pneumothorax are 5.8 / 100,000 cases in women and 16.7 / 100,000 in the case of men. Pulmonary tuberculosis is a major cause of spontaneous pneumothorax. Clinical symptoms were shortness of breath, coughing, in some cases hemoptysis, and malnourished. In spite of an acute and life-threatening, patients have a response to high flow oxygenation, tuberculosis drug delivery and installation of drainage water seal.

Keywords: spontaneous pneumothorax, secondary pneumothorax, pulmonary tuberculosis
Pickwickian Syndrome In A 44 Years Old Indonesian Man

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Background
Moderate to severe degrees of obesity can lead to a restrictive abnormality in lung function due to the mechanical effects of central body fat. Obesity-hypoventilation syndrome (OHS), also historically described as Pickwickian syndrome, consist of Triad of obesity, sleep disorder breathing, and chronic daytime alveolar hypoventilation defined as PaCO₂ ≥45 mmHg and PaO₂ < 70 mmHg. OHS often remains undiagnosed until late in the course of the disease. Early recognition is important because these patients have significant morbidity and mortality.

Case Presentations
A 44-years-old Indonesian man presented to ER department with complaining of shortness of breath since few days before admissions. He diagnosed with respiratory failure mixed type, suspect hypoventilation syndrome, health care associated pneumonia, chronic kidney disease stage v on regular hemodialysis, right heart failure due to lung problems. Then the patient treated with antibiotics, anti hypertension, and Oxygen support as well. On examination showed obesity, height was 1.65 m weight was 86 kg giving BMI 31.59 kg/m², snoring and easy to fall asleep during daytime. There were no upper respiratory obstructive causes or nasal polyps, hypoxia and hypercapnia were confirmed by arterial blood gases and pulse oxymetry. He had been admitted in general ward for 10 days, and discharged from hospital with additional diagnosis Pickwickian syndrome.

Conclusion
Diagnostic criteria for OHS or Pickwickian syndrome are BMI ≥ 30 kg/m², daytime PaCO₂ > 45 mmHg and PaO₂ < 70 mmHg, associated sleep related breathing disorder, and absence of other known causes of hypoventilation. OHS is often unrecognized and treatment is frequently delayed. Clinicians must maintain a high index of suspicion because early recognition and treatment may reduce the high burden of morbidity and mortality.

Keywords: Pickwickian syndrome, obesity hypoventilation syndrome, obesity
Spontaneous Pneumothorax in Young Female with Pulmonary Tuberculosis and Obstructive Airway Diseases

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Introduction

Pneumothorax is defined by the existence of air in the pleural cavity. Spontaneous pneumothorax occurs without any history of trauma. Primary spontaneous pneumothorax occurs when there is no underlying disease while secondary spontaneous pneumothorax if found otherwise. Pulmonary tuberculosis is known as one of the most etiology of secondary spontaneous pneumothorax especially in developing country. Some reported chronic obstructive pulmonary diseases cause pneumothorax complication and rarely asthma. We reported the incidence of spontaneous pneumothorax in young female with pulmonary tuberculosis and obstructive airway diseases.

Case Report

A 25-year-old female has been diagnosed with pulmonary tuberculosis two weeks before admitted to Dr. Sardjito General Hospital. The patient is being treated with tuberculosis combines therapy. Patient was admitted because increasing severity of shortness of breath which was suspected caused by asthma or other obstructive airway disease and also pneumonia. Blood tested for IgE and eosinophil count to support the diagnosis asthma showed normal result. Patient’s shortness of breath became more severe with the worsening of clinical appearance. Patient was diagnosed with right sided pneumothorax and treated with tube thoracostomy that is connected to Water Seal Drainage (WSD) immediately. Patient’s condition became more severe after 4 days. Chest x-ray re-examination showed patient suffered bilateral pneumothorax. WSD then performed in both lungs and held for 28 days. Patient was also given anti tuberculosis, bronchodilator, and antibiotics. Patient got better and WSDs were taken off.

Conclusion

Spontaneous Pneumothorax can be caused by tuberculosis, obstructive pulmonary diseases or both. Clinical presentation could be severely acute and prone to be underdiagnosed. Even though increasing severity of shortness of breath can be caused by other etiology, we have to be careful with such condition. Morbidity and mortality of the spontaneous pneumothorax can be minimalized with proper examination and treatment.

Keywords: spontaneous pneumothorax, pulmonary tuberculosis, obstructive airway diseases, thoracotomy.
Tuberculosis Relapse in Patients Respiratory Failure with B20: A Case Report

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Introduction

The incidence of TB by increasing B20. WHO data on TB patients with B20 in 2011 is 5-19%. Data 2004-2011 WHO TB patients with B20 was 500 thousand, TB patients without B20 is 250 thousand. The death of 33% of patients B20 directly related to tuberculosis. In patients TB 3.8% ICU admission due to ARDS.

