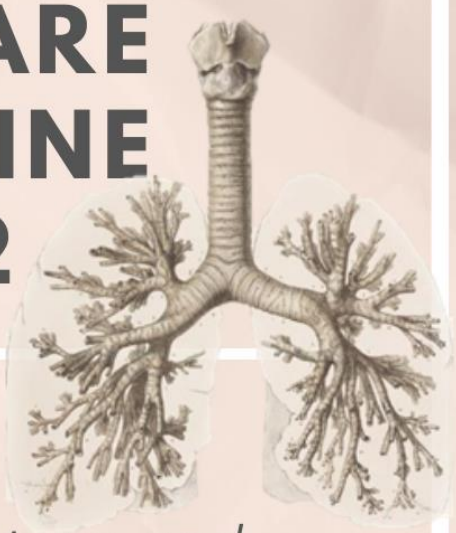
JICCIM

PROCEEDING BOOK

THE 10th JAKARTA INTERNATIONAL CHEST AND CRITICAL CARE INTERNAL MEDICINE (JICCIM) 2022



Updating Knowledge in Respiratory and Critical Illness Medicine

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Updating Knowledge in Respiratory and Critical Illness Medicine

Jakarta, June 4-5th, 11-12th, 18-19th 2022

Editor

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Department of Internal Medicine Faculty of Medicine University of Indonesia

Dr. Cipto Mangunkusumo National General Hospital, Indonesia

THE 10th JAKARTA INTERNATIONAL CHEST AND CRITICAL CARE INTERNAL MEDICINE 2022

Updating Knowledge in Respiratory and Critical Illness Medicine

Jakarta, June 4-5th, 11-12th, 18-19th 2022

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Welcome Message

Dear Colleagues,

Welcome to The Jakarta International Chest and Critical Care Internal Medicine (JICCIM) 2022 organized by Respirology and Critical Illness Division, Internal Medicine Department, Faculty of Medicine Universitas Indonesia, Cipto Mangunkusumo Hospital.

Following the previous success of JICCIM events, we proudly present JICCIM 2022 as the tenth annual international event in respirology and critical care. Participants will be given a big opportunity to get lectures and share sessions about the latest topics in respirology and critical care with our international1medical experts and academicians.

We would like to express our gratitude for the contributions and supports from various organizations, sponsors, and individuals to this event. Finally, to all of participants, we hope you can enjoy and get as many benefits from all of our sequence of symposiums and workshops.

Best regards,

Gurmeet Singh, MD

Chairman JICCIM 2022

Herikurniawan, MD

Head of Orginizing Committee

JICCIM 2022

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Speakers, Moderators, and Facilitators

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International Speakers	Prof. Akash Verma, MD, MBBS, MRCP (UK), FAMS (Resp Med) – Singapore
	Prof. S K Sharma, MD, MBBS, PhD, FNASc, FNA, FASc, JC Bose Fellow, ATS Prof (Dr) J.C. Suri MD, DTCD, DNB, FNCCP – India
	Prof. Bullent Kukurtcu - Spain
	Prof. Dr. Venkatasubramanian Ramasubramanian - India
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	Jeenam Shah, MBBS, MD, DNB, DAA – India
	Assoc. Prof. Jackrapong Bruminhent, MD – Thailand
	Mitzie Marie Montebon Chua, MD – Phillipines
	Steve Yang Tze Yi, MBBS, MRCP, FAMS, FCCP, EDIC - Singapore
	Hari Kishan Gonuguntla, MD, DM, Fellowship of Interventional Pulmonology – India
National Speakers	Prof. Dr. dr. Zulkifli Amin, SpPD, K-P, FINASIM
	Prof. Dr. dr. Cleopas Martin Rumende, SpPD, K-P, FCCP, FINASIM
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	dr. Fathur Nurkholis, SpPD, K-P, FINASIM
	dr. Iceu Kulsum, SpP, SpPD, K-P
	dr. Ika Trisnawati, MSc, SpPD, K-P
	dr. Ananda Wibawa Ginting, SpPD, K-P
	dr. Roza Kurniati, SpPD, K-P
	dr. Fajar Raditya, SpPD, K-P
	dr. Sandra Sinthya, SpPD-KR
	dr. Anna Mira Lubis, SpPD-KHOM
	dr. Muhadi, SpPD-KKV, M. Epid
	dr. Efata Bilivian Polli, SpPD
	dr. Price Maya, SpPD
	dr. Erika Marfiani, SpPD

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The 10th Jakarta International Chest and Critical Care Internal Medicine 2022

Saturday, 4th June 2022

ONLINE SYMPOSIUM

Time	Scientific	Speaker
08.0-09.00	REGISTRATION	
09.10-09.20	Ethic and Patient Safety in The Field of Respirology and Critical Illness	dr. I Putu Eka Krishna Wijaya, Sp.PD, M.Biomed
Session 1 : Update of Asthma and COPD Moderator : dr. I Putu Eka Krishna Wijaya, Sp.PD, M. Biomed		
09.20 – 09.45	Simple Approach in Achieving Asthma Control with Proactive Regular Dosing (PRD)	dr. Herikurniawan, Sp.PD-KP, FINASIM
09.45 – 10.10	Risk-benefit Approach on Managing COPD with ICS	dr. Zen Ahmad, Sp.PD-KP, FINASIM
10.10 – 10.20	Discussion	
Session 2 : Management of MDR and Atypical Pneumonia Moderator : dr. Mira Yulianti, Sp.PD-KP		
10.20 – 10.45	The New Hope for Treatment of Pneumonia MDR Pathogen	dr. Mitzi Marie Montebon Chua, PCP, PSMID
10.45 – 11.10	Management of Atypical Pneumonia : How to Diagnose and Treat?	Prof. Dr. dr. Cleopas Martin Rumende, Sp.PD-KP, FINASIM, FCCP
11.10 – 11.20	Discussion	
Session 3 : Current Issues in Sepsis and Critical Care Moderator : dr. Efata Bilvian Polli, Sp.PD		
11.20 – 11.45	Surviving Sepsis Campaign Guideline: What's New and What's Changed?	dr. Ceva Wicaksono Pitoyo, Sp.PD-KP, KIC, FINASIM
11.45 – 12.10	Saving Lives Through Noninvasive Ventilation for Critically Ill Patient	Hassan S. Alorainy, BSRC, RRT, FAARC
12.10 – 12.20	Discussion	
12.20 – 12.35	BREAK, LUNCH PRAYER TIME	
12.35 – 14.35	E-POSTER SESSION	

Sunday, 5th June 2022

ONLINE SYMPOSIUM

Time	Scientific	Speaker
08.30-09.00	REGISTRATION	
Session 4 : Patient-centered Innovation in COPD Management Moderator : dr. Gurmeet Singh, Sp.PD-KP, FINASIM		
09.00 – 09.25	Not All LAMA/LABAs Are The Same	dr. Iceu Kulsum, SpP, Sp.PD-KP
09.25 – 09.50	The Enhanced Features of Soft Mist Inhaler	dr. Eric Daniel Tenda, Sp.PD, DIC, PhD, FINASIM
09.50 – 10.00	Discussion	
Session 5 : Fungal Infection in Patient with Multiple Comorbidities Moderator : dr. Oke Dimas Asmara, Sp.PD		
10.00 – 10.25	Treatment of Aspergillosis in Patient with Multiple Comorbidities	Prof. Dr. Venkatasubramanian Ramasubramanian MBBS, MD, FRCP
10.25 – 10.50	Management Strategies of Invasive Candidiasis in Patient with Multiple Comorbid	dr. Ika Trisnawati, MSc, Sp.PD-KP
10.50 – 11.00	Discussion	
Session 6 : Current Management of Nosocomial and DTR (Difficult to treat resistance) Pneumonia Moderator : dr. Price Maya, Sp.PD		
11.00 – 11.25	Burden, Diagnosis, and Management of Nosocomial Pneumoniae in High Risk Mortality Patient	dr. Gurmeet Singh, Sp.PD-KP, FINASIM
11.25 – 11.50	Role of Ceftozolane/Tazobactam in DTR Pneumoniae: The Importance of Early Switch	Assoc. Prof. Jackrapong Bruminhent, MD
11.50 – 12.00	Discussion	
12.00 – 13.00	BREAK, LUNCH PRAYER TIME	
Session 7 : The Latest Issues of COVID-19 Moderator : dr. Erika Marfiani, Sp.PD		
13.00 – 13.25	COVID-19 Update: What's The Latest News?	dr. Gurmeet Singh, Sp.PD-KP, FINASIM
13.25 – 13.50	Molecular Activation Product as a Treatment for COVID-19 Patient	Prof. Bulent Kukurtcu
13.50 – 14.00	Discussion	

Saturday, 11th June 2022

ONLINE SYMPOSIUM

Time	Scientific	Speaker
08.30-09.00	REGISTRATION	
Session 8. Update on Progressive Fibrosing ILD Moderator : dr. Sandra Sinthya, Sp.PD-KR		
09.00 – 09.25	How to Identify & Manage Patients with Progressive-Fibrosing ILD	Dr. dr. Arto Yuwono Soeroto, Sp.PD-KP, FCCP, FINASIM
09.25 – 09.50	Efficacy of Antifibrotic Therapy in Progressive-Fibrosing ILD	dr. Ceva Wicaksono Pitoyo, Sp.PD-KP, KIC, FINASIM
09.50 – 10.00	Discussion	
Session 9 : Nutritional Support in Respiratory Diseases Moderator : dr. Ni Nyoman Indirawati, Sp.PD		
10.00 – 10.25	The Role of Megestrol Acetate in Treating Patient with Malnutrition	dr. I Putu Eka Krishna Wijaya, Sp.PD, M.Biomed
10.25 – 10.50	Tipping The Balane Parenteral Nutrition in Respiratory Disease and Critical Illness	dr. Mira Yulianti, Sp.PD-KP
10.50 – 11.00	Discussion	
Session 10 : Antibiotic Use in Respiratory Infection Moderator : dr. Hadiki Habib, Sp.PD, SpEM		
11.00 – 11.25	How to Treat Pneumonia in Special Condition?	dr. Fathur Nurkholis, Sp.PD-KP, FINASIM
11.25 – 11.50	Appropriate use of Fluoroquinolone in TB Endemic Area	Prof. Dr. dr. Cleopas Martin Rumende, Sp.PD-KP, FCCP, FINASIM
11.50 – 12.00	Discussion	
12.00 – 12.30	BREAK, LUNCH PRAYER TIME	
12.30 – 13.10	***Plenary Lecture 1*** Obstructive Sleep Apnea (OSA) definition, consequences, and management	Prof. Surendra K Sharma, MD, PhD.
13.10 – 13.50	***Plenary Lecture 2*** Bronchoscopy in Infectious Pulmonary Diseases	Jeenam Shah, MBBS, MD, DNB, DAA
13.50 – 15.00	E-POSTER SESSION	

Sunday, 12th June 2022

ONLINE SYMPOSIUM

Time	Scientific	Speaker
08.00-08.30	REGISTRATION	
Session 11 : Medication for Respiratory Symptoms Moderator : dr. Fajar Raditya, Sp.PD-KP		
08.30 – 08.55	Clinical Approach to The Patient with Chronic Cough	dr. Chrispian Oktafbipian Mamudi, Sp.PD-KP,FINASIM
08.55 – 09.20	Sleep Disturbance in Advanced Lung Diseases	dr. Gurmeet Singh, Sp.PD-KP, FINASIM
09.20 – 09.30	Discussion	
Session 12 : Optimizing Treatment in ARDS and Respiratory Infection Moderator : dr. Telly Kamelia, Sp.PD-KP, FINASIM		
09.30 – 09.55	Treating ARDS : When The Best Time to Give Corticosteroid and Antioxidant?	dr. Samsirun Halim, Sp.PD-KIC
09.55 – 10.20	The Role of Fluoroquinolones for The Treatment of Respiratory Infection	dr. Mira Yulianti, Sp.PD-KP
10.20 – 10.30	Discussion	
Session 13 : Therapy for Fungal and Bacterial Infection Moderator : dr. Roza Kurniati, Sp.PD-KP		
10.30 – 10.55	Therapeutic Strategies for Invasive Candidiasis and Candidemia in Adults	dr. Ananda Wibawanta Ginting, Sp.PD-KP
10.55 – 11.20	Current Choices of Antibiotic Treatment for Pseudomonas Aeruginosa Infection	dr. Herikurniawan, Sp.PD-KP, FINASIM
11.20 – 11.30	Discussion	
11.30 – 12.10	***Plenary Lecture 3*** The Potential Effects of N-acetylcysteine for Patient with COVID-19 and Post COVID-19	dr. Eric Daniel Tenda, Sp.PD, DIC, PhD, FINASIM
12.10 – 12.30	BREAK, LUNCH, PRAYER TIME	
12.30 – 14.00	**CASE PRESENTATION** **(Difficult to Treat Tuberculosis)**	Case Presentation by dr. Ni Nyoman Indirawati, Sp.PD Panelist: - Prof. Dr. dr. C. Martin Rumende, Sp.PD-KP, FCCP, FINASIM - Dr. dr. Nafialdi, Sp.PD, SpFK, PhD - Dr. dr. Anna Rozaliyani, M.Biomed, Sp.P(K)

Saturday, 18th June 2022

ONLINE SYMPOSIUM

Time	Scientific	Speaker
08.00-08.20	REGISTRATION	
08.20 – 09.00	***Plenary Lecture 4*** Nutrition and Fluid in Intensive Care Unit	Steve Yang Tze Yi, MBBS, MRCP, FAMS, FCCP, EDIC
Session 14: Asthma Exacerbation and Its Prevention Moderator : dr. Anna Ujainah ZN, Sp.PD-KP, MARS		
09.00 – 09.25	Management in Severe Asthma Exacerbation	dr. I Made Bagiada, Sp.PD-KP, FINASIM
09.25 – 09.50	Update of Vaccination Role to Prevent Respiratory Infection	Dr. dr. Eliana Muis, Sp.PD-KP, FINASIM
09.50 – 10.00	Discussion	
Session 15: Looking Deeper in Interventional Pulmonology Moderator : dr Eric Daniel Tenda, Sp.PD, DIC, PhD, FINASIM		
10.00 – 10.25	Bronchoscopy and Interventional Pulmonology Procedures in The Era of COVID-19 and post COVID-19 pandemic	Akash Verma, MD, MBBS, MRCP, FAMS
10.25 – 10.50	Management of Post Infection Airway Stenosis: The Role of Interventional Pulmonology	Hari Kishan Gonuguntla, MD, DM, Fellowship of Interventional Pulmonology
10.50 – 11.00	Discussion	
Session 16: New Perspective of Lung Malignancy Moderator : Prof. Dr. dr. Zulkifli Amin, Sp.PD-KP, FINASIM, FCCP		
11.00 – 11.25	Comprehensive Interventional Pulmonology Approach and Lung Cancer Diagnosis : Best Experience from National General Hospital	dr. Eric Daniel Tenda, Sp.PD, DIC, PhD, FINASIM
11.25 – 11.50	Understanding Targeted Therapy for Non Small Cell Lung Cancer	dr. Anna Mira Lubis, Sp.PD, KHOM
11.50 – 12.00	Discussion	
12.30 – 13.10	***Plenary Lecture 5*** Update of Tuberculosis (TPT- Preventive Treatment of Tuberculosis)	dr. Herikurniawan, SpPD-KP, FINASIM
12.30 – 13.00	**CLOSING AND ANNOUNCEMENT**	

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HANDS-ON WORKSHOP (OFFLINE)

Time	Scientific	Facilitator
08.00-09.00	REGISTRATION	
Workshop : Pleural Diseases Location : R. Prosedur Terpadu (RPT) IPD/IPIN B, Lt. 5 URM – RSUPN Dr. Cipto Mangunkusumo		
09.00 -12.00	Lung Ultrasound	dr. Ni Nyoman Indirawati, Sp.PD
	Thoracocintesis	dr. Mira Yulianti, Sp.PD-KP
	Pleural Drainage	dr. I Putu Eka Krishna Wijaya, Sp.PD, M.Biomed
Workshop : Bronchoscopy Location : R. Prosedur Terpadu (RPT) IPD/IPIN B, Lt. 5 URM – RSUPN Dr. Cipto Mangunkusumo		
09.00 – 12.00	Diagnostic Bronchoscopy	dr. Oke Dimas Asmara, Sp.PD
	Endobronchial Ultrasound	dr. Eric Daniel Tenda, Sp.PD, DIC, PhD, FINASIM
	Argon Plasma Coagulation and Cryotherapy	dr. Gurmeet Singh, Sp.PD-KP, FINASIM
12.00 – 13.00	BREAK, LUNCH, PRAYER TIME	
Workshop : Critical Care Location : ICTEC, Ged. CMU 2, Lt. 2 – RSUPN Dr. Cipto Mangunkusumo		
13.00-16.00	Vascular Access Procedure	dr. Herikurniawan, Sp.PD-KP, FINASIM
	Ultrasound in Critical Care	dr. Muhadi, SpPD-KKV, M. Epid
	Respiratory Monitoring & Oxygen Therapy	dr. Ceva W. Pitoyo, Sp.PD-KP, KIC, FINASIM
16.00 – 16.15	**CLOSING**	

SYMPOSIUM

THE 10th JAKARTA INTERNATIONAL CHEST
AND CRITICAL CARE INTERNAL MEDICINE 2022

SIMPLE APPROACH IN ACHIEVING ASTHMA CONTROL WITH PROACTIVE REGULAR DOSING

Herikurniawan

Division of Respirology and Critical Illness, Department of Internal Medicine
Faculty of Medicine Universitas Indonesia, Dr. Cipto Mangunkusumo National General Hospital

Definition of asthma according to GINA 2021, asthma is heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

Asthma is a common and potentially serious chronic disease than can be controlled but not cured. Symptoms are associated with variable expiratory airflow, i.e difficulty breathing air out of the lungs due to airway obstruction, bronchial hyperresponsive, and airway inflammation. These features usually persist, even when symptoms are absent or lung function is normal, but may normalize with treatment. Symptoms may be triggered or worsened by factors such as viral respiratory infections, allergens or irritant exposure, tobacco smoke, change in weather, exercise and stress. Symptoms and airflow limitation may resolve spontaneously or in response to medication and may sometimes be absent for a week or months at a time.

Making the initial diagnosis is important to avoid unnecessary or over-treatment. In adult with an asthma diagnosis in the last 5 years, one-third could not be comfirmed as having asthma after repeated testing over 12 months and staged withdrawl of controller treatment. Making the diagnosis is based on identifying both characteristic pattern of respiratory symptoms such as wheezing, dyspnea, chest tightness or cough, and variable expiratory airflow limitation. If possible, the evidence supporting a diagnosis of asthma should be documented. But, it’s difficult in this era pandemic cause make a risk potential of transmission COVID-19. With the following features are typical of asthma and if present, increase the probability that the patient has asthma:

- Patients (especially adults) experience more than one of these types of symptoms (wheezing, cough, dyspnea, chest tightness)

- Symptoms are often worse at night or in the early morning
- Symptoms vary over time and in intensity
- Symptoms are triggered by viral infections (common cold), exercisem allergen exposure, changes in weather, laughter, or irritants.

The following features are decrease the probability that respiratory symptoms are due to asthma :

- Isolated cough with no other respiratory symptoms
- Chronic production of sputum
- Shortness of breath associated with dizziness, light-headedness or paresthesia
- Chest pain
- Exercise-induced dyspnea with noisy inspiration

Physical examination in people with asthma is often normal. The most frequent abnormality is expiratory wheezing, but this may be absent or only heard on forced expiration. Examination of the nose may reveal sign of allergic rhinitis or nasal polyposis.

But along with that there is another testing to diagnosing asthma, lung function testing. Asthma is characterized by variable expiratory airflow limitation in varies over time. Lung function may vary between completely normal and severely obstructed in the same patient. This variation in airflow limitation is generally assessed from variation in forced expiratory volume 1 second (FEV_1) or PEF (peak expiratory flow) if there is no spirometry. A reduced ratio of FEV_1 to forced vital capacity (FEV_1/FVC) indicates expiratory airflow limitation. Reference values of ratio (FEV_1/FVC) greater than 0.7, if the spirometry lower than 0.7 indicate that a person has airflow obstruction. In practice, if obstructive defect has been confirmed, then reassess lung function by reversibility test to determine improvement in FEV_1, measured within minutes after inhalation of rapid-acting bronchodilator such as 200-400 mcg salbutamol. In patient with typical respiratory symptom, evidence of bronchodilator responsiveness testing essential component of the diagnosing of asthma. Some specific such as: an increase in lung function after administration of a bronchodilator, a decrease in lung function after exercise or bronchial provocation test, and variation in lung function beyond the normal range when it is repeated over time. Specific criteria for diagnosing of asthma with typical respiratory symptoms, an increase in FEV_1 >12% and >200 ml from baseline or for high probability of

asthma FEV_1 >12% and >400ml (if spirometry not available, a chane in PEF at least 20% from baseline).

Once the diagnosis of asthma has been confirmed, important for clinician to make long-term goals of asthma management to maintain normal activity level and minimize risk of exacerbation. Asthma management has focused not only on symptoms control, but also management of the patient's modifiable risk factors for exacerbations, other adverse outcomes and comorbidities. Based on update GINA 2021, no longer recommends treatment of asthma with SABA alone to relieve the symptoms. The reliever, a short-acting bronchodilator, was merely an addendum, a medication to be used in case the real treatment (the controller) failed to maintain disease control (SABAs effectively induce rapid symptom relief but are ineffective on the underlying inflammatory process). There are some reasons for the changing concept in the treatment of asthma. Airway inflammation occurred in most asthma patients so that ICS has a role in it. The other reason is SABA-alone treatment has some negative impacts. SABA-alone treatment will increase the risk of exacerbation, decrease in lower lung function, increase allergic response, airway inflammation, and decrease bronchodilator response of SABA. Several studies confirmed that most patients simply *increase their use of a short-acting β2-agonist* (SABA) and are less likely to increase the use of their controller medication when the symptoms worsening. From the SABINA study, the overuse of SABA (≥3 SABA canister/year) is related to increasing exacerbation risk and asthma mortality. The overuse of SABA will also increase the risk of hospitalization and outpatient clinic visits. The risk of exacerbations is experienced by all asthma patients, (mild, moderate, and severe asthma. Severe asthma will lead to the higher risk of exacerbation. The more frequent exacerbation, the higher risk of recurrent exacerbation

GINA 2021 recommend the treatment now shows two tracks for symptom relief, based on the choice of reliever. Asthma medications options for long term treatment fall into two main tracks (Figure 1) : track 1, in which the reliever is low dose ICS-formoterol and track 2, in which the reliever is a SABA.

- Track 1 : when a patient at any step has asthma symptoms, they used low dose ICS-formoterol as needed for symptom relief. In step 3-5 (the patient have daily symptoms or waking at night), the also take ICS-formoterol as regular daily controller treatment; (MART).

- Track 2 : is an alternative if Track 1 is not possible, or is not preferred by a patient with no exacerbations on their current therapy. The patient take a SABA and low dose ICS together for symptom relief and controller medication (in combination). Before considering a regimen with SABA reliever, consider whether the patient is likely to be adherent with daily controller

Inhaled corticosteroid (ICS) in asthma as the main of asthma treatment, because their beneficial effects on airway inflammation, remodeling and hyperresponsiveness, which result in symptom, reduce exacerbations and improve lung function. ICS must be used long-term, regularly, and in adequate doses. GINA guideline propose a stepwise approach to asthma management, with maintenance and reliever therapy (MART) with inhaled corticosteroid combination a recommended option at steps 3-5 for both adults and adolescent. MART is a combination in a single inhaler to be used as both controller in the daily maintenance therapy and reliever of symptoms when required, as part of a specific treatment regimen. The example of the ICS-LABA combination is budesonide-formoterol (BUD/FORM), LABA has a fast-acting component. In fact, MART is more effective at reducing exacerbations and improving daily asthma control than the same maintenance dose of BUD/FORM plus as –needed SABA. Recent review has confirmed that patients with asthma treated with BUD/FORM MART achieved the same or better asthma symptom control compared with ICS/LABA plus SABA regimens at similar or higher ICS dose, across a range of severities of persistent asthma, result in a 40-50% reduction.