Case Report

A man aged 31 years with a diagnosis of advanced stage B20, suspected Pneumocystis pneumonia and pulmonary tuberculosis relapse. Complaints at admission were heavy limp, cough with yellowish color sputum. Patients have B20 and a history of tuberculosis treatment for 6 months of 2014. The results of the thoracic roentgen longer active pulmonary TB. Results of blood gas pH 7.48 pCO2 pO2 51.3 33.6 PO2 / FI02 59. Patient received Cotrimoxazole therapy 1x960 mg, Fluconazole 400 mg/24 hours, Methylprednisolone injection of 62.5 mg /6 hours, catagory II anti tuberculosis on hospital.

Discussion

Clinical symptoms of TB in B20 are often non-specific. Clinical symptoms are often found as fever and weight loss is significant. Expert diagnosis with Gent. Management of TB treatment in patients with B20 is the same as in other patients. TB patients with OAT B20 given in advance to reduce morbidity and mortality. ARV treatment should be started immediately first 2-8 weeks after the start of TB treatment. Steroids in patients with respiratory failure 62.5 mg / 6 hours until reduced doses.

Keywords: Respiratory failure, B20, pulmonary tuberculosis
Isoniazid Monoresistance: Do We Missed It?

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Introduction

Multidrug-resistant tuberculosis (MDR-TB), defined by resistance to isoniazid (INH) and rifampin (RIF), is a major threat to the control of tuberculosis. MDR-TB is now widespread throughout the world, with the increase driven largely by transmission. There were estimated 450,000 (range, 300,000 to 600,000) new MDR-TB cases globally in 2012.

INH is one of the most effective first-line drugs in anti-TB therapy. The detection of INH resistance is crucial for the treatment and control of MDR-TB. Although RIF resistance was accepted as a surrogate of MDR-TB, detection of RIF resistance alone could neglect INH-monoresistant patients as well as RIF-monoresistant patients. The results can be interpreted, on one hand, that INH-monoresistant patients would lose an opportunity to initiate effective treatment and develop acquired resistance to RIF, on the other hand, RIF-monoresistant patients (though rare) would exclude INH, a safe and useful drug, from their treatment.

Case Report

A 35 years old woman with Pulmonary Tuberculosis, Atrial Septal Defect Secundum Bidirectional Shunt, and Pulmonary Hypertension was admitted to hospital with a chief complaint shortness of breath increasingly for 1 weeks, productive purulent cough, and intermittent fever. He was a survivor pulmonary tuberculosis since 2 February 2017 (2 weeks ago) with 1st category tuberculosis drugs. During the treatment, the result of drugs sensitivity test came out with the result of INH monoresistance.

Discussion

Detection of rifampin resistance alone could neglect INH-monoresistant patients as well as RIF-monoresistant patients. It is widely accepted that INH resistance and RIF resistance are equally important, and thus their detection is required in various guidelines for drug resistance treatment and prevention.

Keywords: isoniazid monoresistance, multi-drug resistance tuberculosis, pulmonary tuberculosis
Factors Related to a 30 Day Mortality in Critically Ill Patients with Candidiasis Invasive in Cipto Mangunkusumo Hospital

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Introduction
Mortality rate candidiasis invasive is still high, approximately 30-70%. Every study has a variety mortality rate depend on study design and sample. There is no data in Indonesia about profile and mortality factors analysis in critically ill patients with candidiasis invasive.

Objectives
To give information about candidiasis invasive profile and to evaluate some factors related to 30 days mortality in critically ill patients with candidiasis invasive in CiptoMangunkusumo Hospital, Jakarta.

Method
The Study design was Cross Sectional. We studied 102 hospitalized critically ill patients with candidiasis invasive. The demographic, clinical and laboratory data, the risk factors for candidiasis invasive and the outcome of each patient in 30 days were recorded. An analysis bivariate with chi square or Fisher’s test was carried out to analyse some factors such as age > 60 years old, severe sepsis, APACHE score > 20, respiratory failure, renal failure, delayed antifungal treatment > 72 hours after positive culture, Charlson index score, and ICU or Non ICU patients. The logistic regression of multivariate analysis was carried out to identify the most influence of all mortality factors.

Result
Among 102 identified sample, the majority was male (52.9%), the median age was 53 years old and the mortality rate was 68.6%. Laboratory candida findings came from blood (candidemia) (98.03%), liquor cerebrospinal (1.5%) and retina exudat (1.5%). The most common candida species was Candida Tropicalis (34.3%) and Candida Parapsilosis (34.3%). The risk factors for Candidiasis invasive, relate to underlying disease were sepsis (78.9%), malignancy (42.15%), diabetes mellitus (29.4%) and relate to treatment were the usage of broad spectrum antibiotic (99%), catheter vena central (77.5%), and parenteral nutrition (70.6%). From multivariate analysis, severe sepsis (p 0.001, OR 7.7, IK95% 2.4 – 24.7), Charlson Index ≥ 3 (p 0.022, OR 3.5, IK95% 1.2 – 10.2), and respiratory failure (p 0.066, OR 2.7 IK95% 0.9 – 8.0) were independently associated with mortality.

Conclusion
Critically ill patients with candidiasis invasive in CiptoMangunkusumo hospital, male was predominant than female, median age was 53 years old, and mortality rate was 68.6%. The two most species candida caused infection were Candida Tropicalis and Candida Parapsilosis. The most risk factors of candidiasis invasive from underlying disease was sepsis and the one from the treatment was the usage of broad spectrum antibiotic. Severe sepsis, and Charlson index ≥ 3 were associated with a 30 day mortality in critically ill patients with candidiasis invasive.

Keywords: Candidiasis invasive, critically ill, Mortality factors
Validation of Clinical Disease Activity Index Score in Rheumatoid Arthritis Patients at Cipto Mangunkusumo Hospital in Year 2016

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Introduction

Clinical Disease Activity Index (CDAI) stands out amongst other methods in measuring disease activity of rheumatoid arthritis (RA) patient. CDAI is considered to be more practical and cost-effective in daily practice because it requires no laboratory examination. Previous studies conducted overseas reveal that CDAI has good validation, correlation, validity, and reliability compared with other score methods. However, those studies included only subjects with pure RA patients. Indonesian RA patients have distinct clinical profile, in terms of comorbidity conditions, genetic predisposition, and phenotype of the disease.

Objectives

To assess validation performance of Clinical Disease Activity Index in distinct clinical profiles of RA patients in Indonesia.

Methods

A cross sectional study in RA patients, who were visiting rheumatology clinic at Cipto Mangunkusumo hospital on regular monthly basis from April to May 2016. Assessment of each patient include history taking and physical examination. All recent laboratory results and other data in medical record were documented in researcher form. CDAI and Disease Activity Score 28 CRP (DAS28-CRP), as gold standard, were measured in each patient by two observers. Outcomes were in numeric data. Validation analysis was done in terms of validating a model prediction and quantifying how good the predictions from the model are (model performance). Overall performance was measured with R² index.

Result

A total of 119 subjects met the inclusion criteria. All subjects were RA patients with comorbidities and were representing quite numbers of Indonesian races characteristic profile. R² index =0,831 (83,1%).

Conclusion

Clinical disease activity index has good validation performance in assessing disease activity of Indonesian RA patients.

Keywords: Rheumatoid Arthritis, Indonesia, Validation, Clinical Disease Activity Index.
Male Breast Tuberculosis

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Introduction

Breast tuberculosis, a rare extrapulmonary tuberculosis, was first reported by Sir Artley Cooper in 1829. Its prevalence is 0.1% - 0.52%. We are reporting a 23 years old male with chief complaint a lump in his left breast. There is no report of similar case in Indonesia and it is the breast tuberculosis in male first reported in Palembang.

Case Report

A 23 years old male came to the Oncology Outpatient Department with chief complaint a painful lump in his left breast first noticed within a month. The patient was assessed as gynecomastia. He underwent mastectomy, the tissue was sent to Histopathology Department. The finding was consistent with breast tuberculosis. On physical examination, we found post mastectomy scar on the left chest. Chest X-ray was normal but liver enzymes were elevating (AST 54 U/L, ALT 98 U/L).

Discussion

This case was managed by Oncology Department, mastectomy was done and histopathological examination of breast tissue incidentally found chronic specific granulomatous inflammation. Antituberculosis drug is being delayed until liver enzymes are normal.

Conclusion

The breast tuberculosis should be considered as a differential diagnosis in breast tumor, breast abscess or mastitis. Antituberculosis regimen therapy for breast tuberculosis is similar with the extrapulmonary tuberculosis.

Keywords: breast tuberculosis, gynecomastia.

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Added Value of Albumin Level to CURB-65 Score as Mortality Predictor of Hospitalized Pneumonia with Commorbidity Patients

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Background

Pneumonia is an infection disease with high mortality. An accurate prediction rule is needed to help clinician in predicting mortality of pneumonia patients. CURB-65 score is a simple and well-known scoring system to assess the severity of community pneumonia, but several research indicated that the performance is not really good, especially in some group of patients. Added value of albumin serum in CURB-65 score should be evaluated.

Aim

To evaluate added value of albumin serum in CURB-65 score as mortality predictor in pneumonia patients.