Before starting initial treatment important to record evidence for the diagnosis of asthma, level of symptoms and risk factor including lung function. During ongoing treatment, treatment can be stepped up or down along one track; using the same reliever, or it can be switched between tracks. Before stepping up, check common problem such as incorrect inhaler technique, poor adherence and environmental exposure. Review response of treatment, after 2-3 months, or earlier depending on clinical urgency.

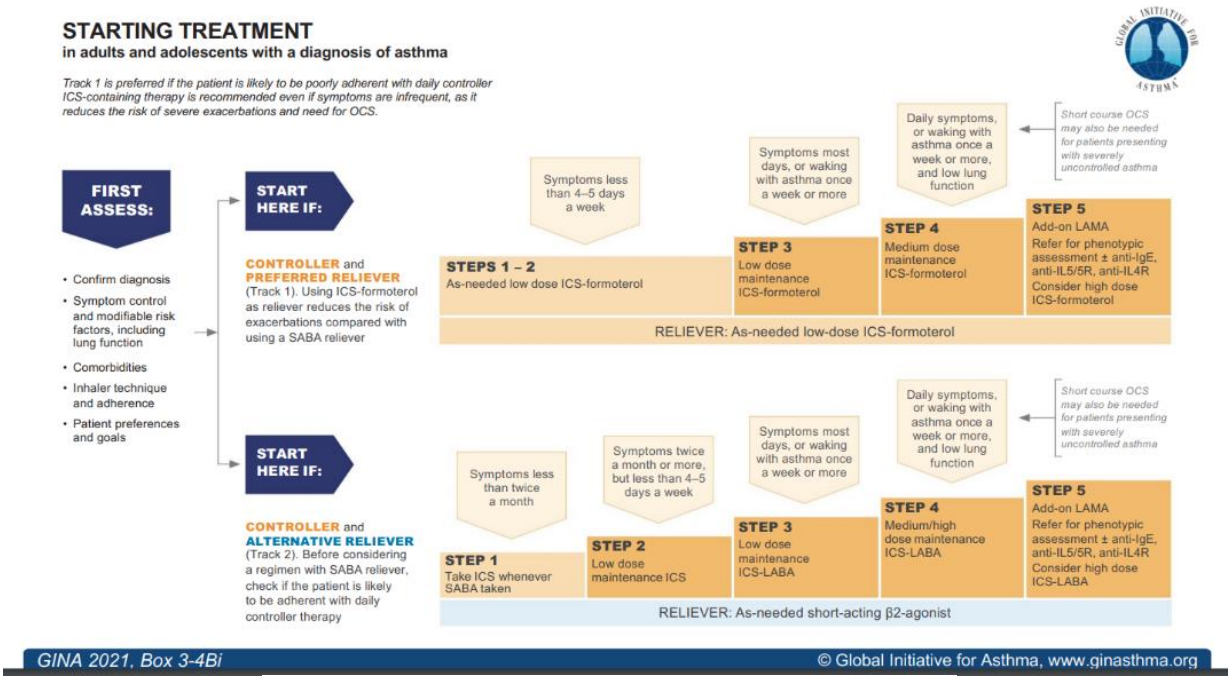

Figure 1 . Treatment stepwise in asthma

The doses of ICS are adjusted with responsiveness of patient. If asthma patient is uncontrolled with good compliance, the physician may increase the doses of ICS with consent of the side effects.

Adults and adolescents (12 years and older)			
Inhaled corticosteroid	**Total daily ICS dose (mcg) – see notes above**		
	Low	**Medium**	**High**
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI, or pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400

Figure 2 . Daily doses of inhaled corticosteroid (ICS)

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PATIENT-CENTERED INNOVATION IN COPD MANAGEMENT: NOT ALL LAMA/LABA ARE THE SAME?

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development.

COPD is the result of a complex interplay of long term cumulative exposures to noxious gases and particles, combined with a variety of host factors including genetics, airway hyper-responsiveness and poor lung growth during childhood. COPD is a leading cause of morbidity and mortality worldwide that induces an economic and social burden.

Pathomechanism of COPD

Cigarette smoke and other environmental noxious agents activates macrophages and epithelial cells to release chemotactic factors that recruit neutrophils and CD8 cells from the circulation. These cells release factors that activate fibroblasts, resulting in abnormal repair processes and bronchiolar fibrosis. An imbalance between proteases released from neutrophils and macrophages and antiproteases leads to alveolar wall destruction (emphysema). Proteases also cause the release of mucous. An increased oxidant burden, resulting from smoke inhalation or release of oxidants from inflammatory leucocytes, causes epithelial and other cells to release chemotactic factors, inactivate antiproteases, and directly injure alveolar walls and cause mucous secretion.

Diagnosis of COPD

COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, a history of recurrent lower respiratory tract infections and/or history of exposure

to risk factors. Spirometry is required to make the diagnosis, the presence of a post-bronchodilator FEV1/FVC < 0,70 confirms the presence of airflow limitation and thus of COPD in patients with appropriate symptoms and significant exposure to noxious stimuli.

COPD Assessment

Spirometry in conjunction with patients symptoms and history of moderate and severe exacerbations remains vital for the diagnosis, prognostication and consideration of therapeutic approaches. This approach is illustrated in Figure 1.

The "ABCD" assessment tool will be derived from patients symptoms and their history of exacerbation. The two measures of symptoms (Modified MRC Dyspnea Scale(MMRC) and COPD assessment Test (CAT) score) are most widely used.

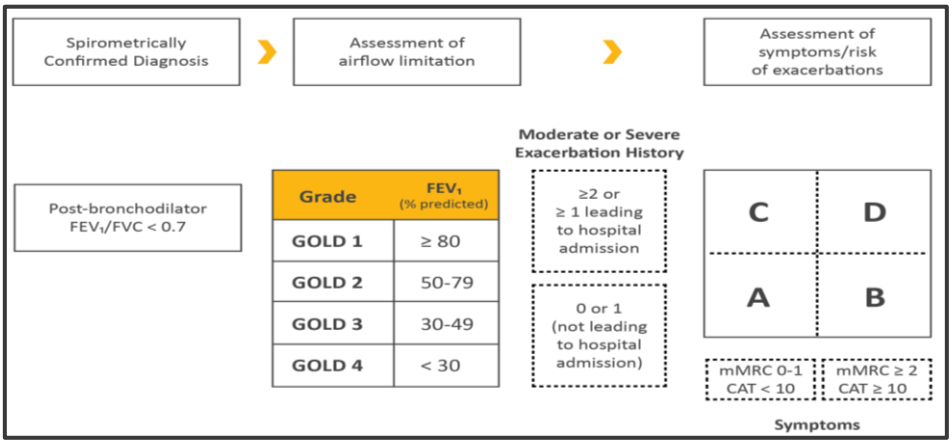

Figure 1. The refined ABCD assessment tool

Stepwise approach in pharmacotherapy in stable COPD

- Inhaled bronchodilators in COPD are central to symptom management Evidence A).
- Regular and as needed use of SABA or SAMA improves FEV1 and symptoms (Evidence A).
- LABAs and LAMAs significantly improve lung function, dyspnea, helath status and reduce exacerbation rates (Evidence A)
- LAMAs have a greater effect on exacerbation reduction compared with LABAs (Evidence A) and decrease hospitalizations (Evidence B)
- Combination treatment with a LABA and LAMA increase FEV1 and reduces exacerbations compared to monotherapy (Evidence B)

- Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance (Evidence B)
- Tiotropium as part of LAMAs drugs is the essential treatment for COPD

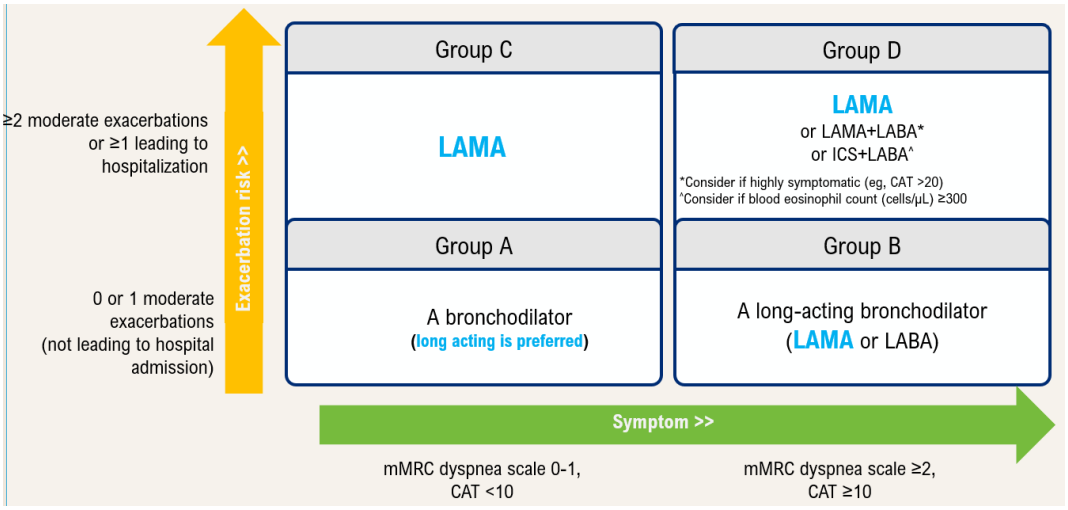

Figure 2. LAMA monotherapy is recommended in all groups of stable COPD

LAMA monotherapy is recommended in all groups, even in Group D without any additional requirement. Tiotropium LAMA was safe and significantly better compared with placebo or active comparators based on studies with various type of patients, provides consistent and sustained improvements in many relevant clinical outcomes of COPD, it may reduce the progression of the disease.

Important to identify appropriate patient before prescribe combination therapy. In COPD, eosinophil counts identify patients well suited for ICS therapy. Combination treatment, can be given if patients in Group D having:

- Highly symptomatic (eg CAT >20) → LAMA+LABA
- Blood eosinophil count (cells/µL) ≥300 → LABA+ICS

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MANAGEMENT STRATEGIES OF INVASIVE CANDIDIASIS IN PATIENT WITH MULTIPLE COMORBID

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Epidemiology

Candidemia is generally viewed as the more common type of the disease and the most common fungal disease among hospitalized patients in the developed world. Invasive candidiasis comprises both candidemia and deep-seated tissue candidiasis. Deep-seated candidiasis arises from either hematogenous dissemination or direct inoculation of candida species to a sterile site.

Incidence rates of candidemia have been reported to be between 2 and 14 cases per 100,000 persons in population-based studies. The incidence of candidemia is age-specific, with the maximum rates observed at the extremes of age.

Pathophysiology

The major risk factors for invasive candidiasis are the presence of central vascular catheters, recent surgery (particularly abdominal surgery with anastomotic leakages), and the administration of broad-spectrum antibiotic therapy constitute. The majority of invasive infections are caused by five pathogens: *Candida albicans (most common pathogen), Candida glabrata, Candida tropicalis, Candida parapsilosis,* and *Candida krusei.*

When perturbations of mucosal microbiota or weakening of host immunity occur, *Candida* transition from commensalism to opportunism is induction of key virulence factors. *Candida albicans* virulence traits:

a. Ability of *C.albicans* to filament and interchange its morphotypes between unicellular yeast cells and pseudohyphae and hyphae can promotes invasive disease.
b. *C. albicans* secretes a variety of factors in the context of invasive infection (aspartyl proteases and phospolipases lead to activate the innate immune response).
c. Effective adherence and invasion of *Candida* spp. in endothelial and epithelial cells enable their dissemination into the bloodstream.

Diagnosis

No clinical signs or symptoms are specific. Invasive candidiasis should be suspected in patients with known risk factors who have an unexplained fever that is unresponsive to antibacterial treatment. If invasive candidiasis is suspected, the diagnostic laboratory should be notified to use selective media (containing inhibitors of bacterial growth).

The armamentarium available for diagnosing invasive candidiasis includes direct detection, in which specimens of blood or tissue from normally sterile sites are cultured, and indirect detection, in which surrogate markers and polymerase-chain-reaction (PCR) assays are used. Classical diagnostic techniques and gold standard : blood culture is insensitive tool (is positive in 21-71% of patients depending on sampling frequency and volume of blood drawn), another test is histopathology from normally sterile site with fluorescent brightener and special staining for fungi.

Mannan antigen and antimannan antibody have sensitivity 55% and specificity 60%. The antigen β-D-glucan can be detected in blood during Candida spp, Aspergillus spp, and Pneumocystis jirovecii infection, the test cannot distinguish between candidiasis and infections caused by other fungi, with sensitivity 76.7-100% and specifity 40.0-91.8%. Combination of positive β-D-glucan test with low porcalsitonin (<2ng/mL) had sensitivity and specificity of 66% and 98% for invasive candidiasis. PCR based tests have not yet been incorporated into official guidelines or classification criteria for Candida spp. Disease. T2Candida Panel Test is an FDA approved test for diagnosis of candidaemia specifically. It detects the five most common Candida spp. from whole blood (Sensitifitas 91.1%; Spesifitas 99.4%).

Management

Different approaches can be chosen and can be judged as the best for given clinical situation. Several management options are:

a. Prophylaxis : administration of an antifungal agent to a patient with no evidence of infection.
b. Empirical therapy : administration of an antifungal in the presence of persistent and refractory fever in patient who are at high risk for fungal infection.
c. Pre-emptive therapy : to better identify patients at high risk fo developing candidemia.
d. Treatment of a culture proven infection.

Biofilm production is a well documented phenomenon for *Candida* species that significantly contributes to *Candida* pathogenicity in catheter related bloodstream infections, resulting in recurrent or persistent infections and biofilm-mediated antifungal resistance leading to treatment failure. Azoles (fluconazole ect) which are static against *Candida*. Echinocandins and amphotericin B offer both bactericidal activity and good penetration into a biofilm formed on vascular device. Echinocandin resistant isolates are frequently also fluconazole resistant or both and seems to be associated with worse clinical outcomes, for this condition most clinician favor a lipid formulation of AmB.

Selection of an antifungal drug for initial treatment should be based: on the patients prior exposure or intolerance to an antifungal agent, severity of illness, relevant comorbidities and involvement of the brain, cardiac valves or visceral organ.

Duration of therapy : determined by the individual clinical and mycological response to therapy. In the absence of organ involvement, the duration (IV/oral) should be 14 days after clearance of Candida spp. from the bloodstream and resolution of all signs of infection. A step-down strategy to an oral azole as early as 5 days after the start of intravenous treatment with an echinocandin, provided that the infecting candida species has been cleared from the bloodstream and is probably susceptible to azoles and that the patient's condition is clinically stable and the patient is capable of taking oral therapy.

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BURDEN, DIAGNOSIS, AND MANAGEMENT OF NOSOCOMIAL PNEUMONIA IN HIGH RISK MORTALITY PATIENT

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Nosocomial or Hospital Acquired Pneumonia (HAP)

Nosocomial Pneumonia is defined as pneumonia acquired during hospital stay. This definition does not include patients who have been in hospital for less than 48 hours. Hospital acquired pneumonia is the second most common hospital-acquired infection, responsible for increased duration of hospitalization and healthcare costs.

Disease Burden

The incidence of HAP in Europe is 0.5-2% among all hospitalized patients, while in the US, a study estimated that 3.5% of patients hospitalized for 3 days or more developed pneumonia. Mortality rates of HAP can go as high as 70%, and can be the leading cause of death from hospital acquired infection in critically ill patients. A survey in 2016 estimated the burden of pneumonia (CAP and HAP) in Malaysia, Indonesia, and the Philippines with the results below:

Item	Malaysia discharges			Indonesia discharges			Philippines discharges		
	CAP	HAP	Total	CAP	HAP	Total	CAP	HAP	Total
No. of discharges (*n*)	-	-	58 075	-	-	134 500	-	-	50 791
No. of pneumonia cases (*n*)	2442	1270	3712	1329	723	2052	7235	2852	10 087
Incidence per 100 000 discharges	4205	2187	6392	988	538	1526	14 245	5615	19 860
No. of deaths (*n*)	102	324	426	24	82	106	100	260	360
Proportion of pneumonia cases among discharged population (%)	4.2	2.2	6.4	1.0	0.5	1.5	14.2	5.6	19.9
CFR among pneumonia cases (%)	4.2	25.5	11.5	1.8	11.3	5.2	1.4	9.1	3.6

A study in Cipto Mangunkusumo Hospital in 2017 found that the 14 day mortality for HAP was 48.2% and 14-day mortality in patients with CURB-65 score higher than 2 was 69.7%.

Diagnosis

Like other diseases, pneumonia diagnosis is qcuired through history, physical examination, and supporting examinations. History includes acute fever, productive cough, while physical examinations may find rhales on lung auscultation. Chest x-ray is still the most common supporting examination to determine pneumonia, where findings can include infiltrates, consolidation, or ground glass appearance. When basic examinations are done, further investigation can be carried out to look for indicators of infection, etiologic agents of pneumonia, and exclude other differential diagnosis.

High Risk for Mortality

European and American guidelines have released criteria for patients at risk of poor outcome/mortality, as explained below

European Guidelines International ERS/ESICM/ESCMID/ALAT	American Guidelines ATS/IDSA
• Septic shock	For all types: HAP, VAP, MRSA, and PsA:

• Previous antibiotic use • Recent colonization with MDR pathogen • Prevalence of resistant pathogens in local microbiological data >25%	Prior IV antibiotic use within 90 days Additional risks for VAP: • Septic shock at time of VAP • ARDS preceding VAP • > 5 days hospitalization prior to occurrence of VAP • Acute renal replacement therapy prior to VAP onset

Studies have found that the most common isolates of HAP include Pseudomonas aeruginosa, Acinetobacter baumanii, and Klebsiella pneumonia, with Pseudomonas aeruginosa being the most prominent across many studies. These bacteria have been found to be resistant to many antibiotics and are associated with high rates of mortality

Treatment

The ATS/IDSA 2016 guideline has released treatment recommendations for HAP and VAP with high risk of mortality. For HAP due to P. aeruginosa, the recommendations are stated as:

- For patients with HAP/VAP due to P. aeruginosa, we recommend that the choice of antibiotic for definitive (not empiric) therapy based upon the results of antimicrobial susceptibility testing (strong recommendation, low quality evidence)
- For patients with HAP/VAP due to P. aeruginosa, we recommend against aminoglycoside monotherapy (strong recommendation, very low-quality evidence)

As for HAP due to Acinetobacter species, the recommendations are as follows:

- Treat with either a carbapenem or ampicillin/sulbactam if the isolate is susceptible to these agents
- If the Acinetobacter is only sensitive to Polymixin, we recommend intravenous Polymixin (Colistin or Polymixin B)
- If the Acinetobacter species is sensitive only to Colistin, we suggest not using adjunctive Rifampicin
- We recommend against the use of tigecyline

COVID-19 UPDATE: WHAT'S THE LATEST NEWS?

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COVID-19

COVID-19 or coronavirus disease is a pneumonia-like condition caused by the SARS-CoV2 virus. Many variants have emerged throughout the 2-year period of this pandemic.

To this date, the highest amount of cases is in the US (85570755 cases), followed by India (43147530 cases), and Brazil (30880512 cases). In Indonesia, Jakarta has the most confirmed cases (1250036 cases), followed by West Java (1106349 cases), and Central Java (627553 cases).

Clinical Presentation

Clinical presentations of COVID-19 remain the same, namely flu-like syndrome, fever, pneumonia (in moderate to severe cases), and acute respiratory distress syndrome (in critical cases). Nowadays, due to high rates of vaccination, clinical presentations are mostly limited to mild-moderate presentations.

Diagnosis

Rapid antigen and RT-PCR swab tests remain the most preferred diagnostic methods to detect COVID-19 due to the accuracy and also fast results. Chest x-ray examinations are done usually if a patient experiences dyspnea or is hospitalized. Radiologic findings in COVID may include ground glass appearance, middle and lower lobes involvement, and maybe pleural effusion. If swab tests seem inconclusive, bronchoalveolar lavage has a higher positivity rate in detecting COVID

Treatment

Treatment for COVID have not changed significantly. Due to cases reducing, while also mostly being mild cases, treatment is mostly aimed at relieving symptoms and administration of antivirus drugs such as Favivirapir or Oseltamivir, as needed.

Anti-SARS-CoV2 Monoclonal Antibodies

Observations were made for the role of bebtelovimab for non-hospitalized COVID patients who are at risk for disease progression. Sotrovimab is no longer recommended as a treatment option because it has substantially reduced in vitro activity against the Omicron variant

Rotinavir-boosted Nirmatrelvir (Paxlovid)

Ritonavir, a string cytochrome P450 (CYP) 3A4 inhibitor and a P-glycoprotein inhibitor, is coadministered with nirmatrelvir to increase it's concentration in the blood. Because this is the only highly effective oral antiviral against COVID, drug interactions that can be safely managed should not preclude the use of this medication

Vaccinations

Vaccinations around the world have been done to reduce disease incidence and prevent disease severity, should an individual get infected with COVID. Vaccines are given to healthy individuals aged 5 and above, or recovered COVID patients after 1-3 months after declared negative. Vaccines are usually given in first 2 doses (with the same vaccine) and a booster vaccine later on. In Indonesia, 73.2% of the population has received at least 1 dose, 61.1% of the population had received 2 doses, while booster doses have been administered to 13.7% of the population

Transitions

Due to the reduction in positive COVID cases, lower mortality, and also increasing rates of vaccinations, countries around the world have now declared COVID-19 as an endemic and no longer pandemic. Many countries have also erased the mask rules as now people can go outdoors without a mask, but must wear one if having common cold or coughs or if doing activities indoors

Efficacy of Antifibrotic Therapy in Progressive-Fibrosing ILD

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Fibrosing ILDs

Interstitial lung disease (ILDs) is a term for a number of acute and chronic lung disorders that affect the lung parenchyma. It was also known as diffuse parenchymal lung disease (DPLD), with one of the known classification being idiopathic interstitial pneumonias (IIP). The incidence and prevalence of ILDs vary according to the type; in 2018, the incidence of ILDs in general ranged between 9,4 – 83,6 per 100.000. The incidence of fibrosing ILDs (F-ILDs) were between 7,7 – 76,2 per 100.000 and idiopathic pulmonary fibrosis (IPF) was at 0,4 – 10,3.