Method

This is a retrospective cohort study of pneumonia with commorbidity patients who admitted to emergency installation of Cipto Mangunkusumo Hospital. Mortality is the outcome that assessed during hospitalization. Performance of CURB-65 score was evaluated before and after addition of albumin in scoring system. Calibration was evaluated with Hosmer-Lemeshow test. Discrimination was evaluated with area under the curve (AUC). Prediction performance of CURB-65 score and albumin were evaluated with ROC curve.

Result

250 patients was included to this study with mortality rate 42.6%. Calibration plot of CURB-65 score of Hosmer-Lemeshow test showed p = 0.990. Discrimination was shown by ROC curve with AUC 0.677 (IK 95% 0.61-0.74). AUC of CURB-65 score added by albumin improved to 0.727 (IK 95% 0.66-0.79).

Conclusion

Serum albumin has added value to CURB-65 score in predicting mortality of pneumonia patients.

Keywords: pneumonia patients, mortality, CURB-65 score, serum albumin
New Cases of Advanced Lesions Pulmonary Tuberculosis and Tuberculous Lymphadenitis with Pneumonia, Anemia of Chronic Disease, Malnutrition: A Case Report

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Introduction

Tuberculosis is a disease caused by infection of \textit{M\.tuberculosis} in pulmonary or extrapulmonary.\cite{1} Pneumonia is acute inflammation of lung parenchyma, distal terminal bronchioles lead to consolidation of lung tissue.\cite{2} Anemia of chronic disease is anemia in chronic infection/malignancy.\cite{3} Malnutrition is state inadequately nourished.\cite{4} The multiple diagnosed of infection occurs in a young man. This wide infection of lungs and lymph glands can be caused by immunocompromised in patient.

Case Report

Mr. S, male, 16 y.o, admitted to the hospital with primary complaints of short breathing 3 days earlier and multiple nodules at the neck, chin and left axilla since two months ago, cough, yellow sputum, febris, loss of appetite, weight loss, night sweats. History of tuberculosis at age 5 with OAT treatment for 20 days and stopped since. Physical examination: tachycardia, dispnoe, fever, BMI underweight, palpebral conjunctival pallor, lymphadenopathy regio colli dextra et sinistra, submental and axilla, rales in both lung. Laboratory findings: hypochrom-microcytic anemia, saturation-transferin index 19, leucocytosis, increase of neutrophyl, decrease of lymphocytes, hypoalbumin, positive on AFB sputum, chest x-ray: advance pulmonary TB lesions with pneumonia, sputum cultures: \textit{Streptococcus viridans}, PA: chronic granulomatous lymphadenitis typically ec tuberculosis. HIV Non-Reactive. This patient diagnosed with new cases of advanced lesions pulmonary tuberculosis and tuberculous lymphadenitis with pneumonia, anemia of chronic disease, malnutrition and treated with OAT Category I, ceftriaxone, azithromycin, the nutrients 1.900 kcal per day.

Discussion

The new cases of advanced lesions pulmonary tuberculosis, TB lymphadenitis and pneumonia in patient with a young age may caused by immunocompromised condition such as HIV, DM and malnutrition. In this patient, the wide infection is caused by malnutrition. Based on decrease of serum iron, saturation-transferin index 19, and an increase of ferritin in chronic infection diagnosis anemia of chronic disease is enforced.

Conclusion

The multiple infection of lung and lymph gland in this young patients occurs because of immunocompromised condition which caused by malnutrition. Therapy with OAT, combination of antibiotics and nutrients gave a good response in the patient.

Keywords: Tuberculosis, Lymphadenitis TB, pneumonia, Anemia of chronic disease, malnutrition

References

Severe Chronic Obstructive Pulmonary Exacerbation, Lost to Follow up Case of Lung Tuberculosis, Compensated Corpulmonale, Severe Malnutrition: A Case Report

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Introduction
Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities.1 Corpulmonale characterized by hypertrophy/ dilatation of right ventricle related to lung disease.2 Lost to follow up case TB is patient treated at least 1 month, stopped >2 months then come back for treatment.3 These is a multiple diagnosed with overlapping symptom, a difficult and complicated case that need specialty skill to diagnosed and therapy.

Case Report
Mr.TBA, 65 years old, admitted to hospital because difficulty of breathing since 1 day earlier. There are symptoms of purulent cough, lost appetite, night sweating, body weight loss and fever. Physical examination showed increased respiratory rate, normal vital sign, underweight BMI, rales and wheezing on both lungs. Laboratory findings showed positive on AFB sputum, Gene-Xpert M.Tb detected high and Rifampicin resistance not detected, and blood gas analysis compensated acidosis respiratory. Anti-HIV negative. Chest X-ray suggests old lung TB with infiltrate on both side, suspecting active infection. Spirometry showed moderate obstruction, right atrial enlargement on ECG, and Echocardiography shows pulmonary hypertension. This diagnosed are severe COPD exacerbation, lost to follow up case of lung TB, compensated corpulmonale and severe malnutrition. Therapy: ceftriaxon, azythromicin, streptomycin, 4FDC, budesonide and formoterol inhaler, tiotropium bromida inhaler and diet high protein low carbohidrate 1500 kcal.

Discussion
From chief complaint difficulty of breathing can be symptom of multiple diagnosed from patient so the diagnosed enforced based on increase RR, cough, rales and wheezing on lungs, underweight, positive AFB sputum, compensated acidosis respiratory, infiltrat TB on chest X-ray, moderate obstruction, right atrial enlargement, and pulmonary hypertension. Steroid needs as therapy for COPD but not suggested for TB. This problem can be solved with a low dose of steroid budesonide and formoterol inhaler that has a little side effect for tuberculosis. Patient got better after treatment.

Conclusion
A multiple and complicated diagnosed of severe COPD exacerbation, lung tuberculosis, compensated corpulmonale, severe malnutrition can be diagnosed with right examination and specific supporting investigation. The choice treatment of steroid for COPD with TB patient is low dose steroid such as inhaler steroid.

Keywords: tuberculosis, COPD, Corpulmonale, malnutrition.

References
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Subclinical Hypothyroid Induced by Anti-Tuberculosis Drugs in Patient with MDR Lung Tuberculosis: A Case Report

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Introduction

Subclinical hypothyroid induced by multi resistant tuberculosis drugs have unspecific symptoms yield to underdiagnosis. Satti et.al. (2012) reported that 69% patients with MDR-TB had subclinical hypothroid and half of them had subclinical hypothroid on the 93rd day of therapy1. Subclinical hypothyroid in MDR-TB patients is caused by etionamide and p-aminosalicylic acid. Both drugs inhibit thyroid hormone synthesis by iodine blockage mechanism2. MDR-TB is M.tuberculosis which is minimally resistant of rifampicin and INH with or without resistance of other anti tuberculosis drugs.3

Case Report

A 20 year-old female came into admission with weakness since 1 month. Six months before admission she was diagnosed with MDR lung TB and received kanamycin, levofloxacin, ethionamide, cycloserine, ethambutol and pyrazinamide. After 6 months of MDR-TB treatment her vital signs were normal, no thyroid gland nor lymphoid notch palpable, rales were present at apex of both lungs. Laboratory findings were FT4 1,24 ng/dl (normal 0,8-2,8 ng/dl), TSH 10,74 μIU/ml (normal 0,3-3,04 μIU/ml). Chest X-ray suggested active TB, VCT rapid test: non reactive, GeneXpert: M.tuberculosis detected low, rifampicin resistance detected, index Billewicz: -38. This patient was diagnosed subclinical hypothyroid induced by multi resistant tuberculosis drugs based on clinical features, physical examinations, chest X-ray and laboratory findings. This patient was given levofloxacin 1x320 mg tablet, ethionamide 1x640 mg tablet, cycloserine 1x640 mg tablet, ethambutol 1x960 mg tab, pyrazinamide 1x960 mg tablet, B6 1x150 mg tablet and levotyroxin 1x50 mcg tablet.

Discussion

This patient responded well to MDR regiment. Hypothyroid induced by MDRTB drugs is a reversible and curable state thus often underdiagnosed. TSH evaluation is needed to all MDR-TB patients at initial of therapy, 3 months, 6 months into therapy and 6 months after therapy.

Keywords: tuberculosis MDR, subclinical hypothyroid, ethionamide, p-aminosalicylic acid

References

Risk-factors of Multidrug-Resistant Tuberculosis Patients at Manado General Hospital

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Introduction
One of current worrisome problems in pulmonary infectious disease is increasing incidence of multidrug-resistant tuberculosis (MDR-TB). Social, medical, and psychological risk-factors might play a role in the development of this condition. This study was aimed to determine risk-factors of MDR-TB patients hospitalized at Manado General Hospital.

Methods
A case-control study of TB relapsing / treatment failure patients was conducted from July 2016 to January 2017. MDR-TB was diagnosed by Gene-Xpert MTB/RIF examination. Variables examined were economical status (poor, middle, high income); co-morbidities (diabetes mellitus, HIV infection, liver / kidney disorder); history of BCG vaccination; history of TB-treatment default – and its causes of discontinuation (side effect of drugs, fear of long-term treatment safety, already feeling well before completion of treatment); inappropriate treatment dose; psychological factors (depression and anxiety examined by Beck depression / anxiety score). Statistical analyses were performed by independent t-test, and odds ratios were calculated.