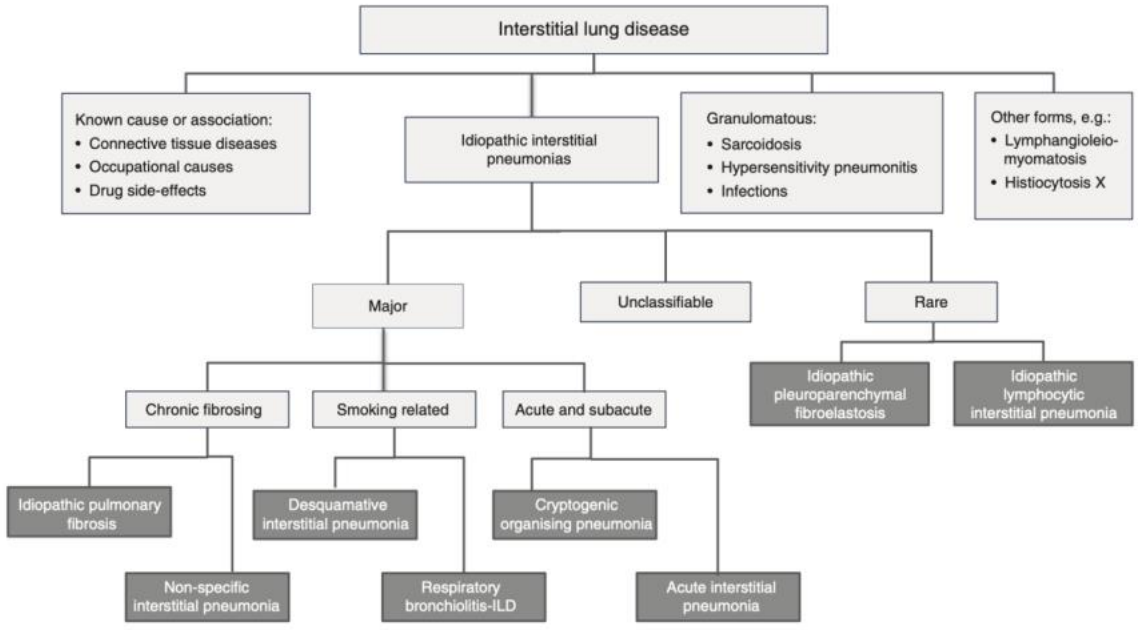


Figure 1. Classification of ILDs.[4]

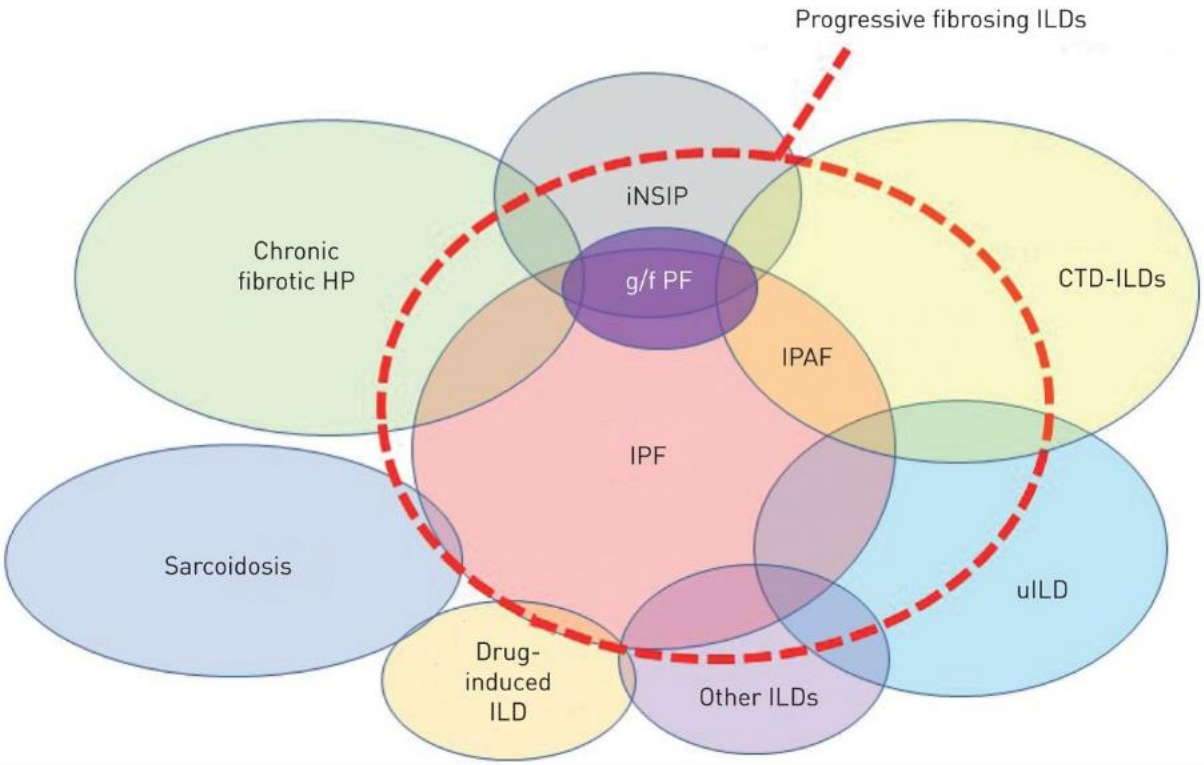
The most common type of ILD is idiopathic pulmonary fibrosis (IPF). It is one of several types of fibrosing ILD with progressive clinical course, where in IPF, lung function declines over time due to progressive fibrosis. IPF is known to have a low survivability prognosis, with the

5-year survival rate (20-40%) being lower than some common cancers. Other forms of fibrosing ILDs have emerged in recent years, however, often IPF and these other fibrosing phenotypes are used collectively for clinical research and treatment purposes. “Progressive fibrosing ILDs” can be used to refer patients with ILD who exhibits a progressive fibrosis over time, regardless of the classification of the ILD. Types of ILDs that may be associated with progressive fibrosis aside from IPF are hypersensitivity pneumonitis (HP), autoimmune ILDs, Non-IPF IIPs, sarcoidosis, exposure-related ILDs.[3]

Several common features are known regarding progressive fibrosing ILDs:[3]

- Common pathogenetic mechanisms
- Self-sustaining fibrosis
- Decline in lung function
- Worsening dyspnea
- Deterioration in quality of life
- Early mortality

Fibrosing ILDs are characterized with increasing fibrosis on a CT scan, a decline in forced vital capacity (FVC) and gas exchange, worsening of symptoms and exercise capacity, deterioration in health-related quality of life. In IPF, the decline in FVC is a predictor of mortality.[3]



Schematic representation of progressive-fibrosing phenotypes of ILDs.[7]

Autoimmune ILDs

Several autoimmune diseases might manifest a clinical course in the form of progressive fibrosing ILDs, such as systemic sclerosis and rheumatoid arthritis (RA). In systemic sclerosis, ILD is common, and occurs early in the disease. It is one of the leading causes of death, and an extensive fibrosis on HRCT is a predictor of mortality. Patients with over 30% of fibrosis on HRCT or 10-30% of fibrosis on HRCT with FVC <70% predicted is associated with mortality risk three times greater than patients with less extensive disease.[3] Patients with RA are estimated to have a lifetime risk of developing significant ILD up to 10%, however, RA-ILD has a variable clinical course. The progressive fibrosing may result in severe lung impairment, and ILD accounts for around 7% of RA-related deaths. A number of factors, including genetic risk factor found in IPF patients (*MUC5B* promoter variant rs35705950) are identified as risk factors for RA-ILD.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP) is a disorder of the lung where immune-mediated inflammation and fibrotic reaction occurs after exposure to an inhaled antigen in sensitized individuals. Abnormal immune response occurs in the small airways and lung parenchyma, and HP often develops with similar presentations with other ILDs.[3] From acute disease HP can progress to subacute and chronic forms, depending on the duration, frequency and intensity of the exposure.[5]

IPF

IPF is the most common type of ILD which presents as a specific form of chronic, progressive fibrosing IIP in older adults that are limited to the lungs. Usual interstitial pneumonia (UIP) is a histopathologic finding associated with IPF which can be found in high-resolution computed tomography (HRCT). IPF is diagnosed after the exclusion of other types of IIP and ILD associated with environmental exposure, medication, or systemic disease.[6]

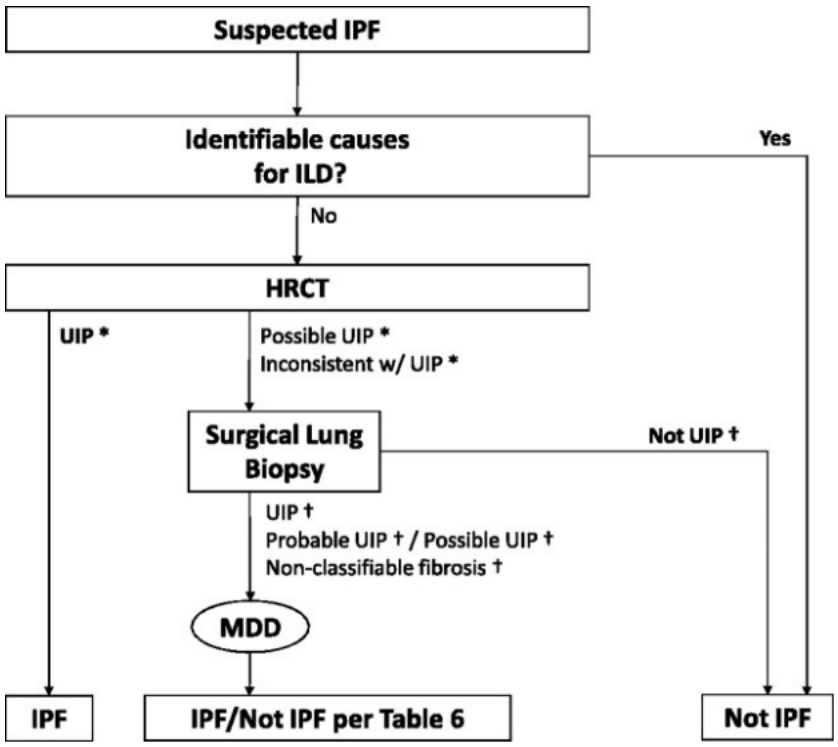
Clinical Presentation

IPF often presents with chronic exertional dyspnea unexplained with other diseases, along with cough, bibasilar inspiratory crackles, finger clubbing. IPF is more common with older patients

above sixty, and IPF patients under 50 years old usually manifest clear features of underlying connective tissue disease.

Diagnosis

The diagnostic algorithm for suspected IPF is presented in the figure below. Generally the finding of UIP can lead to the diagnosis of IPF, and HRCT is an essential tool for diagnosis.[6] UIP pattern is the presence of reticular opacities associated with traction bronchiectasis. Honeycombing is common, seen as clustered cystic airspaces between 3-10 mm in diameter, usually sub-pleural. Ground-glass opacities are commonly seen in a less-extensive manner than the reticulation.[6]



Alternative diagnosis should be considered with the findings of coexistent pleural abnormalities (calcification, effusion), micronodules, air trapping, non-honeycomb cysts, extensive GGO and consolidation, as those are not common findings in IPF.[6]

Risk Factors

A number of risk factors have been identified for IPF based on epidemiological evidence. Patient-related risk factors include older age, male gender, history of cigarette smoking, gastroesophageal reflux disease, genetic polymorphism and several viruses. Epstein-Barr virus

have been identified in lung tissue of IPF patients in alveolar epithelial cells. Other viruses include herpesvirus, and investigations regarding hepatitis C virus in IPF have yielded varying results.[6] For environmental-related risk factors, several studies found association between IPF and raising birds or livestock, vegetable/animal dust, metal dust, stone cutting/polishing, and hairdressing.[6]

Treatment of Progressive-Fibrosing ILD

In regards to clinical research and treatment purposes, IPF sometimes is used as an umbrella term to refer to progressive-fibrosing ILD.[3] However, with the emergence of other types of progressive fibrosing phenotypes, PF-ILDs or progressive-fibrosing ILDs are also used. These grouping terminologies are often useful for clinical research and treatment.

One of the key features of PF-ILDs is disease progression despite conventional therapy. In the stage of ILDs where fibrosing has become progressive and self-sustaining, antifibrotic drugs seem to have benefits to slow disease progression.[7]

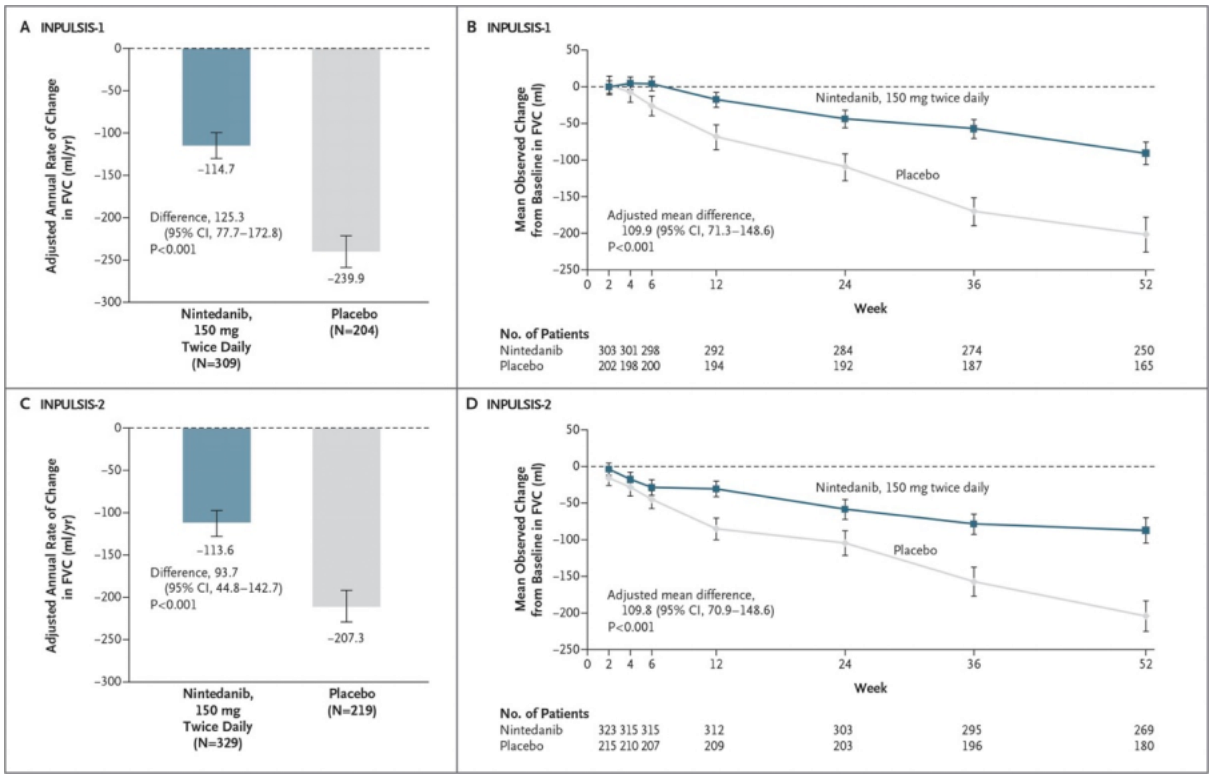
Several antifibrotic agents have shown benefits from various trials. Nintedanib is a potent intracellular tyrosine kinase inhibitor which targets the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) receptors. It acts by blocking intracellular ATP-binding site of the receptor, inhibiting the activation and signaling pathways. It has shown antifibrotic, anti-inflammatory, and vascular remodeling effects. Pirfenidone has also demonstrated efficacy in IPF and is considered for the treatment of other PF-ILDs.[7] It is a small molecule of 5-methyl-1-phenyl-2-[1*H*]-pyridone which reduces TGF-β1-stimulated collagen synthesis, thus inhibiting HSP47 & Col1 RNA upregulation (concentration-dependent). It also blocks PDGF proliferative effects dependent on concentration, and reduces fibroblast proliferation, production of alpha smooth muscle cells actin, and procollagen levels.[,,] Aside from antifibrotic properties, pirfenidone also downregulates proinflammatory cytokines, namely TNF-α, IFN-γ, and interleukin (IL)-6.[12]

Nintedanib

In vitro studies have shown several mechanisms nintedanib may be effective for fibrosing ILDs. Nintedanib inhibits pro-fibrotic mediator release involved in the progression, inhibits M2 macrophage differentiation, migration and differentiation of fibrocytes, proliferation, migration, and differentiation of fibroblasts, and the release of collagen for the fibrosing process.[9,,]

Nintedanib also reduces lung function decline and risk of acute exacerbations in IPF. Several trials have been conducted to investigate nintedanib's efficacy and safety profile for IPF and other PF-ILDs. INPULSIS trials conducted replicate randomized, double-blind trials spanning 52 weeks to evaluate the efficacy and safety profiles of nintedanib, given 150mg twice daily compared to placebo in IPF patients. The primary endpoint of the research was the annual rate of decline in forced vital capacity (FVC).[15]

The study shows nintedanib yielded favourable results in terms of the primary endpoint, with the annual rate of decline in FVC reduced as much as 68% compared with the placebo group. With nintedanib 150 mg twice daily, the adjusted annual rate of FVC reduction was -114,7 mL compared to -239,9 mL with placebo in INPULSIS-1 (difference 125,3 mL; 95% CI 77,7 – 172,8; p<0,001), and -113,6 mL (nintedanib) versus -207,3 mL (placebo) in INPULSIS-2 (difference 93,7 mL; 95% CI 44,8 – 142,7; p<0,001). There was no significant difference for mortality outcome, with all-cause mortality was 5,5% in the nintedanib group and 7,8% in the placebo group (hazard ratio 0,70 for nintedanib group; 95% CI 0,43-1,12 and p=0,14).[15]

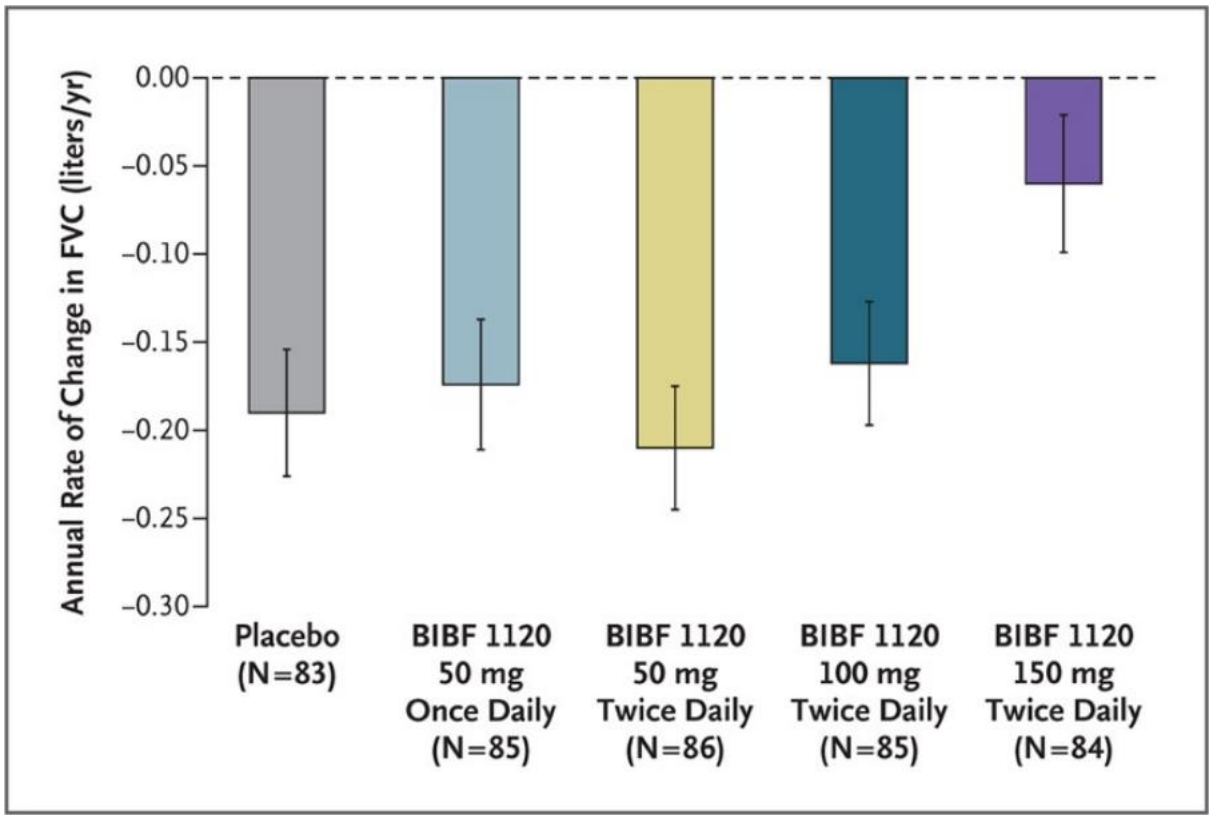


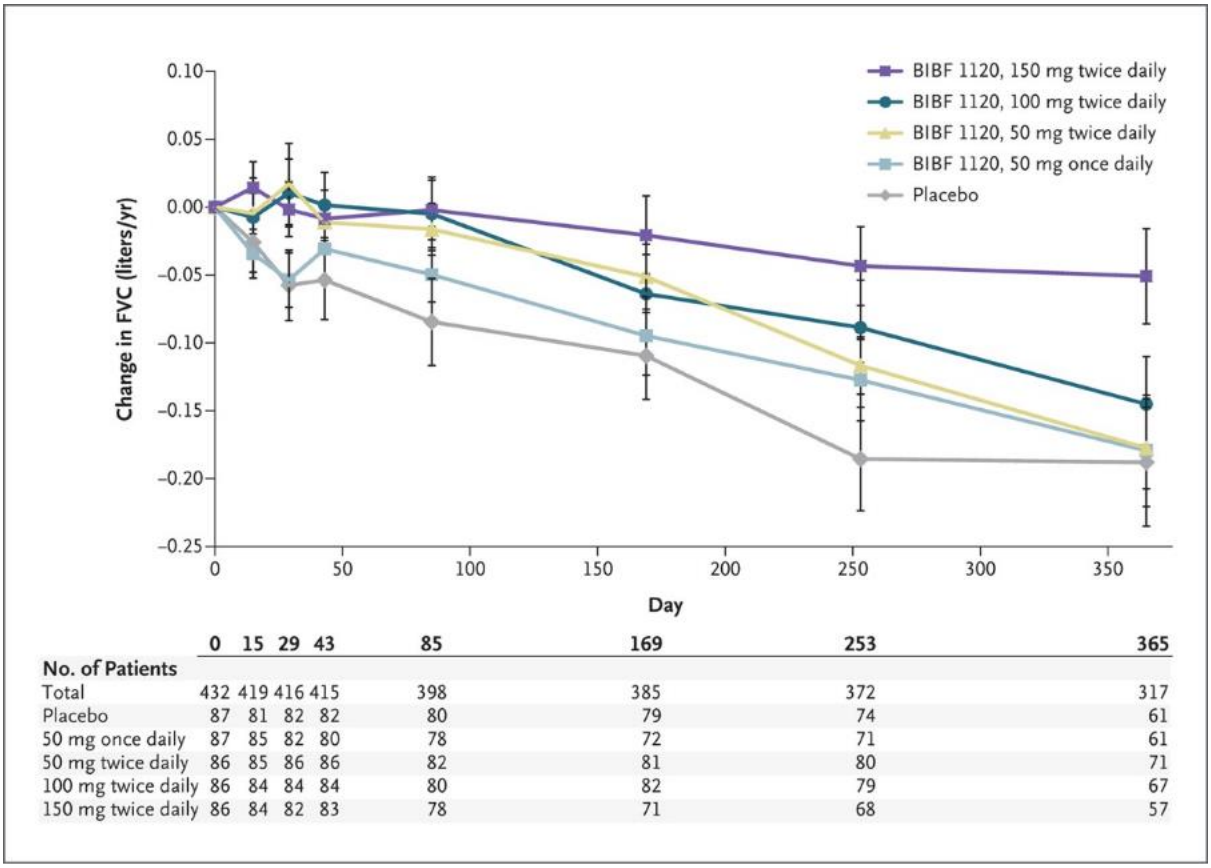
For the secondary endpoint, there was a significant increase in the time to first acute exacerbation of IPF in the nintedanib group compared to placebo (hazard ratio 0,38; 95% CI

0,19 – 0,77; p=0,005) in INPULSIS-2. Nintedanib seemed to be beneficial in increasing the time to first acute exacerbation.[15]

The TOMORROW preceding study, where nintedanib (then BIBF 1120) was compared to placebo for idiopathic pulmonary fibrosis also yielded favourable results. A total of 432 patients were randomized to be given nintedanib (BIBF 1120) 50 mg once a day, 50 mg twice a day, 100 mg twice a day, or 150 mg twice a day, compared to patients receiving placebo. Patients receiving 150 mg BIBF 1120 twice a day were found to have a reduction in FVC decline, 0,06 L per year compared to 0,19 L per year in the placebo group (68,4% reduction, p=0,06). Nintedanib in this dose also resulted in a lower incidence of acute exacerbations compared to placebo (2,4 vs. 15,7 per 100 patient-years; p=0,02). Patients in this nintedanib 150 mg group also showed a small decrease in SGRQ (St. George's Respiratory Questionnaire, a scale of 0 to 100 with lower scores indicating better quality of life) which assessed the quality of life of patients with obstructive airways.[15]

The study found improvements in both categories of the SGRQ (symptoms and activity) in the group receiving 150 mg nintedanib twice daily compared to placebo.[15]





	0	15	29	43	85	169	253	365
No. of Patients								
Total	432	419	416	415	398	385	372	317
Placebo	87	81	82	82	80	79	74	61
50 mg once daily	87	85	82	80	78	72	71	61
50 mg twice daily	86	85	86	86	82	81	80	71
100 mg twice daily	86	84	84	84	80	82	79	67
150 mg twice daily	86	84	82	83	78	71	68	57

In both trials, a higher proportion of patients in the nintedanib groups had higher levels of liver enzymes compared to placebo. The most common adverse event in the nintedanib group in both trials were diarrhea.[15] This adverse event caused less than 5% premature discontinuation of the medication in the INPULSIS trials.[15] Serious adverse events were balanced between nintedanib and placebo groups in the INPULSIS trials with a higher percentage of patients in nintedanib group. Generally, for the common adverse events that were gastrointestinal in nature (mild to moderate diarrhea), most patients continue to receive nintedanib.[15] In TOMORROW study, nintedanib was concluded to have an acceptable safety profile with similar results of common adverse event being diarrhea and a similar outcome of serious adverse events (ischemic heart disease) between nintedanib and placebo groups.[15]

The INBUILD trial investigated the efficacy of nintedanib in a wider selection of patients from other progressive-fibrosing phenotypes of ILD. Patients with PF-ILDs affecting more than 10% of their lung volume according to HRCT were given nintedanib 150 mg twice daily and compared to placebo. The endpoints of this study include the annual rate of decline in FVC for the primary endpoint (over 52-week period) and the secondary endpoints include the absolute change from baseline in total score on King's Brief Interstitial Lung Disease (K-BILD) questionnaire, which assessed the health status of patients with ILD, time until first acute

exacerbation or death during the 52-week period, and the time until death. Populations of the study was divided between the overall population and patients with UIP-like fibrotic pattern in the HRCT.