Results
Of 52 TB relapsing / treatment failure patients, 25 (48.08%) were MDR-TB. Compared to TB non-MDR patients, history of TB-treatment default and inappropriate treatment dose were statistically significant as risk-factors of MDR-TB. (p=0.01, OR=4.77, 95%CI 1.37-16.61), and (p=0.03, OR=3.79, 95%CI 1.14-12.58), respectively.

Conclusion
History of TB-treatment default and inappropriate treatment dose are risk-factors of MDR-TB at Manado General Hospital.

Keywords: tuberculosis, multidrug-resistant, risk-factors.
The Role of N-acetylcysteine in Preventing Exacerbation Among Stable Chronic Obstructive Pulmonary Disease (COPD) Patients: an Evidence-Based Case Report

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a chronic, progressive, irreversible lung disease leading to major cause of morbidity and mortality worldwide.¹,² Our patient, A 75 years old man was hospitalized for recurrent COPD exacerbation since 10 years ago with progressive symptom triggered by smoke exposure. Physical examination revealed purse-lip breathing, barrel chest with decreased bilateral breath sound, hyperresonance, bilateral crackles, and expiratory wheezing. Heart and abdominal examination was normal. Spirometry examination showed FVC 1.05 and FEV1 0.65 (FEV1% 61.9%). N-acetylcysteine (NAC), a drug previously known for its mucolytic effect has been demonstrated to possess potent antioxidant and anti-inflammatory properties.³ NAC acts directly as a reactive oxygen species (ROS) scavenger as well as a precursor of reduced glutathione (GSH) which in turn modulate the inflammatory COPD pathway, and could therefore reduce exacerbation⁴ We conducted an Evidence-Based Case Report regarding this issue and found that high dose NAC (more than 600mg bid) could decrease total number of COPD exacerbation (RR=0.59, 0.47 to 0.74, 95% CI, p<0.001) and COPD exacerbation rate (RR 0.65, 95% CI 0.49-0.88; p=0.03) compare to those without treatment. High dose NAC also showed beneficial effect in high-risk COPD patient (frequent exacerbation and chronic bronchitis type) after administered for at least 8 months. Given its availability and side effect, NAC is a promising therapy for stable COPD. Further evidence is needed to show whether NAC is beneficial regarding COPD-related mortality.

Reference

Tuberculosis Relapse in Pregnant and Postpartum

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Introduction

Tuberculosis is one of the most important infectious diseases. It was believed infect one third of world population. Tuberculosis is most common during a woman’s reproductive years, and the risk in early postpartum women is twice as non-pregnant women.

Case Report

We present a case of a 26 years old mother who was found to have a positive acid fast staining (AFS) for tuberculosis. The mother presented with worsened of dyspnea 3 days after cesarean section delivery. The mother already complains for dyspnea, coughing with productive white colored sputum, fever and loss of body weight in the last 2 months before delivery, and already went to the private hospital, however she only got cough medicine. The mother has a history of active TB 6 years ago, and already completed 9 months of TB treatment with negative AFS in the end of the course. The patient then treated with 2nd category of TB treatment using rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin. However, the status of TB for the newborn baby remains unknown.

Discussion

Multidisciplinary approach was needed to have an effective management of TB during pregnancy and postpartum, including pulmonologist, obstetrician, pediatrician, infectious diseases specialist, and public health department. As we know during pregnancy or postpartum, the mortality of TB is increasing. In the low burden countries, the barrier is the awareness to diagnose TB and in high burden countries the barrier is lack of diagnostic test and based on clinical presentation only. In the other hand pregnancy masks the symptoms of TB. In this case the first hospital failed to diagnose TB in this patient, is a truly example of lack of awareness of TB in other clinicians. However, in high burden countries such as Indonesia, screening for latent TB is not routinely done and not recommended. The treatments for postpartum patients have no difference with regular patients. Examination for sputum smear should be done every 2 months until negative after 2 consecutive samples. Breastfeeding for woman has been on first line anti tuberculosis (ATT) and no longer infectious are recommended by CDC, however for second line ATT need more caution, because there a minimal data regarding drug breast milk and the adverse effect.

Conclusion

Diagnosing and treatment TB in pregnancy and postpartum is challenging, need a lot of multidisciplinary approach to deal with it. There are less clinical trials in pregnant and postpartum woman. Any intervention affecting pregnant woman also affect neonates. There is more research for pregnant and postpartum woman needed include active and latent TB. Economical screening methods and policy by local government for screening active tuberculosis and latent tuberculosis in pregnant and postpartum woman are needed.

Reference

Obstructive Sleep Apnea In Obesity: Case Report

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Introduction

Obstructive sleep apnea (OSA) is characterized with episodes of complete (apnea) or partial (hypopnea) upper airway obstruction. The symptoms observed could be frequent snoring, the patients just stop breathing during their sleep, and sleepiness in the daytime. We can easily observed the decrease in blood oxygen saturation. The prevalence of sleep apnea syndrome is 4% of men and 2% of women. It is an important disease that has been shown to have a close association with obesity and a progressively increasing severe health problem. Most patients do not realise whether they have obstructive sleep apnea and this can also increase the cardiovascular risks, even lead to death.¹ Obese is related to impairment of respiratory mechanism by increased work of breathing and increased need to augment minute ventilation to maintain alveolar ventilation.²

The gold standard method for the diagnosis of OSA is polysomnography (PSG). The stages of sleep and various physiological parameters are recorded during sleep with the polysomnography method. The current study presents a case of obesity-related OSA. The initiation of positive ventilation resulted in the resolution of sleep apneas.¹

Case Illustration

A 55-year-old female patient came to the hospital with chief complaints of worsening exertional dyspnea, fever, and cough for one week. Her complaints did not improve after she took over-the-counter medications. She had been loudly snoring during her sleep and her family sometimes witnessed she stopped breathing while sleeping.

The physical examination showed that the patient’s body mass index was 51 kg/m², arterial blood pressure was 140/90 mmHg, pulse was bpm, respiratory rate was 24/min, and she had tachypnea. She had periodic desaturation during evaluation. On respiratory system examination, there were inspiratory rhonchi in all lung fields. Other system examinations were normal.

She had type II respiratory failure with pH 7.1, pCO₂ 149, pO₂ 98.4, HCO₃ 47.2, sat O₂ 92.6% on free room air. Laboratory examinations were normal except for a neutrophilia (76%). Chest X-Ray revealed bilateral pulmonary infiltrates.

The patient was treated as pneumonia yet her pCO₂ level remained high after the infection resolved. The result of Berlin questionnaire was high risk. The patient underwent the polysomnography test. The apnea-hypopnea index (AHI) was determined as 25.9/h throughout the night. With these findings, the patient was diagnosed with OSA. Her lowest oxygen saturation was 56% with median level was 94.7%. Apnea disappeared at 10 cmH₂O pressure with CPAP (continuous positive airway pressure) treatment. Nocturnal symptoms showed improvement. The treatment was continued at home after the patient was discharged from the hospital. The patient’s physical examination findings were normal on routine control.

Discussion

Obstructive sleep apnea syndrome is characterized by periodic desaturation hypoxemia during sleep and episodes of upper airway obstruction. There is an association between obstructive sleep apnea syndrome and many clinical conditions, including obesity.³ Obstructive sleep apnea patients present to the outpatient clinic with complaints of snoring while sleeping, easily fatigue in the daytime, and witnessed apnea. Recurrent upper airway obstruction may lead to pulmonary inflammation then infection. The association of obese and OSA is caused by increased work of breathing and increased need to augment minute ventilation to maintain alveolar ventilation. The evaluation of obesity hypoventilation syndrome should be done to every obese patient.²,⁴,⁵ In this case report, the patient came with signs and symptoms of pneumonia with type II respiratory failure which partially got better after the infection resolved. After we performed Berlin questionnaire, she was at high risk of OSA. The gold standard diagnostic tool for OSA is polysomnography. Her PSG results showed AHI 25.9/h with the lowest oxygen saturation was 56%. We diagnosed her with OSA moderate. The risk factor of OSA in this patient was morbid obesity. The pneumonia could be caused by repeated airway obstruction.
Positive pressure therapy should be initiated as the first approach to treatment after diagnosis. The pressure is titrated upward until improvement achieved. Clinical symptoms, perifer oxygen saturation, and arterial blood gas are used to evaluate therapy. Control of diet and activities can help to achieve optimal body weight.\textsuperscript{1,3,5,6}

We consider that Berlin questionnaire or any other screening test for OSA should be performed in every obese patient. When the patient is at high risk of OSA, PSG is the next step for diagnosis. This case report may be beneficial as an overview of OSA, especially in obesity.

References

Validation of Arozullah Risk Index Score to Predict Pulmonary Complication in Postoperative Patients in Cipto Mangunkusumo Hospital

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Background

Post operative pulmonary complication had important effect in increasing morbidity, mortality as well as length of stay. Several factor contributing those such as patient’s health status, type of operation and type anaesthesia used. There were risk score develop by Arozullah that can be used to predict the possibility of respiratory failure and post operative pneumonia. Due to the differences of the characteristic population, the study needed internal validation to discover the performance of the Arozullah score.

Objective

To assess the performance of calibration and discrimination of Arozullah’s model risk score in predicting complications of respiratory failure and pneumonia postoperative in patients undergoing non-cardiac surgery in Cipto Mangunkusumo General Hospital (RSCM).