There was a significantly lower rate of decline in FVC in the nintedanib group overall, -80,8 mL per year compared to -187,8 mL per year in placebo group (95% CI 65,4 – 148,5; p<0,001). In patients with UIP-like fibrotic pattern, the adjusted rate of decline in FCV was -82,9 mL compared to -211,1 mL per year for nintedanib and placebo groups, respectively (95% CI 70,8 – 185; p<0,001).[16] For the secondary endpoints, changes were not significant betweel nintedanib and placebo groups for the health-related quality of life (K-BILD questionnaire score) and death.[16]

Pirfenidone

Pirfenidone has been investigated for potential IPF treatment for its anti-inflammatory, antioxidant and antifibrotic effects. In a study by Taniguchi, et al, pirfenidone in low doses and high doses in step-wise increasing manner were investigated for its efficacy to treat IPF compared to placebo. In the low-dose group, pirfenidone was given 600 mg per day for the first 2 weeks, 600 mg per day for the second 2 weeks, and 1.200 mg per day for the rest of 48 weeks. In the high-dose group, pirfenidone was given 600 mg per day for the first 2 weeks, raised to 1.200 mg per day for the following 2 weeks, and 1.800 mg per day for the remaining 48 weeks.[12]

The efficacy endpoints were the change in vital capacity (VC) from baseline to week 52 as primary end-point, and progression-free survival time and the change in lowest SpO_2 during 6MET. Progression of disease was defined by death and/or over 10% decline in VC from baseline. In the results, the changes in VC for the high-dose group was -0,09 L and -0,16 L in the placebo group; this 0,07 L was statistically significant with p=0,0416. A significant difference was also seen between the low-dose, with the adjusted mean change in VC being -0,08 L, and placebo group, however, there was no statistically significant difference between the high and low dose groups.[12] For secondary endpoints there was a significant difference between distribution of PFS time between the high-dose and placebo groups and low-dose and placebo groups.[12]

	Crude mean±SD				Comparison of adjusted means based on ANCOVA#			
	Baseline L	Subjects n	52 weeks L	Subjects n	Subjects n	Adjusted mean±SE	Difference from placebo mean±SE L	p-value
High dose	2.40±0.64	106	2.36±0.73	67	104	-0.09±0.02	0.07±0.03	0.0416
Low dose	2.44±0.68	55	2.34±0.71	38	54	-0.08±0.03	0.09±0.04	0.0394
Placebo	2.47±0.70	104	2.42±0.75	72	103	-0.16±0.02		

#: negative and positive of the changes represent deterioration and improvement from baseline, respectively.
Covariates: baseline vital capacity.

Recent studies have expanded the investigation of pirfenidone for more phenotypes of progressive fibrosing ILDs. In RELIEF study, for 48 weeks patients between 18-80 years with progressive fibrosing ILD other than IPF, namely connective-tissue disease-associated ILDs, fibrotic non-specific interstitial pneumonia, chronic hypersensitivity pneumonitis, asbestos-induced lung fibroses were given either pirfenidone in step-wise dosing increase or placebo. One of the eligibility criterias were an annual decline of FVC at least 5% from baseline despite conventional therapy, based on measurements within 6-24 months before enrolment. From 127 patients in total (64 in pirfenidone group and 63 in placebo group), it was found that the pirfenidone group showed a significantly lower decline in FVC% predicted.

Paradigm in Progressive-Fibrosing ILDs and Its Treatment

Aside from IPF, a number of diseases with progressive-fibrosing phenotypes should be promptly diagnosed to allow for early treatment. In IPF, preservation of lung function could be beneficial to reduce risk of acute exacerbations.[,] Aside from antifibrotic agents, some non-IPF fibrotic lung diseases may show response or improvement with immunosuppressive agents (connective tissue disease-associated ILD/CTD-ILDs), removal of antigenic sensitizers (HP), however the progressive fibrosing process may still continue in the clinical course. In non-IPF PF-ILDs, while immunosuppressive agents have been found to improve or stabilize several cases, with the INBUILD trial antifibrotic agents might be considered to be used for PF-ILDs and their efficacy was also found in studies. Several other studies such as SENSCIS for nintedanib and uILD for pirfenidone trials demonstrated the safety and efficacy of concurrent use of antifibrotics and immunosuppressant medications.[,] While optimal treatment for PF-ILDs are still varying and needs adjustment to clinical cases, and safety profiles need to be better

established for the current available antifibrotics, the current findings of available treatments such as nintedanib and pirfenidone may strongly be considered to treat and prevent the worsening of lung function in progressive-fibrosing ILDs.[21]

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HOW TO TREAT PNEUMONIA IN SPECIAL CONDITION: Pregnancy, Autoimmune, and Other Diseases

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Pneumonia is a common clinical condition. It results from an infectious inflammatory process that involves the lung parenchyma and results in the impairment of gaseous exchange. There are special conditions that requires special consideration in treating pneumonia due to several risk factors pertaining to them that may influence prognosis and outcome.

1. Pneumonia in Pregnancy

Community-acquired pneumonia (CAP) is one of the most common non-obstetric diseases in pregnant women. In the USA, the incidence of antepartum CAP is around 0.5 to 1.5 per 1,000 pregnancies, and the reported incidence of CAP in pregnancy was 0.7% over a one-year period in East Asia.[1] A true estimate of the incidence of pneumonia during pregnancy is difficult to obtain because the few published studies in this area are mostly case reports.[2]

Several physiological and immunological changes that are experienced during pregnancy may increase the risk of pneumonia, and may predispose pregnant women to a more severe course of pneumonia, which may result in greater maternal and fetal morbidity and mortality.[2] The management of severe pneumonia in gravid patients is even more challenging. Early recognition and prompt treatment are essential to improve outcomes in patients with pneumonia during pregnancy.[3]

1.1. Risk Factor

The risk of pneumonia during pregnancy appears to be lowest during the first trimester,[4] while advanced gestational age has been proven to be an independent maternal risk factor for pneumonia.[3] This risk increases as the pregnancy advances, especially because there are several

alterations in pregnancy that were known to increase the incidence and risk of complications from pneumonia, such as:[1,2]

- **Immunologic changes:** Reduced lymphocyte proliferative response, diminished cell-mediated cytotoxicity, reduced number of helper T cells, and reduced lymphokine response to alloantigens.
- **Maternal anatomical and physiological changes:** Increase in oxygen consumption, decrease in functional residual capacity, increase in lung water, and elevation of diaphragm that weakened the ability to clear the airway secretions and aggravate airway obstruction associated with pulmonary infections.
- **Labor and delivery:** Increases risk of aspiration pneumonia.
- **Others:** Smoking, anemia, asthma, the use of antepartum corticosteroids and tocolytic agents.

Women with pneumonia had a higher prevalence of preeclampsia/eclampsia than women without pneumonia as the result of the pathophysiological changes associated with pneumonia. On the other hand, Preeclampsia may cause pulmonary edema, thus aggravating the oxygen desaturation caused by pneumonia, predisposing the patient to require a mechanical ventilator. Preeclampsia complicated with pneumonia may be an unfavorable predictive factor for a poor maternal outcome.[2]

1.2. The Multi-Etiology Microorganism

Bacteria is the most common pathogen for pneumonia in pregnancy.[1] In a retrospective analysis of 1,462 patients with pneumonia in pregnancy, Chen et al. found that 93% of patients suffered from bacterial infections.[5] *Streptococcus pneumoniae* was found to be the most dominant cause of CAP in pregnancy (reported in 15-20% cases).[1,6] Other pathogens causing pneumonia in pregnancy in decreasing order of frequency were: *Hemophilus influenzae, Legionella* species (more common in severe pneumonia), *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Staphylococcus aureus* (including MRSA strain), and *Pseudomonas aeruginosa*.[7]

1.3. Management and Drug of Choice

Based on the expected organisms in pregnant women with CAP, therapy should be directed at *Streptococcus pneumoniae* (including drug resistant strain [DSRP] in patients with recent antibiotic therapy, underlying chronic heart or lung disease, and those with exposure to a child in daycare), *H. influenzae* (especially in cigarette smokers), and the atypical pathogens such as *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, or *Legionella pneumophila* (in severe CAP).[7]

In choosing an antibiotic for bacterial pneumonia, the agent's safety in pregnancy and efficacy must be considered. The pregnancy safety profile of several antibacterials commonly recommended to treat CAP in adults are as follows:[7]

- Penicillins, cephalosporins, azithromycin and erythromycin: all safe and potentially effective antimicrobials for CAP.
- Clarithromycin should not be used during pregnancy unless there are no alternatives and the benefit outweighs the risk to the fetus.
- Doxycycline is not recommended during pregnancy because it can affect fetal tooth and bone development.
- Vancomycin poses serious risk to the fetus, causing fetal nephrotoxicity and ototoxicity, and similarly, should only be used if absolutely necessary.
- Linezolid has no safety data available in human pregnancies.
- Fluoroquinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin) are not recommended in pregnancy because of the risk of fetal arthropathy and malformations. However, sporadic reports of safe use in pregnancy have appeared, suggesting that they can be used if alternatibe therapy is not available.

Recommended empiric therapy of community-acquired pneumonia in pregnancy.[7-9]

Outpatients	**Recommended antibiotic regimens**
No comorbid illness, no recent antibiotics	Azithromycin (500 mg on first day then 250 mg daily) **OR**
No DRSP risks (including exposure to a child in daycare) and pneumococcal resistance to macrolides < 25%	Erythromycin (500 mg four times a day for 5 days)

Co-existing cardiopulmonary disease, recent antibiotic therapy, or DRSP risk factors	Combination therapy: Amoxicillin/clavulanate (500 mg/125 mg 3 times daily, or 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily) **OR** Cefpodoxime (200 mg twice daily) **OR** Cefuroxime (500 mg twice daily) **AND** Azithromycin (500 mg daily) **OR** Erythromycin (500 mg four times a day for 5 days)
Inpatients	
Non-severe CAP, no comorbid illness or DRSP risks	Intravenous macrolides (azithromycin **OR** erythromycin)
Non-severe CAP, co-existing cardiopulmonary disease or DRSP risk factors	Intravenous beta-lactam (cefotaxime 1–2 g every 8 h **OR** ceftriaxone 1–2 g daily) **AND**
Severe CAP, no pseudomonal risks	Intravenous macrolides (azithromycin **OR** erythromycin)
Severe CAP, pseudomonal risks present	Intravenous anti-pseudomonal beta-lactam (cefepime 2 g every 8 h **OR** imipenem 500 mg every 6 h **OR** meropenem 1 g every 8 h **OR** piperacillin/tazobactam 4.5 g every 6 h) **AND** Intravenous macrolides (azithromycin **OR** erythromycin)

2. Pneumonia in Autoimmune and Other Diseases

Community-acquired pneumonia (CAP) in autoimmune diseases induced immunocompromised host had a high incidence and poor prognosis. A population-based study of community-acquired pneumonia (CAP) in older adults showed that the incidence rate of CAP among immunocompromised patients is almost 3-fold higher than that in immunocompetent subjects. Immunocompromising conditions are present in approximately 20% to 30% of hospitalized patients with CAP.[10] Furthermore, immunocompromised patients with CAP had higher mortality and morbidity.[11] Immunocompromised patients requires

complex, often individualized, treatment, and has an expanded spectrum of potential pathogens.

2.1. Risk Factor

The main therapeutic option for autoimmune disorders is suppression of the pathologic autoimmune response. However, treatments with glucocorticoids and immunosuppressive drugs, which are commonly known as disease-modifying anti-rheumatological drugs (DMARDs), to biological therapies such as tumor necrosis factor-alpha (TNF-α) inhibitors were reported to decrease both cellular and humoral immunity and leading to an immunocompromised state, which carries an inherent risk of patient susceptibility to opportunistic infections.[11]

Several other conditions were also reported be associated with immune deficiency and increased susceptibility to bacterial pneumonia, such as primary immune deficiency diseases, patients receiving cancer chemotherapy, HIV infection with a CD4 T-lymphocyte count < 200 cells/μL, or patients receiving immunosuppressive drugs after solid organ transplantation and hematopoietic stem cell transplantation.[10] Additionally, high levels of NLR, LDH and serum creatinine (sCr) at different time points were also reported to be predictive of poor prognosis in immunocompromised patients with CAP.[11]

2.2. The Multi-Etiology Microorganism

Immunocompromised patients are susceptible to infection with the same respiratory bacteria that cause CAP in nonimmunocompromised patients. The core respiratory pathogens included Gram-positive bacteria (*Streptococcus pneumoniae, Staphylococcus aureus [MSSA], Streptococcus pyogenes*), Gram-negative bacteria (*Haemophilus influenzae, Moraxella catarrhalis, Klebsiella* species, *Esterichia coli*), and atypical bacteria such as *Legionella pneumophila, Chlamydophila pneumoniae, Mycoplasma pneumoniae, or Coxiella burnetii*.[10]

When considering likely etiologies of CAP beyond the core respiratory pathogens, it is important to focus attention on organisms that are amenable toantimicrobial treatment. Common respiratory pathogens that may cause CAP in the immunocompromised host and for which antimicrobial therapy is available are Enterobacteriaceae, nonfermenting Gram-negative bacili (*Pseudomonas* or *Acinetobacter*), MRSA, *Nocardia* species, *Rhodococcus equi*,

Mycobacterium tuberculosis, and nontuberculous mycobacteria. Different types of immunocompromising conditions may also predispose to different types of etiologic agents. Examples of pathogens that were specifically reported to cause pneumonia in autoimmune patients receiving corticosteroids were *Pseudomonas aeruginosa*, *Pneumocystis jirovecii*, *Staphylococcus aureus*, and mycobacteria, whereas Mycobacterium (tuberculous and nontuberculous) and *Nocardia* were reported in patients receiving tumor necrosis factor inhibitors.[10]

2.3. Management and Drug of Choice

Immune restoration is important for the treatment of pneumonia in immunocompromised patients, thus it is necessary to decrease the use of immunosuppressants as much as possible.[12] In this group of patients, the initial empirical antibacterial therapy would be the same as the initial empirical therapy for patients with CAP who are not immunocompromised. Additional treatment should be considered according to the presence of risk factors for drug-resistant or opportunistic pathogens.[10]

The recommended antibiotic regimens and dosing according to the American Thoracic Society (2020) are as follows:[9]

- **Healthy outpatient adults with no comorbidities or risk factors for MRSA or *P. aeruginosa***
  - Amoxicillin 1 g three times daily, **OR**
  - Doxycycline 100 mg twice daily, **OR**
  - A macrolide (azithromycin 500 mg on first day then 250 mg daily **OR** Clarithromycin 500 mg twice daily **OR** clarithromycin extended release 1,000 mg daily) only in areas with <25% pneumococcal resistance to macrolides.
- **Outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia (in no particular order of preference)**
  - Combination therapy:
    - Amoxicillin/clavulanate 500 mg/125 mg three times daily, or 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily, **OR**

        - A cephalosporin (cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily); **AND**
        - Macrolide (azithromycin 500 mg daily, clarithromycin [500 mg twice daily or extended release 1,000 mg once daily]), or doxycycline 100 mg twice daily;

          OR
    - Monotherapy:
        - Respiratory fluoroquinolone (levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily).
- **Inpatient adults with nonsevere CAP without risk factors for MRSA or *P. aeruginosa***
    - Combination therapy:
        - A β-lactam (ampicillin 1 sulbactam 1.5–3 g every 6 h, cefotaxime 1–2 g every 8 h, ceftriaxone 1–2 g daily, or ceftaroline 600 mg every 12 h); **AND**
        - A macrolide (azithromycin 500mg daily or clarithromycin 500mg twice daily);

          OR
    - Monotherapy:
        - A respiratory fluoroquinolone (levofloxacin 750 mg daily, moxifloxacin 400 mg daily).
    - A third option for adults hospitalized with CAP who have contraindications to both macrolides and fluoroquinolones:
        - Combination therapy with a β-lactam (ampicillin 1 sulbactam, cefotaxime, ceftaroline, or ceftriaxone, doses as above) and doxycycline 100 mg twice daily.

- **Adults hospitalized with severe CAP: (specific agents and doses are the same as above)**
    - A β-lactam plus a macrolide; **OR**
    - A β-lactam plus a respiratory fluoroquinolone.
- **Empiric treatment options for MRSA**
    - Vancomycin (15 mg/kg every 12 h, adjust based on levels) or linezolid (600 mg every 12 h).
- **Empiric treatment options for *P. aeruginosa***
    - Piperacillin-tazobactam (4.5 g every 6 h), cefepime (2 g every 8 h), ceftazidime (2 g every 8 h), aztreonam (2 g every 8 h), meropenem (1 g every 8 h), or imipenem (500 mg every 6 h).

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CLINICAL APPROACH TO THE PATIENT WITH CHRONIC COUGH

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Introduction

Cough is a vital protective reflex preventing aspiration and enhancing airway clearance.[1] However, pathologically excessive and protracted cough is a common and disabling complaint, affecting perhaps 5– 10% of the adult population.[2] When severe, it causes a major decrement in the quality of life, with comorbidities such as incontinence, cough syncope and dysphonia leading to social isolation, depression and difficulties in relationships.[3] While a wide range of diseases may be associated with chronic cough, it has become increasingly clear that the majority of adult patients presenting with chronic cough as the primary complaint have a common clinical presentation.[4] They often complain of exquisite sensitivity to inhalation of environmental irritants such as perfumes, bleaches and cold air which result in sensations of tickling/irritation in the throat and an urge to cough; features suggestive of heightened sensitivity of the neuronal pathways mediating cough.[5] In addition, there is a unique epidemiology with two-thirds of patients being female and the peak prevalence in the fifties and sixties.[1]

Definition, classification, and pathophysiology of cough

Cough is a defensive reflex for clearance of excessive secretions and foreign bodies from airways. However, severe cough frequently affect quality of life badly.[6] Cough is classified into three types based on the duration: acute, subacute, and chronic cough. Acute cough is defined as cough lasting for <3 weeks, subacute cough lasts 3–8 weeks, and chronic cough (CC) persists for >8 weeks.[7] Chronic cough has been defined by both the European Respiratory Society (ERS) and the American College of Chest Physicians (ACCP)[8] as a persistent daily cough for > 8 weeks which should be based on a global clinical assessment of the patient's symptoms and how they may relate to the many phenotypes of CC.[9] For the purposes of drug trials, patients with chronic cough have been stratified into one of two categories: Unexplained Chronic Cough (UCC), usually defined as cough with no obvious cause for > 1 years duration, and Refractory Chronic Cough (RCC), that being an unexplained chronic cough that persists despite rigorous investigation and treatment in accordance with best practice guidelines.[10] These definitions may be further simplified, with RCC being the failure of the treatment to improve a patient's cough and UCC being the failure of the physician to identify the cause of the patient's cough. These definitions have been shown to have little utility in the differentiation of patients with CC, as conveyed in COUGH-1 and COUGH-2 trials, where both UCC and RCC displayed similar symptom profiles.[11] Cough can also be categorized as dry and wet cough, and a wet cough is defined as sputum volume >10

mL per day. Different types of cough have a spectrum of different underlying causes. Based on chest radiography, CC can be further classified into two subtypes: (I) presence of pulmonary lesions on radiography (for example, pneumonia, tuberculosis, and bronchopulmonary carcinoma), and (II) lack of overt identifiable abnormalities on radiography. Chronic cough is related to air pollution.[12]

The underlying pathophysiology of CC has been described as "cough hypersensitivity syndrome," as many patients cough after exposure to low levels of thermal, chemical or mechanical stimulation.[13] Patients often describe sensations of "itch," "irritation" and "unpleasantness" or "something physically stuck in the throat." Cough is often triggered by changes in temperature, perfumes, aerosols, strong smells, talking, laughing and singing.[13,14] Cough hypersensitivity syndrome is considered a neuro-pathological mechanism implicating both the central and peripheral nervous system.[13] Cough can be under both voluntary and automatic control at the same time, but it is widely recognized that the cough reflex is the archetypal airway defensive reflex to prevent aspiration of foreign bodies or inhalation of noxious chemicals like smoke.[15] The lungs are innervated by two sub-types of the vagus afferent nerve"[16] unmyelinated c-fibers and myelinated A-delta fibers projecting sensory nerve terminals to the epithelium and sub-epithelium, respectively. The c-fibers are predominantly chemically sensitive and express ion channels and g-protein coupled receptors on their terminals that, upon activation, allow cations to flow inside resulting in membrane depolarization. The A-delta fibers are mainly mechanosensitive, but also respond to change in pH and osmolarity. Depolarization generates action potentials that are transmitted to the central nervous system. Once the signal reaches the first order synapse in the nucleus tractus solitarius (NTS) and paratrigeminal nuclei, second order neurons relay the signal to the thalamus, and third order neurons to the primary somatosensory cortex. This causes the unpleasant conscious sensation of urge to cough, which if strong enough, will evoke coughing. Importantly, cough is also under voluntary control and recent evidence suggests the presence of descending inhibitory control neurons that inhibit impulses arriving at the brainstem, thus limiting the urge to cough.[17,18] Excessive cough in patients with RCC/UCC could be due to i) increased activation of the airway peripheral nerve terminals by chemical irritants/mucus/alarmins (eg, extracellular ATP), ii) hypersensitivity and/or hyper-responsiveness of the afferent vagal nerve, brainstem and higher cortical projections and iii) impaired voluntary control and/or descending inhibitory control pathways. Recent studies suggest patients with RCC have impairment in the descending inhibitory control neurons[17] and lack of voluntary cough suppression.[18] It is currently unknown which of these potential mechanisms of disease predominate or if there is a combination of effects.

Medical history and laboratory tests

A thorough medical history and physical examination are important for physicians to develop a differential diagnosis, select laboratory tests, make a tentative diagnosis and empiric therapy.[19]

Medical history

Information regarding the duration of cough; phase; characteristics; triggers; effect of altering body position; and concomitant symptoms should be identified. Sputum volume, purulence and characteristics; smoking history; occupational or environmental exposure; medication history, including angiotensin converting enzyme inhibitors (ACEI) or other drugs, can indicate the diagnosis.[20] Occupational cough

should be considered when patient has an occupational exposure history. Acue cough is often attributable to the common cold and acute tracheobronchitis, while subacute cough is the result of post-infectious cough (PIC). The timing of cough provides additional diagnostic information. Cough variant asthma (CVA) should be considered for patients with predominantly nocturnal cough.[21] A dry cough indicates a non- infectious cough, while a wet cough is more commonly seen in patients with an infectious cough. Respiratory infectious disease should be considered in patients with a large amount of sputum production or purulent sputum.[20,21] Chronic bronchitis is characterized by mucoid sputum and the cough is usually aggravated in the winter and spring. Tuberculosis, bronchiectasis, and lung cancer should be considered with bloody sputum or hemoptysis. Allergic rhinitis and asthma-related cough should be carefully excluded in patients with a personal or family history of allergy. Upper airway cough syndrome (UACS) should be considered in patients with nasal congestion, runny nose, sneezing, postnasal drip, or post-laryngeal reflux.[21] In the presence of acid regurgitation, belching, or retrosternal burning, gastroesophageal reflux-related cough (GERC) should be considered.[21]

Physical examination

Physical examination focuses on the somatotype, nose, larynx, throat, trachea, and lungs; lung sounds; and presence/absence of wheezing, moist rales, and crackles. The possibility of obstructive sleep apnea (OSA)- or GER-related chronic cough should be considered in patients with obesity. A majority of patients with chronic cough have normal findings on a physical examination. Expiratory wheezing suggests the possibility of asthma. Sounds of "velcro opening" at the lower lung lobes may indicate interstitial lung diseases. Inspiratory wheezing may suggest central airway tumor or bronchial tuberculosis. Cardiac signs, including enlargement of heart border, premature beats, and murmurs should also be evaluated.