Methods

A cohort retrospective study in patients undergoing non-cardiac surgery in RSCM from January to December 2015. Considered variable were type of surgery, age, emergency surgery, history of Chronic Obstructive Pulmonary Disease (COPD), serum albumin, urea, functional status, weight loss, history of smoking, alcohol use, blood transfusions pre surgery, general anaesthesia, history of cerebrovascular disease, acute impaired sensorium, chronic steroid use. Outcomes assessed were complications of respiratory failure and pneumonia 30 days post-operative. Performance calibration were assess with Hosmer-Lemeshow test and performance discrimination were assess with area under the curve (AUC).

Result

403 subjects were meet the inclusion criteria with 74 of subjects had pulmonary complications (18.4 %). There are 52 subjects had respiratory failure, 34 subjects had pneumonia post-operative, and 12 subjects had both complication. Hosmer - Lemeshow test on the complications of respiratory failure showed p = 0.333 and the AUC value is 0.911. While pneumonia complications showed p = 0.617 and AUC value is 0.789.

Conclusion: Arozullah score perioperative had good performance in predicting respiratory failure and pneumonia 30-days post operative in RSCM.

Key Word: respiratory failure, pneumonia, non cardiac surgery, validation, risk index score perioperative Arozullah
POEMS Syndrome Diagnosis Approach
(Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gamopathy and Skin changes)

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Introduction
POEMS Syndrome is a rare medical syndrome. It is defined as the combination of a plasma-cell proliferative disorder. POEMS is acronym of the syndrome Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gamopathy and Skin changes.

Case Report
38 years old women present with pleural effusion, she already taken TB medication for 9 months and no improvement. Multiple lymphadenopathy present in neck and femoral, lower limb weakness, and hyperpigmentation. The effusion serohemoragic and transudate. Sitology and TB culture are negative, ADA (Adenosine Deaminase) 30.4. Hypertiroid labs is present. USG found hepatomegaly dan acites, multiple sclerotic lesion in corpus vertebra found in MRI. In EMG conclude motoric and sensory polineuropathy dimyelinitation types. Papilloedema in oftamloscopy. Electrophoresis and imunofixation found monoclonal IgG lambda but still found policional. Biopsy of the neck and temporal glands showed Castleman disease.

Discussion
Diagnosing POEMS is a challenge. There are criteria for the diagnosis of POEMS, divided into mandatory, major and minor criteria. Mandatory criteria are Polyneuropathy (demyelination), and monoclonal plasma (almost always λ). Major criteria are including Castleman disease, sclerotic lesions and increased VEGF. Minor criteria include Organomegaly, volume overload, endocrinopathy, skin changes, Papilloedema and thrombocytosis, or polycythemia. In this case she almost fullfil all of the criteria. For mandatoy criteria, she came with polyneuropathy in lower limb and monoclonal plasma in imunofixation. For major criteria castleman, sclerotic lesion in vertebra are presents. Minor criteria found in hepatomegaly for organomegaly, pleural effusion and acites as a volume overload, hyperthyroid for endocynopathy, skin changes and papilloedema is present.

Conclusion
POEMS syndrome is a rare disease. Often misdiagnosis with tuberculosis, lupus or malignancy. Their diagnostic criteria in the diagnosis of POEMS syndrome petrified to uphold this disease.
Central Airway Obstruction due to Bronchorrhea in Non Malignant Patient: A rare case report

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Abstract

Bronchorrhea is an excess production of watery sputum (≥100 ml/day). It is found in lung diseases such as tuberculosis, chronic bronchitis, asthma, bronchiectasis or malignant disease. Bronchorrhea in non malignant patient is a rare case.

Male, 72 years old was hospitalized for Central Airway Obstruction caused by excessive production of sputum due to community acquired pneumonia. Patient has bilateral of tumor around the neck for 25 years without a medical contact. 3 weeks before admission patient has a purulent cough, fever and dyspnea. Physical examination revealed a tachypnea, bilateral mass around the neck, bilateral crackles. Chest Xray shows infiltrates in left perihilar, Leukocyte 24.300/uL. Patient was desaturated and intubated. Patient underwent a bronchoscopy for a bronchoalveolar lavage (BAL) and was found an excessive of pinkish red smelly milky mucous, there was no evidence of malignancy. Klebsiella pneumoniae was found in BAL culture treated with Imipenem cilastatin 3x1 g based on BAL cultured. There are a few literature review about bronchorrhea, in 1980 there was a report about the use of glucocorticosteroids in bronchorrhea appear to be the most clinically effective but was not clearly explained. In 1991 there was a case report using etythromycin may play a role in the treatment of patients with bronchorrhea and may have asteroid-sparing effect. There are only very limited data on the pharmacological management of bronchorrhea in malignant disease either. Further research is needed.