Relevant additional testing

The main tests include chest imaging, induced-sputum cytology, spirometry, the bronchial provocation test, fractional exhaled nitric oxide (FeNO) measurement, and 24-h esophageal pH-multi-channel impedance monitoring. (I) Imaging: chest radiographs are routinely recommended for chronic cough . The flow chart for the diagnosis of chronic cough should be followed (see supplementary file 1). If an obvious abnormality is observed on plain films, additional investigation is selected based on the characteristics of the lesion. Chest CT can be used to detect lesions anterior and posterior to the mediastinum; small pulmonary nodules; thickening and calcification of trachea; stenosis of the trachea; and enlargement of mediastinal lymph nodes. The uncommon conditions can be identified by radiography, including broncholithiasis, relapsing polychondritis, and bronchial foreign body can be identified by CT. High-resolution CT is helpful for the early diagnosis of interstitial pulmonary diseases and atypical bronchiectasis. If sinusitis is suspected, sinus CT is preferred.[22] Repeated radiographs within a short time span should be avoided. (II) Pulmonary function tests: pulmonary function tests include pulmonary ventilation tests and the bronchial provocation test. These tests are valuable for the etiologic diagnosis of chronic cough and should be routinely used.[23] Positive findings on the cough provocation test are important in the diagnosis of CVA. Hospitals unable to perform the cough provocation test can monitor the average peak expiratory flow (PEF) variation overtime.[24] An average daily PEF variation of >10% suggests CVA. (III)

Induced sputum test: induced sputum test is a safe, well-tolerated, non-invasive method for the etiologic diagnosis of chronic cough and airway inflammation.[25] Eosinophilia identified by induced sputum is suggestive of eosinophilic bronchitis (EB), and can also be seen in patients with CVA.[25] Induced sputum cytology can be used to monitor response to inhaled corticosteroids (ICS) in patients with chronic cough.[26] The use of 3% hypertonic saline via ultrasonic nebulizer is recommended, but repeated induced sputum tests within 48 hours should be avoided.[27] (IV) FeNO measurement: this is a novel non-invasive technology for the diagnosis of airway inflammation. An increase in FeNO (>32 ppb) suggests eosinophilic inflammation or corticoid- sensitive cough.[28] However, the sensitivity is not high when FeNO measurement is used for screening of eosinophilic inflammation. Approximately 40% of patients with increased numbers of eosinophils have normal FeNO.[28] (V) Allergy skin prick tests and serum IgE test: these tests can identify patients predisposed to allergen sensitization and identify specific allergens. They may be useful in the diagnosis of atopic diseases (e.g., allergic rhinitis and atopic cough). Approximately 60–70% of CVA patients and 30% of EB patients are predisposed to allergen sensitization.[29] (VI) The 24-h esophageal pH-multi- channel impedance monitoring: this is the most commonly useful method of diagnosing gastroesophageal reflux. Dynamic monitoring measures changes of esophageal pH, the number of times the esophageal pH is <4, the longest duration of reflux, and the percentage of time for which the esophageal pH is <4. The grade of reflux is represented as the DeMeester scores. Cough should be recorded in a real-time manner during the monitoring, so that the symptom-associated probability (SAP) between reflux and cough can be calculated. The non-acid reflux, such as weak acid or weak alkaline reflux, can be detected by esophageal impedance monitoring. (VII) Bronchoscopy: bronchoscopy is not routinely recommended for chronic cough except for the diagnosis is not confirmed by routine tests or in patients with a poor response to the treatment for common causes of cough. Bronchoscopy can be used for the diagnosis or exclusion of uncommon airway conditions associated with cough, including lung cancer, foreign body, tuberculosis, and relapsing polychondritis.[30] (VIII) Other examinations: peripheral eosinophilia is indicative of atopic diseases, but in most patients with CVA and EB, the peripheral eosinophil counts are within the normal ranges. Severe peripheral eosinophilia (eosinophil count >20%) indicates the possibility of parasitic infections or eosinophilic pneumonia.

Diagnostic principles and algorithm of cough

The etiological diagnosis of chronic cough should follow the principles as described below:[31] (I) Attention should be paid to the medical history, including ear, nose, and throat, and digestive tract diseases, occupational and environmental exposure, smoking and medication history. The diagnosis can be determined if clinical signs are alleviated after being away from occupational or environmental exposure. (II) Selecting investigations, from simple to complex, based on the medical history. The most common causes of chronic cough are EB and CVA. Together they are responsible for approximately 50% of chronic cough cases.[32] Spirometry, the bronchial provocation test, and induced-sputum cytology are recommended as the initial tests for chronic cough.[20,25] The measurement of FeNO is recommended as to supplement of the induced sputum test.[33] The 24-h esophageal pH-multi-channel impedance monitoring is an important method for the diagnosis of GERC, but it is recommended as the second-line test because it is time-consuming and costly. (III) The common causes of cough,

including UACS, CVA, EB, GERC, and atopic cough (AC) should be initially considered as the most possible etiology for chronic cough.[32] Bronchoscopy is valuable in the diagnosis of uncommon causes of chronic cough. (IV) Diagnosis and management can be implemented simultaneously or sequentially. If certain tests are unavailable, the treatment should be based on the clinical characteristics and the therapeutic response.[19] Further evaluation should be considered if patients fail to respond to the treatment. With typical symptoms of rhinitis, sinusitis, or postnasal drip, treatment for UACS should be initially prescribed. If patients present with symptoms related to gastroesophageal reflux cough after eating food, treatment for GERC should be given empirically. (V) Response to the treatment is the prerequisite for confirming etiologic diagnosis. When the cough is partially relieved, the factors affecting the effectiveness of treatment or other causes of chronic cough, such as UACS concurrent with GERC, CVA, or EB, GERC concurrent with EB or CVA should be evaluated. (VI) When the treatment is ineffective, the following factors should be evaluated: diagnosis, therapeutics, and occupational or environmental exposure.

Assessment of cough

The assessment of cough includes: the visual analogue scale (VAS), cough symptoms score, quality of life questionnaire, cough frequency monitoring, and the cough provocation test. These tests are used to monitor the disease status and treatment efficacy.[34]

The VAS scoring system

Patients mark a point on a straight line corresponding to their perception of the severity of cough. The score ranges from 0–10 cm (0–100 mm), with 0 representing minimal severity and 10 representing extreme severity. Compared with the cough symptoms score, the intervals between grades with the VAS are smaller, which is helpful for longitudinal comparison before and after treatment.[34]

Coughing score

This is a quantitative scoring system of cough used to assess the severity of cough and efficacy of treatment. Daytime and nighttime scoring is done, however it may be difficult to discriminate between grades[34] (see Table 1).

Quality of life questionnaire

The Chronic Cough Impact Questionnaire (CCIQ), Cough- Specific Quality of Life Questionnaire (CQLQ), and Leicester Cough Questionnaire (LCQ) are specific for chronic cough and demonstrate good reliability, validity, and responsiveness. These questionaires are important in the assessment of cough severity and efficacy of treatment.[34]

Coughing frequency monitoring

The cough symptoms score, VAS, and quality of life questionnaire are subjective assessment tools. Cough frequency monitoring is used for evaluation of cough severity and treatment efficacy.[35] There is diversity in tolerance of patients to coughing, and cough frequency does not definitively correlate with cough severity

Table 1 Scoring of cough

Score	Daytime cough symptom score	Nighttime cough symptom score
0	No cough	No cough
1	Occasional, transient cough	Transient cough when falling sleep or occasional cough during the night
2	Frequent cough, slightly influencing daytime activities	Cough slightly influencing sleep
3	Frequent cough, significantly influencing daytime activities	Cough significantly influencing sleep

Cough provocation test

This test is used to assess therapeutic efficacy and study cough mechanisms. It is not a routine test in clinical practice. Patients inhale nebulized aerosol particles, which stimulate the cough receptors. Capsaicin is commonly used for the cough provocation test. The cough sensitivity is expressed as the cough threshold C5, defined as the lowest concentration of capsaicin inducing ≥5 coughs (C5).The concentration that induces ≥2 (C2) or ≥5 (C5) coughs is an indicator of cough sensitivity. In China, the reference value for C5 in the capsaicin provocation test in normal subjects is ≥125 mol/L.[36] Increased cough sensitivity isan important characteristic of chronic cough, and is frequently observed in AC, GERC, UACS, CVA etc.[36] In addition, significantly increased cough sensitivity is identified in viral post-infectious cough (VPIC).[37] The cough provocation test is safe, well tolerated, and repeatable, and is useful in identifying patients with cough hypersensitivity, and to quantitatively evaluate chronic cough. However, the cough provocation test cannot be used to assess cough frequency and severity.[37] In Europe and USA, women have higher cough sensitivity than men.[38]

Diagnosis and management of CC due to common etiology

Common causes of chronic cough including CVA, UACS, EB and GERC should be initially considered when diagnosing chronic cough; AC is also a common cause of chronic cough. The common causes account for 70–95% of cases of chronic cough.[32] Since a majority of patients with chronic cough are not related to infection,[6] antibiotics should be not be used.

Upper Airway Cough Syndrome (UACS)—Postnasal Drip Syndrome (PNDS)

Postnasal Drip Syndrome is characterized by cough, which may result from the direct or indirect stimulation on the cough receptors in the postnasal and pharyngeal areas. Because it is not clear that upper airway-related cough is caused by direct stimulation of postnasal dripping or stimulation on upper airway cough receptors by inflammation, the ACCP Guidelines for Diagnosis and Management of Cough [2006] suggested using the term UACS to replace PNDS.[6] However, this change in terminology remains controversial.[39] Since PNDS is more intuitive and visual in a certain proportion of patients with typical postnasal dripping, this guideline continues to use PNDS.

Upper airway cough syndrome/ postnasal drip syndrome is one the most common causes of chronic cough, generally related to rhinitis and sinusitis. The diagnosis of UACS/PNDS

are confirmed by the effectiveness of empirical treatment.[32] In addition to nasal diseases, UACS/PNDS may be related to throat and pharynx diseases, including chronic laryngopharyngitis and chronic tonsillitis.[20] Chronic cough may also be caused by cough hypersensitivity.[40]

Clinical manifestation

(I) Symptoms: in addition to cough and sputum production, other symptoms include nasal congestion, excessive nasal secretions, frequent throat clearing, post-laryngeal mucus adherence, and postnasal dripping. Allergic rhinitis can also present with nasal itching, sneezing, and watery nasal mucus production. Rhino-sinusitis usually presents with nasal congestion, purulent nasal mucus, and can be accompanied occasionally with facial ache/swelling, and abnormal sense of smell.[41] (II) Signs: the common signs of allergic rhinitis include pale or swollen nasal mucosa, and clear or sticky mucus in the nasal tract and in the bottom of nasal cavity. For non-allergic rhinitis, the nasal mucosa shows hypertrophic or congestive changes, and the oropharyngeal mucosa may have "cobblestone- like changes" or post-pharyngeal mucus adherence. (III) Auxiliary examinations: sinus imaging may reveal signs of chronic sinusitis, including mucosal hypertrophy and fluid within the sinus cavity. Seasonal cough suggests the possibility of contact with specific allergen (such as flower pollen, dust mites) and the allergen skin prick test is helpful for the diagnosis. Chronic sinusitis can be divided into subtypes based on etiology: viral, bacterial, fungal, and allergic sinusitis. Nasal polyps may occur with UACS/ PNDS. If sinusitis is suspected, CT imaging should be initially performed, and nasal endoscopy, allergen skin prick tests, and immunological tests should be selected when necessary.

Diagnosis

The etiological causes of UACS/PNDS can involve several conditions of the nose, sinus, pharynx, and throat and multiple nonspecific symptoms and underlying signs. Diagnosis should be made based on the history, physical examination, and tests. Effective treatment to the disease, following by exclusion of lower airway diseases or GERC is recommended. The criteria for diagnosing UACS/PNDS are:[7] (I) paroxysmal or persistent cough, often in the daytime and rare after sleep; (II) history and clinical manifestations of nasal and/or throat conditions; (III) auxiliary tests supporting nasal and/or throat conditions; (IV) cough improve after specific therapy. Treatment should be determined based on potential conditions related to UACS/PNDS.

Treatment

(I) Etiological therapy: (i) for non-allergic rhinitis and the common cold, first-line treatment consists of the first- generation antihistamines and decongestants, which are efficacious in most patients within several days to two weeks; (ii) intranasal ICS, including budesonide, fluticasone propionate and betamethasone acetate, and oral second- generation antihistamines is used for allergic rhinitis.[42] Second-generation antihistamines include loratadine, desloratadine, and desloratadine citrate disodium. If second- generation antihistamines are not available, first-generation antihistamines can be used with the similar clinical response except for the greater drowsiness. Leukotriene receptor antagonists are effective to allergic rhinitis.[43] For patients

with severe allergic rhinitis that fails to respond to routine treatment, immunological therapy to specific allergens may be effective. However, immunological therapy require a longer time to demonstrate effectiveness.[42] (iii) Chronic sinusitis: (a) bacterial culture of nasal secretions in patients with chronic sinusitis primarily identify Staphylococcus aureus, Staphylococcus epidermis, and Streptococcus pneumonia that are generally colonized bacteria related to acute onset of d is ea s e. Moreover, culturing bacterial colonies can result in the formation of bacterial biofilms.[44] In general, bacterial sinusitis is caused by a mixed infection, and broad-spectrum antibiotic therapy is necessary. The antibacterial spectrum should cover Gram-positive, Gram-negative, and anaerobic bacteria. For patients with acute onset, the therapeutic duration should be no less than 2 weeks, and for patients with chronic diseases treatment should be longer than 2 weeks. Amoxicillin/clavulanic acid, cephalosporins, or quinolones are the most commonly used antibiotics.[31] (b) Evidence to support the efficacy of long- term low-dose macrolides for chronic sinusitis treatment is limited.[45] Long-term treatment with macrolides are not recommended. (c) Combined regimens with nasal ICS for more than 3 months are recommended. For patients with chronic sinusitis and coexisting nasal polyps, ICS can be used to avoid unnecessary operation.[46] Sequential treatment with ICS following oral steroids has better efficacy than ICS alone.[47] d. It is uncertain whether surgical or medical treatment has a better response.[48] However, when medical treatment is not satisfactory, nasal endoscopic surgery can be considered.[49] (II) Symptom- targeted treatment: (i) local decongestants can relieve the congestion and swelling of the nasal mucosa and help drainage of secretions, and alleviating the nasal congestion. However, long-term use is not recommended because of the potential to develop medicamentous rhinitis. The therapeutic course of nasal decongestant spray is less than 1 week.[50] The combination of first-generation oral antihistamines plus decongestants is recommended for 2–3 weeks.[51] (ii) Mucolytics (carbocisteine/ erdosteine) may be beneficial for chronic sinusitis.[52] (iii) Nasal washing with normal saline can provide an effective therapy for chronic nasosinusitis and chronic rhinitis.[53] Avoidance or reduction of the exposure to allergens is helpful to relieve the symptoms of allergic rhinitis.

Cough Variant Asthma

Cough variant asthma is an atypical form of asthma and one of the most common causes of chronic cough.[54] Itpresents with cough as the predominant or sole symptom. There is no wheezing or dyspnea, expect to bronchial hyperresponsiveness. A multicenter prospective study showed that CVA accounted for 33% of chronic cough in China (62). In some patients, cough may be the sole or predominant symptom despite significant impairment in lung function. Cough may become the predominant symptom after wheezing has improved in classic asthmatics.[6]

Clinical manifestation

Patients have severe, irritating dry cough, particularly at night or early morning.[21] The patients are sensitive to cold air, dust, odors, and smoke, but these factors alone can trigger other causes of chronic cough.[21]

Diagnosis

Diagnosis is based on history, physical examination, the bronchial provocation test, and the response to asthmatic treatment. Responding well to bronchodilators is an important feature of CVA. However, a few CVA patients (approximately 30%) are not responsive to bronchodilators alone[55] and the response to bronchodilators is not necessary as a diagnostic criterion of CVA. Average PEF variation can be selected for diagnosis, if the bronchial challenge test is not available. Sputum eosinophilia and elevated FeNO level suggest a diagnosis of CVA.[25]

The following diagnostic criteria for CVA are recommended:

(I) Chronic cough, usually with irritating cough occurring during the night;

(II) Positive bronchial challenge test (fall in FEV1 from baseline of ≥20% with 12.8 micromole of methacholine or with 7.8 micromole of histamine), or average daily diurnal PEF variability ≥10% over 2 weeks, or positive bronchodilator reversibillity test (increase in FEV1 ≥12% and 200 mL from baseline, 10–15 minutes after 200–400 mcg albuterol or equivalent); (III) Cough resolved after asthma treatment.

Treatment

The therapeutic principles for CVA are the same as those for typical asthma . (I) Combined treatment with ICS plus bronchodilators can improve the cough more rapidly and effectively than treatment with ICS or a bronchodilator alone.[56] A combination of ICS and bronchodilator (β2 receptor agonist), such as budesonide/formoterol and fluticasone/formoterol, is recommended. The treatment should last for more than 8 weeks, and in some patients, long-term treatment may be required. (II) A short-term oral corticosteroid (10–20 mg/d, for 3–5 days) is recommended for patients refractory or less responsive to ICS treatment, or in patients suffering from severe inflammation of the airway. If patients are not responsive to oral corticosteroids, the patient should be evaluated again. A false positive provocation test or the existence of other diseases, such as early-stage eosinophilic granulomatosis with polyangiitis and GERC, should be considered. (III) Leukotriene receptor antagonists are effective in improving cough, airway inflammation, and the quality of life.[57] For a minority of patients refractory to treatment with ICS, leukotriene receptor antagonists may be effective. However, the treatment course and effects of inhibition on airway inflammation need to be further studied.

Prognosis

About 30–40% patients with CVA will develop typical asthma. A longer duration of disease, higher airwayhyperresponsiveness, and higher level of eosinophils in induced sputum are the risk factors for developing classic asthma. Long-term use of ICS may be helpful to prevent development into typical asthma.[58]

Eosinophilic Bronchitis

Eosinophilic bronchitis is one of common causes of chronic cough and accounts for 13–22% of chronic cough.[54] Characteristics of EB include chronic eosinophilic inflammation of airway, inflammation of the central airway, and with more infiltration of mast cells which is located more in the airway smooth muscle cells. These pathologic features may explain why there is a lack of bronchial responsiveness in EB. The degree of inflammation and level of oxidative stress are lower than in patients with CVA.[59] Approximately one-third of the patients have concurrent with allergic rhinitis.[29]

Clinical manifestations

Patients present with dry cough or a little mucoid sputum that is more common during the day. Patients are often sensitive to smoke, dust, odors, and cold air, which induce cough. Patients do not have wheezing or dyspnea. The pulmonary ventilation function and variations of PEF are normal without signs of airway hyperresponsiveness.

Diagnosis

Eosinophilic bronchitis shares similar clinical features to CVA. Sputum eosinophilia is the key to diagnosis, with eosinophils being more than 2.5% of cells in sputum.[60] The sensitivity of FeNO is not high for diagnosis of EB, but FeNO of >32 ppb suggests eosinophil-related chronic cough (e.g., EB or CVA).[28] Exposure to ocyanic acid and chloramine in flour can induce EB.[61] Occupational factors, the history, eosinophil counts in induced sputum (or bronchoalveolar lavage fluid), airway responsiveness, and the response to steroid treatment should be considered when diagnosing EB,. The following diagnostic criteria are recommended: (I) chronic cough, presenting as irritating dry cough or with bit amounts of sticky sputum; (II) unremarkable chest radiographic findings; (III) normal pulmonary ventilation function, a lack of airway hyperresponsiveness, and normal average weekly PEF variation; (IV) sputum eosinophil count $\geq$ 2.5%; (V) exclusion of other diseases with eosinophilia; (VI) cough improves after treatment with corticosteroids.

Treatment

Eosinophilic bronchitis patients respond well to corticosteroids. Cough will be resolved or relieved shortly after the treatment. The use of ICS is the first therapeutic option, and treatment course with more than 8 weeks is recommended. Initial treatment is a short course of oral prednisone (10–20 mg/d for 3–5 days)[20] followed by ICS. If the patients show no response to the treatment with low-dose corticosteroids, systemic diseases related to eosinophilia, including hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis, should be considered.

Prognosis

Over half of the EB patients will relapse after treatment. Patients with concurrent rhinitis and persistent eosinophilic inflammation are at risk for recurrence.[29] Previous

reports showed that a small proportion of patients with EB develop chronic airway obstructive diseases (asthma or COPD).[62] A recent study with a large sample and long-term follow-up demonstrated that only 5.7% patients with EB would develop asthma, suggesting that EB might be a distinct disease and not an early stage of asthma, COPD.[29]

Gastroesophageal Reflux-Related Cough

Gastroesophageal reflux-related cough is a special kind of gastroesophageal reflux disease that presents with chronic cough as the sole or predominant symptom. Studies have showed that GERC is a common cause of chronic cough.[23,32] The prevalence of patients with GERC is lower in China than that in Western countries. The pathogenesis of GERC involves microaspiration, esophageal-bronchial reflux, esophageal motility dysfunction, autonomic nervous system dysfunction, or neurogenic airway inflammation.[63] Esophageal-bronchial reflux plays an important role in GERC. In addition to gastric acid reflux, cough in some patients may be related to abnormal nonacid reflux that is a weakly acidic or alkaline reflux, such as bile reflux.

Clinical manifestations

Apart from cough, 25–68% of patients with GERC have classical reflux symptoms, such as regurgitation, heartburn, and belching. However, cough may be the sole symptom in some patients.[64] Cough generally occurs after meal, daily in an upright position. The cough is usually nonproductive (dry) or accompanied by small amounts of mucoid sputum, and is triggered or aggravated by ingestion of acidic or fatty foods.[64]

Diagnosis

(I) Chronic cough primarily during the day. (II) 24-h ambulatory esophageal pH monitoring or multi-channel intraluminal impedance-pH monitoring (MII-pH) shows a DeMeester score of $\geq$12.70[65] and symptom association probability (SAP) of $\geq$80%.[66] A symptom index of $\geq$45% is useful for the diagnosis of GERC.[67] (III) Cough resolves or disappears after anti-reflux treatment.

It should be noted that negative findings of 24-h ambulatory esophageal pH monitoring do not exclude GERC as cause of cough. In a minority of patients with concurrent or predominant nonacid reflux (e.g., bile reflux) or intermittent reflux, the results of the ambulatory esophageal pH monitoring may be normal. Esophageal pH monitoring combined with intraluminal impedance can identify nonacid reflux. When 24-h ambulatory esophageal pH monitoring or MII-pH is not available, the followings indicate GERC: (I) cough related to eating, such as coughing after or during meal; (II) typical reflux symptoms, including heartburn, regurgitation, or a score of Gastroesophageal Reflux Disease Questionnaire (GerdQ) of $\geq$8; (III) no evidence of CVA, UACS, or EB, and the cough does not improve with treatment for CVA, EB, or UACS. In patients who meet the above criteria, GERC should be considered as a cause of chronic cough, and diagnostic/empirical therapy for GERC may be initiated.[20,21]

Proton pump inhibitor (PPI) is recommended for patients suspected to be due to GERC.[68] A standard or intensive dose of PPI (e.g., omeprazole 20–40 mg, twice daily) should be prescribed for no less than 2 weeks. If cough disappears or is significantly improve after reflux treatment, GERC can be determined. However, GERC cannot be ruled out if patients fail to improve with PPI treatment. When compared with the laboratory investigations (24-h ambulatory esophageal pH monitoring or MII-pH), a trial of PPI is simpler and more cost-effective,[68] but has the disadvantage of lower specificity.

Treatment

(I) Lifestyle modification: weight loss is recommended for the overweight patients. Patients should avoid late-night meals, and foods which are acidic, spicy, or fatty, coffee and acidic beverages, smoking and strenuous exercise. (II) Antacids: acid suppression is recommended as the standard treatment for GERC.[69] Common choices are either PPI (omeprazole, lansoprazole, rabeprazole and esomeprazole, etc.) or H2 receptor antagonists (ranitidine or other equivalent drugs). Generally, PPI are superior to H 2 receptor antagonists in acid suppression and symptom relief, and should be administered 30–60 min pre-prandially,[70] with a treatment course of at least 8 weeks. (III) Prokinetic agents: most patients with GERC have esophageal motility dysfunction, therefore the addition of prokinetic agents (domperidone and mosapride) is recommended.[6]

If standard antireflux therapy fails to resolve the chronic cough in patients with evidence of reflux, the dosing scheme and treatment course should be reviewed. In addition, refractory GERC due to nonacid reflux should be considered. The persistent cough may not be related to reflux or may be caused by multiple etiologies.[71] If the treatment fails, it is recommended to perform 24-h ambulatory esophageal pH monitoring or MII-pH again to exclude the possibility of under- treatment or misdiagnosis.

Refractory GERC can be treated with baclofen. Adverse effects of baclofen include drowsiness and fatigue.[71] When the treatment with the standard dose of PPI is not effective, increasing the dose of PPI may be helpful.[72] If treatment with one kind of PPI fails, switching to another PPI may be effective.[73] Combining H2 receptor antagonist with PPI may ameliorate cough symptoms due to refractory gastroesophageal reflux or nighttime acid reflux.[74] If necessary, a consultation with gastroenterology specialists can determine the optimum therapeutic regime. For a minority of patients with severe reflux resistant to pharmacological treatment, antireflux surgery (primarily laparoscopic fundoplication) or endoscopic therapies may be effective[75]. Currently, no data are available that directly compare the efficacy of endoscopic therapy with medical management. Because of postoperative complications and the potential for relapse, surgical indications should be clearly defined. It is recommended that antireflux surgery be considered only when the cough is poorly controlled, severely impacts the patient's quality of life, and despite acid suppression, significant residual reflux identified by 24-h ambulatory esophageal pH monitoring or MII-pH.

Atopic Cough

Atopic cough is a kind of chronic cough that characterized by atopy, and response to corticosteroids or antihistamines, but no sputum eosinophils and airway responsiveness. Patients present with an irritating, paroxysmal dry cough, that occurs during the day and night. Cough can be induced by smoke, dust, cold air, and talking, and is usually accompanied by itching of the throat.

The surveys conducted in China demonstrated that AC was one of the common causes of chronic cough.[32] In patients with chronic cough, without airway hyperresponsiveness, and a sputum eosinophilia, AC should be considered as the possible cause of cough. The pathogenesis of AC has not been fully elucidated.

Japanese researchers reported that anti-fungal treatment is effective in fungus-induced cough where fungi have colonized the airway, serving as allergen.[76] It is unclear if fungal-related cough occurs in other countries and regions and further studies are needed.

The following diagnostic criteria are recommended

(I) Chronic cough, primarily dry, irritating cough. (II) Normal pulmonary ventilatory function and bronchial responsiveness. (III) Lack of sputum eosinophilia. (IV) Presence of one of the followings: (i) a history of allergic diseases or exposure to allergens; (ii) positive allergen skin prick test; (iii) increased level of totalserum or positive specific IgE. (V) Clinical response to corticosteroids or antihistamine treatment.

Treatment

Corticosteroids, antihistamines, or a combination of both are the treatment options. The treatment course of ICS should last for more than 4 weeks, and oral corticosteroids can be used initially for a short period (3–5 days) for treatment.[20]

Diagnosis and management of CC of the other etiologies

Chronic Bronchitis

Chronic bronchitis is defined as a productive cough that lasts for 3 or more months per year for at least two consecutive years, after the other causes of chronic cough have been excluded. The cough is aggravated in the winter, with white foamy or mucoid sputum. Nocturnal cough may also occur during acute exacerbations.

Based on the epidemiological investigation, chronic bronchitis is common, but accounts only for a small proportion of the patients with chronic cough referred to specialty clinics. The discrepancy may be related to the lack of objective standard for the diagnosis of chronic bronchitis, therefore patients with chronic cough due to other diseases may be misdiagnosed as chronic bronchitis. Since chronic bronchitis is an early stage or subtype of COPD, the severity of chronic cough and sputum is associated with an increased frequency of acute exacerbation and increased mortality.[77]

Investigations in Asian regions demonstrated that acute exacerbations of chronic bronchitis are generally caused by Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Klebsiella pneumoniae, Pseudomonas aer uginosa , and Acinetobacter baumannii . Epidemiological studies should be conducted to determine antibiotic resistance in those regions, providing guidance for selection of antibiotics.[78] Moxifloxacin and levofloxacin are the commonly used antibiotics for the treatment of acute exacerbation of chronic bronchitis due to their broad anti-bacterial spectrum and few side effects.[78]

Chronic Obstructive Pulmonary Disease

The symptom burden from cough is high in COPD—a fifth of patients with moderate airflow limitation report cough as a highly distressing symptom.[79] Patients rank cough as the second most prevalent symptom. Chronic cough with sputum production is common and is often considered to be the first symptom of COPD. Patients with chronic cough have an increased risk of disease progression and exacerbations that might require admission to hospital. There are opportunities to evaluate speech pathology treatment and pharmacologic therapy of cough in COPD.[80]

Bronchiectasis

Bronchiectasis is characterized by irreversible bronchial enlargement and distortion due to the chronic inflammation. The primary abnormality is in the subsegments of the bronchi. Typical clinical manifestations include chronic cough, production of mucoid or purulent sputum, and intermittent hemoptysis, which may coexist with chronic rhinosinusitis. Diagnosis for patients with a typical medical history is not challenging, whereas m is diagnosis can easily occur in patients with mild bronchiectasis and unclear medical history. In patients with suspected bronchiectasis, positive findings in the chest radiographs (such as curly hair sign) may suggest the diagnosis, but high-resolution chest CT is the best method to confirm the diagnosis.[81]

Regular use of ICS is not recommended for the patients with stable bronchiectasis.[82] Nonetheless, the combination of ICS with long acting beta agonists (LABA) or long acting antimuscarinics (LAMA) may improve cough in patients with bronchiectasis who have chronic airflow obstruction or airway hyperresponsiveness.[81] Postural drainage is helpful in eliminating the accumulated sputum. Intravenous administration of antibiotics is recommended in patients with severe conditions, including highly pathogenicbacteria resistant to oral antibiotics, or failure to respond to oral antibiotics.[82] Macrolides are helpful to improve symptoms and reduce the risk of acute exacerbation in patients with stable bronchiectasis, bacterial resistance and the adverse effects of long-term antibiotics administration should be considered.[83] Regular inhaled mucolytics are not recommended.[84] Statins[85] and mannitol inhalation may also help manage bronchiectasis, but this is not routinely recommended.[86]

Bronchial Tuberculosis

Bronchial tuberculosis is not rare among patients with chronic cough. Bronchial tuberculosis is generally co-existed with pulmonary tuberculosis, but may exist alone in a considerable proportion of patients. The main symptoms are chronic cough, possibly concomitant with tuberculosis-associated symptoms including low-grade fever, night sweats, and emaciation. For some patients, cough is the only manifestation. Localized inspiratory, dry rales can occasionally be heard. In clinical practice, patients with bronchial tuberculosis and normal chest radiographic findings may be misdiagnosed and under diagnosed.[87]

If bronchial tuberculosis is suspected, sputum smears hould be conducted first for the detection of acid-fast bacillus. Patients may have a Mycobacterium tuberculosis- positive sputum culture. Pulmonary radiographic signs may be minimal, whereas abnormal findings of the trachea and main stem bronchi, including bronchial wall thickening, airway stenosis, and obstruction can be detected. Bronchial lesions especially lesions located in the subsegmental bronchi may be identified by CT. Computed tomography, particularly high-resolution CT, is more sensitive than radiographs. Bronchoscopy is the important approach to confirm bronchial tuberculosis, which has a high positive rate when combined with routine brushing and tissue biopsy.[88]

Cough in Idiopathic Pulmonary Fibrosis

Interstitial lung diseases are a heterogeneous group of diseases that result in progressive functional decline and death. Idiopathic pulmonary fibrosis is the most common of these diseases and cough is a prominent but not universal symptom.[89] Cough is estimated to be present in 84% of patients with idiopathic pulmonary fibrosis and is more prevalent in patients who have never smoked or who have more advanced disease.[90] The cough can be extremely debilitating, with a detrimental effect on quality of life,[91] and it is an independent predictor of disease progression.[90] The cause of this cough is not clear. Mechanical factors may be at play, including destruction of the cough inhibitory fibers as the lung is distorted by the fibrotic process,[89] leading to increased cough sensitivity.[89-91] Cough reflex sensitivity in this disease responds to prednisolone and corticosteroids,[92] Speech pathology intervention for cough associated with pulmonary fibrosis has not been studied.

Cough due to ACEI or other medications

Cough is a common adverse event of ACEI, the incidence is 5–25% in patients taking the drugs, and ACEI-induced cough accounts for 1.7–12% of chronic cough.[93] The independent risk factors are smoking, previous ACEI- induced cough,[94] and nationality (East Asian or Chinese population).[95] Cough is not related to the age or sex of the patient[96] or the dose of ACEI.[97]

The diagnosis can be confirmed when cough resolves after ACEI cessation. Usually, cough will disappear or be significantly relieved within 1–4 weeks after discontinuing the drug.[6] For patients with prior administration and the current risk of ACEI-induced cough,

angiotensin II receptor antagonists can be used to replace ACEI for the treatment of the underlying disease.

Cough can also be caused by mycophenolate mofetil, macrodantin, propofol, β-receptor blockers, leflunomide, simvastatin, γ-interferon, and omeprazole.[98]

Bronchogenic Carcinoma

Cough is an early-stage and common symptom of central bronchogenic carcinoma, with an incidence of 25–86%.[99] Chest radiographs may be normal in the early stage, therefore misdiagnosis and under diagnosis may occur. In patients with a history of smoking, irritating dry cough, bloody sputum, chest pain, emaciation, and changes in the initial characteristics of cough, lung carcinoma should be suspected. The diagnosis can be confirmed by radiological imaging and bronchoscopy biopsy. Treatment for cough due to lung carcinoma should target at the underlying disease, including radiotherapy, chemotherapy, radiofrequency ablation, and surgical resection.[100] Postoperative cough in patients with lung carcinoma is a common issue in clinical practice, and the underlying mechanisms are unclear. The cytokine inhibitor suplatast tosilate resolves cough.[99] Protracted and refractory cough may be attenuated with the treatment of central-acting or peripheral- acting antitussives.

A systematic review of cough treatments in cancer found some effect of morphine, codeine, dihydrocodeine, levodropropizine, sodium cromoglycate, and butamirate citrate linctus (cough syrup), although all of the studies had risk of bias.[101] Speech pathology treatment for cough suppression in cancer has not been studied.

Psychogenic Cough

Psychogenic cough, also known as habitual cough, is caused by severe psychological conditions. It is more common in children than in adults. Within the classifications of mental disorders, there is no diagnostic terminology for psychogenic cough, and the pathogenesis of psychological cough may involve not only psychological factors, but also disorders of central nervous system control. The term of somatic cough syndrome may be a better descriptor.[102] Cough occurs only during the daytime, and disappears when focusing and when asleep. Multiple psychogenic factors such as sensation, belief, mood, learning, and habit can stimulate the cough, and these factors would be addressed in clinical practice.[103]

There are no specific diagnostic criteria for psychogenic cough. When the common and rare causes of chronic cough are excluded, psychogenic cough should be considered. For the children with psychogenic cough, psychological intervention including suggestive therapy and psychological counseling may be beneficial.[104] The short- term use of antitussives can be used as adjuvant therapy. For the adult patients, antianxiety or antidepressant medications, in combination with psychological interventions, may be helpful.

Chronic Cough and OSA

The prevalence of OSA increases with age and body mass index.[105] Obstructive sleep apnea prevalence based on values of AHI ≥ 5 increases with age, from 8% in 20- to 44-year-olds to 20% in 45- to 64-year olds, and to 30% in 65- to 100-year-old men.[105] Even though the prevalence of cough is quite high in the general population, unexplained cough is higher in middle-aged females, with the mean age of chronic cough in studies being 46-60 years.[106] This overlaps with the age group in which the prevalence of OSA as assessed by clinical and laboratory criteria (AHI ≥ 10) starts peaking.[105] Even though the prevalence of sleep apnea is lower in adult females, there is a significant increase in OSA prevalence in postmenopausal females, with a higher prevalence of REM-related sleep disordered breathing in women under the age of 55 years.[107] In addition, sleep apnea tends to be underdiagnosed in women because of atypical manifestations of sleep disordered breathing.[108] The relationship between OSA and BMI is relatively a linear one, especially until the age of 60.[108] Even a 10% increase in weight in subjects with mild or no OSA increases the risk of developing significant OSA (AHI ≥ 15) by 6-fold.[109] In contrast, despite the high prevalence of cough reported in general population that has been attributed to airway diseases, GERD, smoking, and air pollution,[110] only 2 studies have reported BMI values in their subjects.[111,112] One retrospective study showing linkage between chronic cough and OSA had a mean BMI of 32 in its 75 chronic cough subjects, with a female-to-male ratio of 1.5.7 The study by Smith et al. looking at cough-reflux associations found a mean BMI of 27.3 in 71 subjects, with a femaleto-male ratio of 77%.[112] Future studies on chronic cough should report the BMI values of their subjects, especially given the associations of obesity with asthma and GERD,[113] conditions that are implicated often in the etiology of chronic cough.[114] sleep apnea can lead to cough. Obstructive sleep apnea worsens the postulated triggers of GERD, UACS, and asthma. In addition, OSA is associated with a higher frequency of upper respiratory tract infections that may initiate cough.

Obstructive sleep apnea and GERD:

Obstructive sleep apnea and GERD are inextricably related with the plausible increase in reflux during the increasing negative intrathoracic pressures encountered during an apneic episode.[115] Studies have shown increased reflux events in patients with OSA, characterized by increased nocturnal time spent with an esophageal pH < 4.0 and delayed esophageal clearing.[116] However, a temporal relationship between reflux and apneic events has not been clearly established,[116,117] and obstructive apneic events have not been shown to decrease lower esophageal or upper esophageal tone.[117] A relationship between OSA and non-acid esophageal reflux has not been shown. In addition, the effect of lax lower esophageal sphincter tone,[117] hiatal hernias,[118] and reflux esophagitis[119] in furthering acid reflux in patients with OSA is also unclear. Despite the lack of clear cut mechanistic associations, CPAP therapy improves GERD with CPAP therapy by abolishing apneic spells and reflexly increasing lower esophageal sphincter tone.[116] With regard to chronic cough, a link between chronic cough and OSA occurring through GERD was postulated a decade ago.[120] Even though an improvement in GERD (and possibly non-acid esophageal reflux) can be anticipated in chronic cough patients with concomitant OSA, further studies examining acoustic cough monitoring and combined pHimpedance measurements during apneic episodes are needed.

Obstructive sleep apnea and UACS:

Obstructive sleep apnea can be associated with increases in nasal inflammation that is improved with humidification of nasal CPAP.[121] Nasal inflammation in OSA patients occurs directly from the OSA itself[105] and from the effects of CPAP therapy.[121] Whether there is any relation between nasal inflammation occurring in OSA patients and propensity to cough is unknown. Apart from these studies, the bulk of the literature pertaining to nasal and sinus disease in OSA relates to the effects of increased nasal resistance causing sleep disturbances, particularly in children.

Obstructive sleep apnea can be associated with all major etiologies of chronic cough, upper respiratory infections that initiate chronic cough, and abnormal upper airway pathology There are several likely mechanisms by which obstructive

Obstructive sleep apnea and Asthma:

Current asthma guidelines recommend testing for OSA in overweight or obese patients with poorly controlled asthma.[122] Recent studies indicate that the association of OSA with uncontrolled asthma may be independent of obesity.[123] A number of different pathways can bring about heightened airway inflammation and hyperresponsiveness in patients with OSA.[124] These include local and systemic mechanisms that can cause heightened airway inflammation and potentiate asthmatic responses in patient with OSA.[124]

Obstructive sleep apnea and Triggering Respiratory Infections:

Obstructive sleep apnea patients experience frequent respiratory infections, especially common colds.[125] These upper respiratory infections initiate cough in a third of patients with chronic cough.[111]

Obstructive sleep apnea and Upper Airway Pathology:

Abnormalities in the soft palate, uvula, and upper airway musculature are invariable in patients with OSA secondary to trauma stemming from recurring obstructive events.[126] The implications of upper airway abnormalities in triggering cough receptors are unknown.

Obstructive sleep apnea can be associated with airway inflammation

Obstructive sleep apnea and obesity have been shown to increase airway inflammation.[127] While it is not clear whether the airway inflammation seen in OSA patients can initiate or perpetuate chronic cough in susceptible patients, the association of airway inflammation with OSA points to the possibility of airway inflammation being the substrate for chronic cough. It is therefore imperative to understand the mechanisms of airway inflammation in OSA patients that may be responsible for cough. Since obesity per se can lead to airway inflammation,[128] there exists controversy about the contributions of OSA vs. obesity in the causation of increased airway inflammation in obese sleep apnea patients.[129] Similarly, bronchial hyperreactivity has been reported in OSA,[130] with the additional development or worsening of bronchial hyperresponsiveness with CPAP.[130] Bronchial wall thickness is increased in patients with OSA and shows a positive correlation with AHI, the most widely used measure of OSA severity.[130]

A number of mechanisms have been postulated to increase airway inflammation in sleep apnea patients:

a. Recurrent trauma secondary to obstructive apnea.[127,129] Even though this kind of mechanical trauma is well understood in the case of upper airways,[131] models explaining the mechanisms of lower respiratory tract inflammation from recurrent upper airway obstruction are lacking.

b. Ischemia-reperfusion injury to lower airways occurring from obstructive episodes.[127,132] This remains the most widely ascribed mechanism for airway inflammation secondary to OSA. The correlation of degree of hypoxemia (most profound in REM sleep of OSA patients) and degree of lipid peroxidation measured in exhaled breath condensates lends weight to this hypothesis.[132]

c. Coaggregation of obesity in OSA patients.[127,130] Obesity can be independently associated with airway inflammation and ongoing research to explain the occurrence of a higher prevalence of asthma in obese patients has focused on leptin-mediated systemic inflammation.[133] Adipose tissue acts as an endocrine organ serving as a reservoir for cytokines (adipokines) that can lead to low-grade systemic inflammation that may account for the increased inflammation observed in the respiratory tract.[133]

d. Spillover from systemic inflammation secondary to OSA.[134] Apart from local inflammation brought about the above-mentioned mechanisms, systemic inflammation occurring in OSA patients is manifested in the form of increased levels of C-reactive protein, TNF-α, IL-6, elevated oxidant tone,[135] and increased sympathetic tone.[136]

Positive pressure therapy may improve cough via multiple mechanisms

A case series and a large retrospective study till date have shown a benefit with CPAP on chronic cough.[111] Improvements in these reports occurred in patients that had been tried on multiple other therapies for cough.[111] Interestingly, the clinical profile of patients improving with CPAP and those who did not require CPAP therapy does not appear different.[137] CPAP has also been shown to be helpful in treating chronic nocturnal cough that is present in the supine position.[105] This study had a small sample size and did not clearly address if these patients underwent a polysomnogram.[105]

A number of potential mechanisms can explain the improvement of cough with CPAP therapy

1. Continuous Positive Airway Pressure and the cough reflex: Widdicombe's groundbreaking studies on elucidation of afferent vagal activity following lung inflation and deflation identified a variety of stretch receptors.[138] Among these, the tracheal/bronchial rapidly acting receptors and intermediate receptors mediate the cough triggered by mechanical and chemical stimuli.[138] In addition to these stretch receptors, the activation of unmyelinated C-fibers that account for the majority of afferent nerves innervating the lungs leads to cough.[139] While a number of these "cough" receptors are likely to be affected by the increase in pulmonary functional residual capacity induced by positive pressure therapy, it is not clear how stabilization of the mechanical stresses induced during sleep disordered breathing affects peripheral cough sensitivity.
2. Impact of CPAP on the purported etiologies of cough a. GERD: Despite the lack of clear relation between GERD and OSA as discussed above, CPAP therapy has been shown to improve reflux as measured symptomatically[105]and as measured using esophageal pH impedance

measurements.[115,116,119] These benefits may be more pronounced in patients with a patulous lower esophageal sphincter, hiatal hernia, and abnormal esophageal motility.[118] The main mechanism of increased reflux in OSA patients is via an increase in transient lower esophageal relaxations rather than the increased gradient between the negative esophageal pressure and the positive gastric pressure.[117,119] Postulated mechanisms for improvements in CPAP-related reductions in GERD include increases in tone of the lower esophageal sphincter, thereby reducing the gradient for reflux.[117,119] In addition, patients on CPAP have less frequent and lesser durations of transient lower esophageal sphincter relaxations.[117,119] The effect on GERD by CPAP has been postulated to be the main mechanism by which CPAP can improve chronic cough.[120] b. Asthma: No studies exist on the effect of CPAP on cough-variant asthma. While large scale prospective studies on asthma improvement following OSA treatment are lacking, current studies indicate an improvement in asthma control following CPAP therapy.[140] There is, however, a concern about CPAP use causing bronchial hyperactivity.[141] c. UACS: CPAP use has been shown to cause increased nasal inflammation that can improve with heated humidification.[121]

3. Effect of CPAP on airway inflammation: Measurements of exhaled breath condensates in OSA patients show improvement following CPAP therapy.[132] In addition, multiple studies show improvement in systemic inflammation following CPAP therapy in OSA patients.[142] How this improvement in systemic and airway inflammation can improve chronic cough remains to be proven. In addition to the above, while the mechanisms perpetuating chronic cough remain elusive, factors that lead to resolution of cough remain largely unexplored. It is expected that patients resolve cough following acute respiratory infections with the inflamed airway "healing" with time following resolution or removal of the acute insult. However patients with OSA may not be able to "heal" this acute insult due to sleep deprivation related immune dysfunction[143] and/or perpetuation of ongoing mechanical and inflammatory insults to the respiratory tract during apneichypopneic episodes. The impact of restorative sleep in improving disease-related injury and inflammation may be most significant in the respiratory tract, where the effects of recurrent mechanical trauma coupled with inflammatory effects of arousals has the potential to cause continuation of airway inflammation. While most series have concentrated upon the approach and management to a single protracted episode of cough, 18% of patients' cough reoccurs within 3 months of follow-up.[105] While this recurrence of cough has been attributed to ongoing reflux, UACS, or CVA,[105] untreated OSA as a cause of cough recurrence has not been investigated.

Other uncommon or rare causes of CC

The uncommon and rare etiologies account only for a minor proportion of CC, but involve a broad spectrum of conditions. Some uncommon or rare causes of chronic cough reported in the literatures are listed in Table 2.

Unexplained chronic cough, chronic cough hypersensitivity syndrome

In most patients with CC, an etiologic diagnosis can be determined and cough can resolve after treatment. However, in some patients with chronic cough an etiologic diagnosis cannot be confirmed after a comprehensive investigation and therapy aimed at known causes. Traditionally, this type of cough is called unexplained cough, chronic refractory cough,

or idiopathic cough. The diagnosis of unexplained chronic cough should include the following: all known causes of CC have been excluded through systematic evaluation and patients fail to respond to etiology-targeted treatment. In these patients, many of whom are middle-aged women, triggered by acute infection of upper airways. In addition to chronic dry cough, patients have an itchy throat or an uncomfortable sensation in the throat. Patients are sensitive to smoke, dust, abnormal smells, and cold air, and sometimes talking or nervousness can induce coughing. Because the patients show the characters of cough hypersensitivity, a new diagnostic term, chronic CHS is now used to describe patients with this type of chronic cough.[144]

Based on the pathophysiological characteristics of CHS, the treatment should be aimed to reduce the sensitivity of cough. However, therapeutic options for CHS including medicinal and non-medicinal treatment are limited. Clinical studies show that neuromodulators, for example gabapentin, are effective in the treatment of CHS.[145] Other medicines including amitriptyline, baclofen, carbamazepine, and pregabalin may be useful in CHS.[146] Other potential treatments including speech therapy, and cough suppression physical therapy. Cough suppression physical therapy improves the quality of life related to cough, cough hypersensitivity, and cough frequency.[147]

Table 2 Uncommon or rare causes of chronic cough

Anatomical area	Causes
Upper airway diseases	Subglottic pleomorphic adenoma, subglottic mucosa-associated lymphoid tissue lymphoma, laryngeal carcinoma, epiglottic hypoplasia, heterotopic salivary gland, enlargement of the tonsils, elongated uvula, obstructive sleep apnea syndrome
Tracheal diseases	Tracheobronchomalacia, ossifying bronchopathy, relapsing polychondritis, tracheobronchomegaly, tracheal stenosis, endobronchial hamartoma, tracheal diverticulum, bronchial foreign body tracheal adenoid cystic carcinoma, tracheobronchial amyloidosis, broncholithiasis
Pulmonary diseases	Pulmonary alveolar microlithiasis, pulmonary fibrosis, pulmonary alveolar proteinosis, lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis
Mediastinal diseases	Cardiac paraganglioma, pericardial cyst, thymoma, post-traumatic pseudo-aneurysm, arrhythmia and left heart failure, esophageal cyst, esophageal cancer, Hodgkin's lymphoma, mediastinal lipolysis
Others	Cervical spondylosis, hepatic cavernous hemangioma, vagus nerve tumor, celiac disease, sublingual thyroid ectopy, external auditory canal cerumen, pleural endometriosis

Empirical management of CC

Successful treatment of chronic cough depends on etiologic diagnosis. Etiologic diagnosis may require specific equipment and techniques, which are not available in primary care hospitals, and are difficult for patients of low socioeconomic status to afford. Consequently, empirical treatment is an alternative in cases where conditions are limited.[148] Empirical treatment should follow the principles below.

(I) Treatment schedules targeting the common causes of CC are preferred. Many studies have referred that the common causes of CC are CVA, UACS/PNDS, EB, AC and GERC.[135,137]

(II) Possible causes of CC should be identified based on the patient's medical history.[148] If nonproductive irritating cough is predominant symptom and cough frequently occur at night or early morning, initial treatment for CVA is recommended. If cough is concurrent with overt acid regurgitation, belching, and heartburn, treatment for GERC can be considered. If protracted cough is secondary to the common cold accompanied by runny nose, nasal congestion, nasal itching, frequent clearing of the throat, and postnasal drip, empirical treatment should initially target UACS/PNDS.

(III) According to the patient and treatment response, chronic cough can be classified into steroid- responsive cough (including CVA, EB and AC), UACS and GERS for empirical treatment. This may reduce the blindness of empirical therapy and increase the success rate.[19] Patient- driven therapeutic strategy in a step-by-step and sequential manner is a diagnostic management regimen, which initially involves the most common causes and simple treatments. The treatment regimens may lead to a longer duration of therapy for patients with chronic cough of uncommon causes. The strategy is targeted at the most common causes first suitable for those patients with unclear characteristics and multiple possible causes of chronic cough.[149] Pseudoephedrine hydrochloride and methoxyphenamine is recommended for the empirical treatment of UACS/PNDS, AC, and PIC.[19] If steroid-responsive cough is suspected, oral administration of low-dose steroids for 1 week is recommended, followed by ICS or combined therapy with β2-receptor agonists.[19]

(IV) For those with purulent sputum or mucus nasal discharge, antibiotics are recommended. Since most causes of CC are not related to infection,[32] antibiotic abuse should be avoided during empirical treatment.

(V) It is recommended that the course of empirical treatment for UACS, PNDS, CVA, and EB should be 1–2 weeks, and that for GERC should be 2–4 weeks. Oral corticosteroids should be given for no more than 1 week.[20] If the patient is responsive to the treatment, the standard therapeutic regimen for the corresponding etiology should be used.

(VI) Empirical treatment may result in the risk of misdiagnosis of severe conditions. Empirical treatment should be used with caution, and serious conditions including bronchial malignant tumors, tuberculosis, and other pulmonary diseases should be ruled out. If empirical therapy is not effective, further investigations should be carried out to identify the etiologic diagnosis.[149]

Cough suppressants and mucolytic agents

Mild cough does not require antitussive treatment. Antitussive agents can temporarily relieve the symptoms, and etiological therapy is the key to cough management. However, if severe dry or frequent cough impacts daily life, antitussive treatment can be prescribed. Mucolytic agents are indicated for patients with productive cough.

Antitussive agents

Antitussive agents can be divided into two types based on the pharmacologic effects: central-acting and peripheral- acting agents. Central-acting agents are those that act on one or several sites of cough center in the medulla oblongata, and peripheral-acting agents act on receptors on afferent or efferent nerves and effectors of the cough reflex arch.[150]

Central-acting antitussive agents

These medications have inhibitory effects on the medulla oblongata. Based on the addiction potential and analgesic effects, they can be further subdivided into narcotic and non-narcotic antitussive agents. The former refers to morphine and its derivatives, which is a powerful cough suppressants. However, because of the possibility of addiction, they should only be used temporarily when other treatments failed. The latter refers to synthetic antitussive agents, such as dextromethorphan and pentoxyverine, which are widely used in clinical settings. (I) Narcotic antitussive agents: (i) Codeine:[150] rapidly and directly inhibits the medulla oblongata and suppresses the cough, and has analgesic and sedative effects as usual. This type of medication can be used for patients who have unexplained severe dry cough or refractory irritating cough, in particular a dry cough with chest pain. (ii) Pholcodine: the effect is similar to codeine, but is less addictive. (II) Nonnarcotic antitussive agents: (i) dextromethorphan: it is similar in effect to codeine without analgesic and sedative effects. Therapeutic dosage usually does not have the inhibitory action on the respiratory center, nor side-effect related to medication addition. Dextromethorphan are recommended for chronic cough in adults.[150] (ii) Pentoxyverine: cough suppressant strength is equal to one-third that of codeine with anticonvulsant and antispasmodic effects. It should be used cautiously in patients with glaucoma or heart failure. (iii) Dextrophan: a metabolite of dextromethorphan with better tolerance. It may replace dextromethorphan for clinical treatment in the future.

Peripheral-acting agents

They primarily act on inhibiting at least one element in the cough reflux arch. These drugs include local anesthetics and mucosal protectors. (I) Narcotine: it is a benzylisoquinolines alkaloid antitussive with effectiveness similar to codeine but without analgesic properties. It is suitable for cough induced by various causes. (II) Benproperine: it is a nonnarcotic drug with pharmaceutical effects 2–4 times greater than that of codeine. It inhibits both peripheral afferent nerves and the cough center. (III) Moguisteine: it is a peripheral non-narcotic antitussive drug, with a relatively stronger effect than that of codeine. (IV) Benzonatate: it is a local anesthetic that is a derivative of tetracaine and inhibits the afferent nerves of cough reflux.

Mucolytics

Mucolytics can improve clearance of airway secretions. The mechanisms of mucolytic agents include: increasing the clearance of secretions, decreasing the viscosity of secretions, and improving ciliary activity. There are a variety of mucolytics available, however, their effectiveness would require more evidence-based data. The common mucolytics are listed below.

Guaifenesin

It increases airway secretions and reduces sputum viscosity. It has been shown to cause bronchial dilation. It is used in combination with antihistamine, antitussive agents, and decongestants.[152]

Myrtol

It is the extract of myrtaceae leaves, a volatile vegetable oil. The major components are eucalyptol, limonene, and alpha pinene. The commonly used preparations are eucalyptus and standard myrtol, which can improve the ciliary movement of the airway and nasal sinus mucosa, and are indicated for acute bronchitis, chronic bronchitis, and rhinosinusitis.[6]

Ambroxol and bromhexine

These are mucolytic agents. Ambroxol is the metabolite of bromhexine, which can decompose the mucus acidic polysaccharide, decrease the viscosity of the secretion, improve ciliary activity, and increase the concentration of antibiotics in the respiratory tract.

N-acetylcysteine

It breaks down the sulfide bonds of the polypeptide chains of the glycoproteins to reduce the viscosity of sputum.

Carbocisteine

It breaks down the disulfide bonds of mucins to reduce the viscosity of secretion. Erdosteine is the precursor of carbocisteine. Oral administration can generate metabolites containing free sulfhydryl to exert pharmacological effect.

Others

Inhalation of hypertonic saline and mannitol can increase hydration of airway secretions, thus improving the rheology of mucus to enhance clearance. They can improve cough clearance in combined with bronchodilators.[86]

Treatment of RCC

Recent ACCP guidelines identified four categories of treatment that were supported by randomized controlled trials (RCTs)—non-pharmacologic therapies, inhaled corticosteroids, neuromodulatory therapies, and other therapies. The two main advances in treatment during the past decade have

been non-pharmacologic approaches, such as speech pathology management, and the use of centrally acting neuromodulators.[153,154] There is not yet evidence to support the use of non-pharmacologic approaches before medical treatment, and thorough medical investigation by a specialist respiratory or general physician or an otolaryngologist is recommended before using non-pharmacologic approaches. Non-pharmacologic therapies A systematic review found support for cough suppression strategies based on speech pathology and physiotherapy.[154] The review included one single blinded randomized controlled trial,[153] three prospective noncomparison studies,[155] and one retrospective review.[156] Meta-analysis was not possible so the included studies are discussed separately below. The RCT investigated 87 patients with chronic refractory cough.[153] Participants received either four sessions of speech pathology intervention for chronic refractory cough or an equivalent course of healthy lifestyle education. The cough score significantly decreased by a mean of 3.9 in the treatment group (95% confidence interval 3.0 to 4.9; P<0.001) and by 0.3 in the placebo group (0.3 to 2.2; P<0.001); the decrease was significantly greater in the treatment group than in the placebo group (mean difference in score 2.8; 1.3 to 4.0; P<0.001). Treatment significantly improved the total symptom score (mean difference before and after treatment 12.7; 9.0 to 16.1; P<0.001) v placebo (2.9; −0.7 to 6.5; P=0.170) and daily limitation score (treatment mean difference 0.7; 0.4 to 1.0; P<0.001) v placebo mean difference 0.3; 0.0 to 0.6; P=0.038). In addition, the clinical judgment of outcome was positive in 88% of participants in the treatment group versus 14% in the placebo group, although this particular measure has a risk of overestimation of treatment effect.

The first prospective study looked at 24 participants with chronic refractory cough, 14 of whom had coexisting PVFM.[155] Participants underwent four sessions of speech pathology management as described previously.[153] Quality of life assessed using the Leicester cough questionnaire (LCQ) improved from 10.5 to 16.2 (P=0.001) in the RCC+PVFM group and from 10.4 to 17.5 (P=0.01) in those with RCC only. Cough reflex sensitivity (capsaicin dose needed to elicit five or more coughs 30 s after administration (C5)) improved from 5.88 μmol/L to 15.7 μmol/L (P=0.008) in the RCC+PVFM group and 2.94 μmol/L to 7.84 μmol/L (P=0.04) in the RCC only group. PVFM resolved in eight of 10 participants. The effect of a speech pathology intervention on cough reflex sensitivity testing was examined in the second prospective study of 17 participants with RCC.[157] After four sessions of the intervention the LCQ score improved from 13.5 to 16.9 (P=0.002)—twice the minimal important difference of 1.3, the smallest change in quality of life considered to be clinically meaningful.[158] Log CRS C5 improved from 0.88 to 1.65 (P<0.0001). Ambulatory cough monitoring showed that cough frequency dropped from 72.5 to 25.0 coughs/h (P=0.009). Urge to cough reduced significantly from 5 points to 1 point on the urge o cough scale (P=0.01).[159] Three uncontrolled longitudinal case series have confirmed that speech pathology treatment improves laryngeal hypersensitivity, cough reflex hypersensitivity, and the aberrant laryngeal motor response (PVFM) in RCC (fig 3).[155-7] The third prospective study assessed a physiotherapy intervention for 23 patients with RCC.[155]The intervention comprised education and lifestyle advice, cough suppression exercises, breathing retraining, and vocal hygiene. LCQ scores improved from 12.4 to 15.1 (P<0.001). Cough frequency measured on a seven point Likert scale improved from 5.4 to 4.3 (P=0.001). Sleep disturbance improved from 4.5 to 3.6 points on a 7 point Likert scale (P=0.02). The retrospective review looked at 16 patients with RCC who underwent a series of breathing retraining exercises with a speech pathologist including rhythmic breathing, breathing with vocal resistance, pulsed exhalation, and abdominal focus at rest.[156] Fifteen patients reported improved cough symptoms. The reflux symptom index score improved by a mean of 3.74 points and all patients improved (P<0.01). PVFM improved or resolved in 15

patients and laryngeal sensory thresholds improved or resolved in 14 patients (P=0.02). Pathophysiological assessment The first step in speech pathology management of RCC is to evaluate the pathophysiological features of the condition, including cough characteristics, urge to cough, PVFM, and voice symptoms. This assessment is conducted by the speech pathologist and takes 45-60 minutes. The information obtained during the assessment provides baseline measurements and informs the structure and focus of the behavioral management program. Urge to cough Urge to cough is an important concept in cough. Patients with chronic cough report a consistent and characteristic sensory experience, which suggests a common somatosensory disturbance associated with the urge to cough and excessive coughing.[160] An assessment of cough triggers and the urge to cough can provide valuable information about the person's cough control. Formal exposure to potential triggers can be trialed in the clinical setting.[161] In such an assessment, the magnitude of the urge to cough[159] and the number of coughs observed are rated at baseline and after exposure to various olfactory, exercise, phonatory, respiratory, and swallowing triggers. The triggers include deep inspiration, reading aloud, exercise, voice assessment tasks, perfume, soap powder, eating, and drinking. Patients can also be coached in strategies to relieve the urge to cough and to implement cough suppression techniques once the urge is recognized, before the cough develops. Voice assessment Because dysphonia and laryngeal symptoms are common in RCC,[162] voice assessment is part of the speech pathology management of RCC. Voice assessment tasks themselves—particularly ones that extend the voice to the limits of pitch, loudness, and duration—can trigger cough.[163] The extent to which this occurs can be measured during the assessment. Formal voice assessment tasks also provide information about the coordination of respiration and phonation that might not be evident during an informal conversation. We therefore suggest that minimal voice screening is included in the speech pathology assessment of patients with RCC, with more complex acoustic, electroglottographic, and aerodynamic assessment reserved for severe cases or professional voice users.[164] Laryngeal assessment Cranial nerve motor deficits have not been reported in RCC. Patients commonly have laryngeal discomfort,[163] and oromusculature examination invariably identifies a dry oral cavity. This may be a side effect of drugs or due to dehydration. Poor hydration is common in RCC, and speech pathology treatment programs often target hydration.[163,164] Extrinsic laryngeal muscle tension is often seen around the thyrohyoid and geniohyoid regions. A similar pattern of muscle tension is reported in hyperfunctional voice disorders.[165] This tension might be a result of cough or patients holding their larynx in a tense state in an unconscious attempt to avoid triggering cough. Minor swallowing deficits may also be present.[166] An objective assessment of swallowing in 33 patients with RCC and 28 with combined cough and PVFM found that all patients had significantly lower (worse) timed swallow test results than healthy controls.[166] Patients might be over-protecting their airway to reduce uncomfortable laryngeal and pharyngeal sensations. It consists of four components: education, cough suppression strategies, vocal hygiene training, and psychoeducational counseling. It is typically conducted by speech pathologists with a special interest in the treatment of dysphagia and voice disorders, and training resources are available to ensure the consistency of the treatment program.[167] The goals of speech pathology interventions are to improve voluntary control over the cough by teaching patients to identify sensations that precipitate the cough and to substitute the cough with another response for example, a breathing or swallowing exercise, and to change behaviors that contribute to laryngeal irritation. It probably acts on both peripheral and central parts of the cough pathway. Pharmacologic therapy Neuromodulators Centrally acting neuromodulators—including gabapentin, pregabalin, morphine, amitriptyline, and baclofen— act on the heightened neural sensitization that is involved in the pathogenesis of RCC.[168] All of these agents have improved

cough specific quality of life in patients with RCC. However, although these treatments are promising, adverse effects can be serious and limit the maximum tolerable dose of these agents.[168]

Morphine

A double blind placebo controlled crossover trial of slow release morphine sulfate (5 mg) versus placebo included 27 patients with RCC. The mean LCQ score was 12.3 (standard deviation 2.5) points at baseline, 13.3 (2.7) on placebo, and 15.5 (2.7) on morphine

Gabapentin

Gabapentin binds to the α2δ subunit of the voltage dependent calcium channel, thereby regulating neurotransmitter release. It was originally developed as an antiepileptic agent but has been more useful in neuropathic pain syndromes. Gabapentin prevents mechanical and thermal allodynia and hyperalgesia in neuropathic pain models. The specific mechanisms of action of gabapentin in the treatment of neuropathic pain and neuropathic cough are yet to be determined. An RCT of gabapentin randomized 62 non-smokers with refractory cough to treatment with gabapentin 1800 mg/day as the maximum tolerable dose or to a matched placebo dose over 10 weeks.[169] Objective and subjective measures of cough were taken before, during, and after treatment. Gabapentin significantly improved cough specific quality of life (treatment 2.5 v placebo 1.1; difference 1.8, 95% confidence interval of the difference 0.56 to 3.04; P=0.004), reduced cough severity (treatment −11.1 v placebo 8; −12.23, −23.22 to −2.88; P=0.029), and cough frequency (treatment −22.5 v placebo −4.3; −27.31, −51.75 to −2.88; P=0.028). The drug's onset of action was within four weeks and the effect was maintained during maximal dosing at eight weeks. However, the improvement in LCQ was not sustained after treatment withdrawal and the LCQ score returned to baseline. Adverse events, including confusion, dizziness, dry mouth, fatigue, nausea, blurred vision, headache, and memory loss were reported by 31% of the participants taking gabapentin.[169] Adverse events were reported in 10% of the placebo group. The side effects of gabapentin often limit its use, especially at higher doses, but they can diminish with time.

Amitriptyline

Amitriptyline has been investigated in a randomized controlled trial of 28 patients with RCC.[170] Patients were randomized to receive either amitriptyline or codeine or guaifenesin for 10 days. Amitriptyline showed a greater than 50% response compared with codeine or guaifenesin (P=0.0007).

Baclofen

Baclofen has been investigated as a potential antitussive agent but no randomized trials have been performed. A non-randomized study compared the effect of baclofen 20 mg, baclofen 10 mg, and placebo on cough reflex sensitivity in 41 healthy volunteers.[171] In the patients taking 20 mg baclofen, cough reflex sensitivity decreased after 14 and 28 days compared with baseline, but no significant change was seen with 10 mg baclofen or placebo. Another non-randomized study assessed the effects of baclofen in 16 patients with GORD induced chronic cough.[172] It found improvements in cough, cough reflex sensitivity, and the number of acid reflux episodes. The main adverse events associated with baclofen were somnolence, dizziness, and fatigue.[172] Although baclofen remains a potential area for development,[173] no conclusions can be drawn about its effectiveness until RCTs are available.

Combined pharmacologic and non-pharmacologic therapy

An RCT examined the effect of combined speech pathology treatment and pregabalin on RCC.[153] Forty patients were randomized to combined speech pathology treatment and pregabalin 300 mg or combined speech pathology treatment and placebo. Cough severity, cough frequency, and cough quality of life improved in both groups. However, the improvement in cough severity and cough quality of life was significantly greater with combined speech pathology and pregabalin than with speech pathology alone. The mean difference in Leicester cough questionnaire scores was 3.5 (1.1 to 5.8) which is greater than the minimally important difference of 2. The mean difference in cough severity visual analog scale scores was 25.1 (10.6 to 39.6). There was no significant difference in improvement in cough frequency between groups. Importantly, and unlike the study of gabapentin,[169] symptoms did not get worse once pregabalin was withdrawn. Capsaicin cough reflex sensitivity (C5) also improved in both treatment groups from 15.7 µmol to 47.5 µmol with combined speech pathology and pregabalin and from 3.92 µmol to 15.7 µmol with speech pathology alone. At this stage, the choice of intervention may be influenced by patient and physician preference. Although speech pathology and neuromodulators improve cough they have limitations: speech pathology treatment reduces cough but does not eliminate cough, and neuromodulators are limited by side effects and a non-sustained treatment response. These treatments act on different aspects of the cough pathway and therefore combined treatments might provide more complete resolution of the cough.

Inhaled corticosteroids

Eosinophilic airway inflammation (eosinophilic bronchitis) is an important cause of chronic cough that can occur as a discrete condition or as part of asthma, cough variant asthma, rhinitis, or atopic cough. Inhaled corticosteroids are effective in eosinophilic airway inflammation. Two of three randomized controlled trials of inhaled corticosteroids, including mometasone, budesonide, and beclometasone, showed no significant improvement in cough severity.[174] There were no adverse effects. Optimal assessment of eosinophilic bronchitis requires the measurement of airway eosinophils (from induced sputum or bronchoalveolar lavage) or exhaled nitric oxide. This should be performed as part of the investigation of RCC. A randomized controlled clinical trial found no beneficial effect of inhaled budesonide on cough symptoms in patients with chronic unexplained cough who did not have asthma or eosinophilia.[174] A systematic review to assess whether inhaled corticosteroids could result in cure of chronic unexplained cough in adults identified eight eligible RCTs with 570 participants.[175] The studies were of good quality but were heterogeneous in terms of cough duration (fewer than three weeks to more than eight weeks) and the exclusion of other cough related conditions. Treatment with inhaled corticosteroids significantly reduced cough score but analysis of the primary outcome (cure) was not possible because of study heterogeneity.

Other treatments

Gastroesophageal Reflux Disease is thought to be a contributory factor to chronic cough, with reflux of gastric contents (acid and non-acid) into the esophagus and laryngopharyngeal areas stimulating cough. Symptomatic GERD should be evaluated and treated if present before patients are diagnosed as having RCC. A trial of high dose esomeprazole, a proton pump inhibitor, in patients with RCC in the absence of symptomatic GERD found no benefit on cough severity or quality of life.[176] This suggests that the cough is not due to acid reflux and does not support the use of empiric antireflux treatment. The role of the investigation and effective treatment of non-acid

reflux in RCC is unclear, as is the place of surgical intervention to prevent reflux of gastric contents into the esophagus and laryngopharyngeal area. An observational study of 67 patients with GERD and cough undergoing fundoplication showed an improvement in cough, as measured on a four point ordinal scale of cough frequency, in 85% of patients. The study was limited by the lack of a standardized measure of cough and the absence of a control group. Ipratropium bromide, a bronchodilator used in the treatment of asthma, has been investigated in RCC. A randomized controlled trial found a significant reduction in cough severity and a good safety profile.[80] Subsequent work has identified an inhibitory effect of this class of drug on neuronal TRPV1 receptors.[177]

Outcome assessment after treatment

Routine collection of outcome measures after treatment for RCC using validated tools such as the cough severity index,[178] the LCQ,[179] and the laryngeal hypersensitivity questionnaire.[180] These are easily adaptable and do not require additional equipment. Tests such as ambulatory cough frequency monitoring and cough reflex sensitivity testing can be used to provide objective measures.[181] Speech pathologists may also use objective measures of voice, such as maximum phonation time and auditory perceptual voice evaluation, to monitor changes in phonation after treatment.

Emerging therapies for RCC

Several novel treatments have been evaluated. A randomized double blind placebo controlled crossover trial assessed an oral purinergic (P2X3) receptor antagonist (AF-219) in RCC.[80] P2X3 receptors in airway vagal afferent nerves contribute to the hypersensitivity of sensory neurons, and treatment with AF-219 was associated with a 75% reduction in cough frequency compared with placebo. Daytime cough frequency fell from a mean 37 coughs per hour to 11 coughs per hour. Dysgeusia occurred in 88% of participants and led to treatment withdrawal in six.

In recent years novel P2X3 receptor antagonists have shown much promise as a therapeutic option for patients with chronic cough.[182] Initial proof of concept studies showed a reduction in cough frequency with P2X3 inhibitors almost 10 years ago, with all patients reporting side effects of taste disturbance (hypogeusia or ageusia).[183] Since this study, further developments of this and other P2X3 inhibitors have shown a significant reduction in objective cough count at 12-week follow-up.[1] Phase 3 randomized controlled trials COUGH-1 and COUGH-2 [184] have demonstrated an 18% reduction in cough at 12 weeks and a near 15% reduction at 24 weeks vs. placebo in those treated with gefapixant. Despite a large placebo effect observed in the control group,[185] its efficacy was confirmed and it is likely that gefapixant and other P2X3 inhibitors will soon be made widely available for patients attending cough clinics.

Conclusions

Chronic cough is a common troubling symptom that can severely affect the physical, social and psychological well-being of patients. Current guidelines recommend treatment of any identifiable

conditions, but if the cough is refractory or unexplained, speech and language therapy along with neuromodulator treatments, such as low dose opioids, pregabalin and gabapentin, can be trialed. Clinicians should monitor and minimize the dose and length of treatment with centrally acting neuromodulator treatment to limit side effects and tolerability in a respiratory or specialized cough clinic. However, there is hope for patients with the ongoing development of novel oral P2X3 antagonists.

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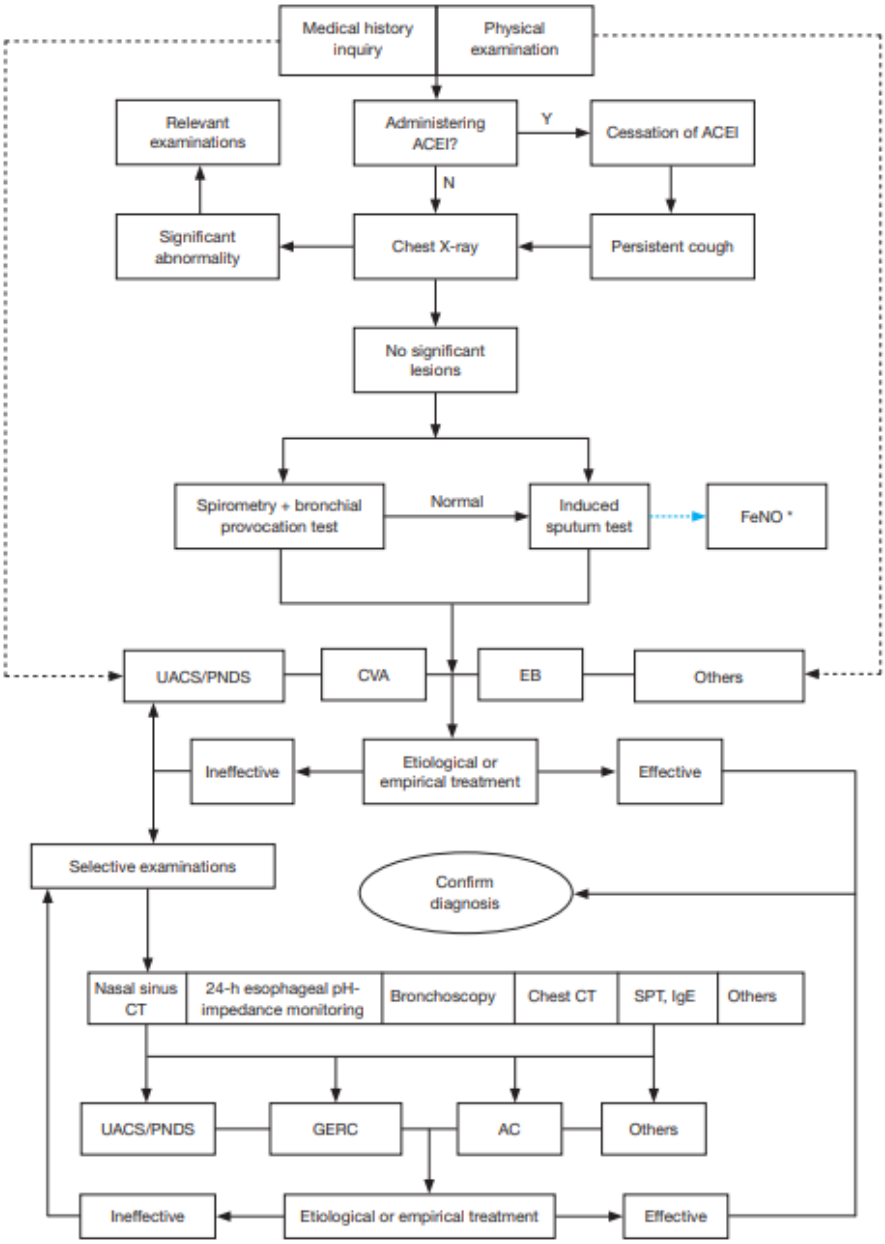
Supplementary

Supplementary file 1 Algorithm for the etiological diagnosis of chronic cough



Note: *, cannot be used as criteria for diagnosis, but can be used as an indicator for eosinophilic inflammation-related cough. (I) For patients with low economic status or for those in primary health care centers, empirical treatment can be adopted based on the medical history and cough-related symptoms. If the empirical treatment fails, to avoid the delay in proper diagnosis and therapy, patients should be referred to hospitals where the tests are available. (II) ACEI, angiotensin converting enzyme inhibitor; FeNO, Fractional exhaled nitric oxide; UACS, upper airway cough syndrome; PNDS: postnasal drip syndrome; CVA, cough variant asthma; EB, eosinophilic bronchitis; CT, computed tomography; Bronchoscopy, fiberoptic bronchoscopy; SPT, skin prick test; IgE, immunoglobulin E; GERC, gastroesophageal reflux-related cough; AC, atopic cough.

SLEEP DISTURBANCE IN ADVANCED LUNG DISEASES

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Advanced Lung Disease

Advanced lung disease is defined as any lung disease that has advanced or worsened to the point where the patient becomes severely disabled or is close to death (caused by the disease) within a short period of time. Advanced lung disease can occur in all three basic tyoes of lung disease:

- Obstructive lung disease: characterized by blocked airways, can occur due to chronic obstructive lung disease (COPD) and bronchiectasis (from cystic fibrosis)
- Interstitial lung disease: includes many primary diseases of the lung such as idiopathic pulmonary fibrosis. This condition can also occur as a result of diseases like systemic lupus erythematosus which can engulf the lung tissue during its systemic destruction
- Pulmonary vascular disease: affect the blood vessels that go through the lung to carry oxygen. An example of this is primary pulmonary hypertension, which causes progressive narrowing of these blood vessels, and progressively low oxygen in the blood

Sleep Disturbance/Insomnia

Insomnia is defined as difficulty in either falling asleep, staying asleep, waking up to early, or having low quality sleep. Etiologies of insomnia may include: genetic disorders, disturbance in the brain chemistry, hormones, or immune system, psychiatric illness, or medications. Insomnia can be categorized into acute and chronic:

- Acute: also known as short-term insomnia or adjustment insomnia. This is when a patient suffers from insomnia fewer than 3 times a week for less than a month. Usually occurs due to changes in the environment or a short illness
- Chronic: a long-term pattern of difficulty sleeping where the patient has insomnia at least three nights per week for three months or longer. Can be psychophysiological, idiopathic, paradoxical,

inadequate sleep hygene, behavioral insomnia of childhood, insomnia due to mental disorder, medical condition, or drug consumption

Effects of Lung Disease on Sleep

Patients with lung disease, chest wall restriction, and neuromuscular abnormalities often have distrubances in sleep and breathing during sleep, resulting in poor sleep quality, frequent awakening, hypoxia, and hypercapnia

Obstructive pulmonary disease

In patients with COPD who are severely hyperinflated and have a flat diaphragm, the occurrence of severe gs exchange abnormality is predicted by time spent in REM sleep. In COPD, hypoxemia occurs more during sleep compared to during wakefulness. This event is caused by hypoventilation, increased ventilation perfusion mismatching and decrease in FRC

Restrictive lung disease

Diseases that can cause restrictive lung disorder include pleural disease, neuromuscular disorders, scoliosis, parenchymal lung disease, and massive obesity. Parenchymal lung disease causes increase in ventilatory drive and dyspnea by neural mechanism, whereas other forms increase work of breathing. A restrictive lung disorder, like obstructive lung disease, interrupts the continuity of sleep and causes sleep-related hypoventilation and/or hypoxemia. ventilatory support in these conditios will help improve daytime sleepiness, daytime hypoventilation, chronic respiratory muscle weakness, exercise endurance, and pulmonary hemodynamics

Hypoventilation syndromes

Patients with obstructive or restrictive pulmonary disease might experience hypoventilation which reflects mechanical restraint on ventilation and also on dead space increase CO2 production in pulmonary diseases. Patients experience increased hypercapnia during sleep and excessive breathing efforts during wake state. Individuals with an increased set point for PaCO2 experience less dyspnea yet increased hypercapnia during

wakefulness and increase more during night. Some degree of ventilator reserve may be inferred by the ability to voluntarily lower PaCO2 during the day and with daytime improvement in hypoventilation when ventilation is supported during the night

TREATING ARDS: WHEN THE BEST TIME TO GIVE CORTICOSTEROID AND ANTIOXIDANT?

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is an acute hypoxemic state caused by the sudden development of diffuse injury to the terminal respiratory units with exudative pulmonary edema and is associated with very high mortality. The management of ARDS has evolved over decades and there is consistent increase in survival among these patients over the last few years[1]

Patients with ARDS represent about 10% of ICU admissions, 25 % of patients require mechanical ventilation and mortality ranges from 35% to 46%[2,3]

To date, there are no specific drugs or therapies available to directly treat / prevent ARDS. Mechanical ventilation with an aim to minimize ventilator induced lung injury (VILI) and management of refractory hypoxemia are the keystones in supportive management of ARDS[4]

Corticosteroid and antioxidant have attracted attention because they anti-inflammatory and antioxidant properties that are relevant to ARDS pathology. However their use in improving clinically meaningful outcomes remains controversial.[5,6]

DEFINITION

Since the initial description of ARDS in 1967[7] the definition of ARDS has undergone multiple revisions and currently the most accepted definition of ARDS known as the Berlin definition of ARDS is formulated by European Society of Intensive Care Medicine (ESICM) and endorsed by American Thoracic Society (ATS) and Society of Critical Care Medicine (SCCM) [8,9]

Table 1. Berlin Definition of the Acute Respiratory Distress Syndrome (ARDS).*

Criteria	Rationale
Onset within 7 days after a known clinical insult or new or worsening respiratory symptoms	Observational data suggest that ARDS will develop within 72 hr in the majority of patients at risk for the syndrome and within 1 wk in nearly all patients at risk
Bilateral opacities that are "consistent with pulmonary edema" on chest radiographs or chest CT	There is poor interobserver reliability in interpreting the chest radiograph for the presence of edema. To address this issue, the Berlin definition offers more explicit criteria (e.g., opacities should not be fully explained by effusions, lobar or lung atelectasis, or nodules or masses), with illustrative radiographs provided
Categorization of ARDS severity	A patient-level meta-analysis validated three thresholds for hypoxemia, all consisting of a Pao_2:Fio_2 ratio ≤300 mm Hg
Mild	Pao_2:Fio_2, 201 to 300 mm Hg; mortality, 27% (95% CI, 24–30)
Moderate	Pao_2:Fio_2, 101 to 200 mm Hg; mortality, 32% (95% CI, 29–34)
Severe	Pao_2:Fio_2, ≤100 mm Hg; mortality, 45% (95% CI, 42–48)
Minimum PEEP setting or CPAP, 5 cm of water; Pao_2:Fio_2 assessed on invasive mechanical ventilation (CPAP criterion used for the diagnosis of mild ARDS)	Estimates of Fio_2 are not accurate with oxygen-delivery systems other than invasive or noninvasive ventilation (with a tight-fitting mask), with the exception of nasal high-flow oxygen delivery systems (at flow rates ≥45 liters per minute); requiring higher PEEP settings does not increase predictive validity of the Berlin severity strata and adds complexity

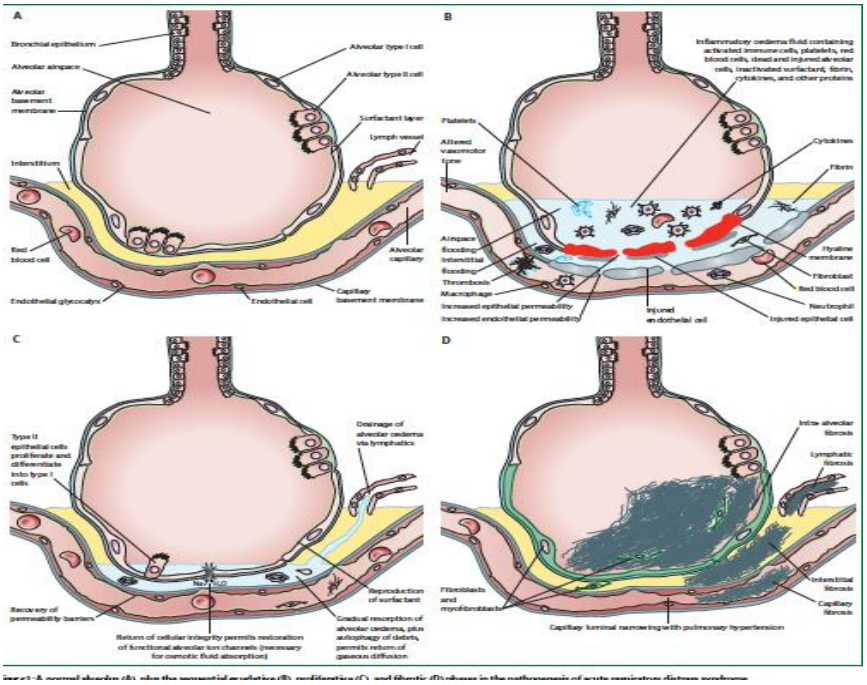
Table 1. adapted from thomson[9]

PATHOPHYSIOLOGY[9]

After the primary disease process runs, inflammation in the alveoli can be explained into 3 phases that overlap each other between phases. The exudative phase begins with the breakdown of the alveoli-interstitial epithelial and endothelial complex barrier mediated by immune cells. As the result of the damage to the barrier, plasma proteins and cells will flood the interstitial and alveoli air space. Alveolar macrophages present in the alveoli secrete proinflammatory cytokines that recruit neutrophils, monocytes and macrophages so that inflammatory processes and tissue damage continue. Exudate inflammatory will interact to reduce surfactant production and the breakdown of the ion pump in the epithelium alveoli will result in the pump of fluid to the interstitium becomes disrupted. This damage coupled with the formation of hyalin membrane in the next phase decreases pulmonary compliance resulting in impaired gas diffusion. The combination of epithelial and endothelial damage will worsen the balance of perfusion ventilation and loss of pulmonary hypotension vasoconstriction leading to refractory hypoxia.

The next phase is the proliferative phase. In this phase there is an important repair process for the recovery of the host. After the integrity of the epithelium is repaired again then the reabsorption of alveoli edema begins and a restoration of the architecture and function of the alveoli occurs.

The third phase is the fibrotic phase which does not always occur in all patients. In this phase it is related to the lengthening of the installation of mechanical ventilators and increased mortality.

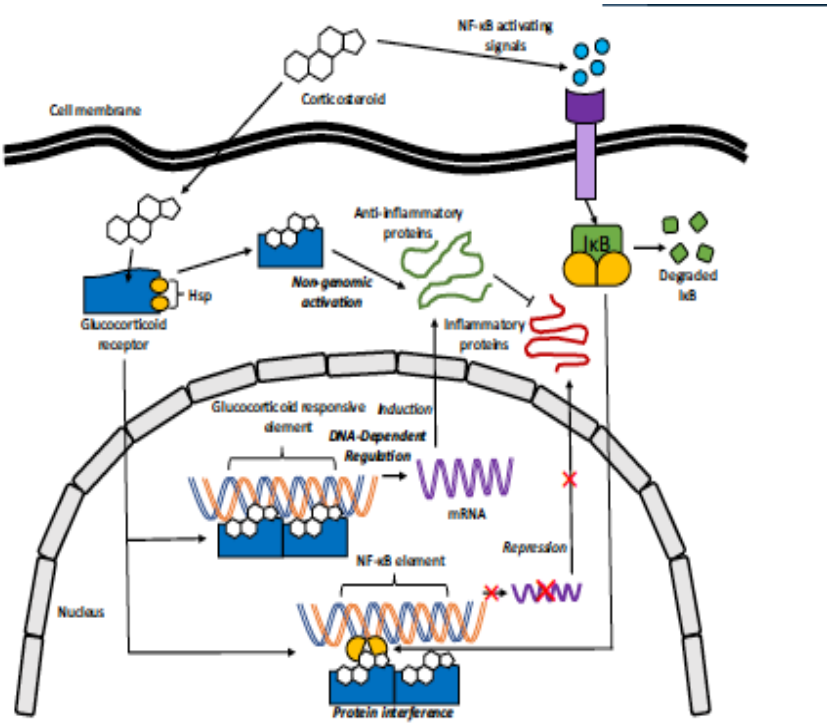


Adapted from Sweeney [10]

ROLE OF GLUCOCORTICOID

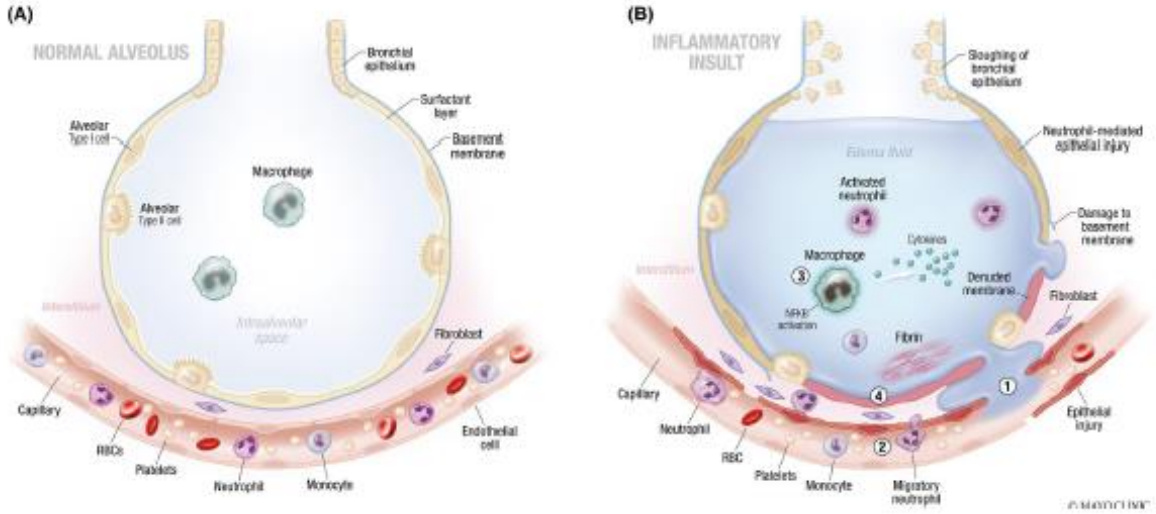
MECHANISM OF CORTICOSTEROIDS IN ARDS[11]

Glucocorticoids have potent anti-inflammatory and immunomodulating effects via non-genomic and genomic mechanisms.



Pharmacology of Glucocorticoids[11]

Cytosolic glucocorticoid -glucocorticoid receptor (GC-GR) complexes directly modulate the transcription of glucocorticoid response elements and inhibit transcription factors nuclear factor kB (NF-kB) and activating protein -1. Through these mechanism , glucocorticoid attenuate the production of pro inflammatory cytokines. They also work synergistically with natural anti-inflammatory cytokines, including IL-4,-10and -13 and increase the expression of IL-1 receptor antagonist. The three main pathways of glucocorticoid pharmacology include DNA dependent regulation of anti inflammatory proteins, non genomic modulation across cell membranes and blind with cytosol bound glucocorticoid receptors



Action of Corticosteroids in ARDS[11]

Panel A depicts a normal alveolus with intact alveolar cell structures and vascular epithelial membrane. Panel B shows alveolar changes following an acute inflammatory insult. Corticosteroids mitigate multiple pathways in acute state. (1) reduce extravasation of plasma through the intercellular junction, (2) inhibit adhesion of neutrophils to the endothelial cell and migration across the capillary wall to into the alveoli, (3) modulation of pro inflammatory cytokines through genomic and non genomic pathway. (4) inhibition of fibroblast proliferation and collagen disposition

SELECTION OF CORTICOSTEROIDS

Given the physiologic benefits derived from glucocorticoid activity, corticosteroids with glucocorticoid effects are preferred in ARDS.[12] Methylprednisolone, a potent glucocorticoid, leads to increases concentrations in the lung compared to other corticosteroids due to it's larger volume of distribution and tendency to be retained in lungs for a longer period. When used for ARDS, guidelines suggest weaning methylprednisolone over days to weeks because a rebound increase in pro inflammatory cytokines may precipitate the recurrence of cytokine storm[13] Dexamethasone, also a potent glucocorticoid , has a biological half-life up to 54 h allowing concentrations to auto-taper, decreasing the potential for a rebound effect upon discontinuation and need for a prolonged taper when treating ARDS[14] Hydrocortisone, a potent mineralocorticoid effects, increase the expression of epithelial sodium channels and activate the basolateral Na+/K+ ATPase pump in the distal portion of nephron. This promotes sodium reabsorption and increases effective circulating

volume , which may lead to pulmonary edema, worsening lung function and increased duration of mechanical ventilation[15]

CLINICAL TRIAL RESULTS

Bernard and colleagues studied the effects of high dose methylprednisolone (30mg/kg intravenously every 6 h for 24 h on mortality in ARDS to understand the effect of corticosteroids on chest radiograph, oxygenation and lung compliance[16]. There was no difference in the rate of mortality between the corticosteroid 60% and placebo groups 63%, in the subgroup analysis of patients with ARDS secondary to sepsis, patient treated with methylprednisolone had a lower reversal of chest radiograph and arterial blood gases vs placebo (9%vs 56 %) $p < 0.018$) but no difference in survival

In 1998, Meduri and colleagues look at the effect of prolonged iv methylprednisolone therapy (2mg/kg/day days 1-14, 1 mg/kg/day days 15-21, 0,5 mg/kg/day days 22-28, 0,25 mg/kd/day days 29-30, and 0.125 mg/kg/day days 31-32) in late (≧7days of MV with LIS ≧2,5 and < 1 point reduction from ARDS day 1) ARDS on improvement in lung function and mortality. Methylprednisolone therapy was associated with improvement in ARDS defined as > 1 point reduction in LIS (1,7 vs 3; $p <0.001$) and also led to more ICU survivors (16/16 vs 3/8 survivors; p 0.002) and survivors of hospital admission (14/16 vs 3/8 ,$p =0.03$). [17]

Confafonieri and colleagues in a RCT evaluated the effects of hydrocortisone (200 mg loadind dose iv followed by a 7-day infusion at 10mg/h) on improvement in P_aO_2/FiO_2, MODS score by study day 8 and reduction in septic shock. In this study did not evaluated ARDS patients specifically, it assessed patients with severe community acquired pneumonia with a high predisposition to systemic inflammation. The result identified a greater improvement in PaO_2/FiO_2 at day 8 as well as hospital mortality (30% vs 0 %). This study had a small sample size, including only 3 patients with ARDS at day 8 in the placebo group.[18]

Meduri and colleagues investigated prolonged administration of low dose methylprednisolone (1 mg/kg/day iv days 1-14, 0,5 mg/kg/day days 15-21, 0,25 mg/kg/day days 22-25, 0,125 mg/kg/day days 26-28) in early ARDS (≦72 h of diagnosis) with a primary outcome of LIS at day 7, with the result by day 7 methylprednisolone group 69,8% attained a 1 point reduction in LIS compared with 35,7% in the placebo group ($p=0.002$). Mortality and ICU Length of Stay (LOS) were significantly reduced in the methylprednisolone group)20,6% vs 42,6% $p=0.03$ and 7 vs 14,5 days $p=0.007$ respectively) but hospital mortality and LOS failed to reach statistical significant[19]

As early data demonstrating corticosteroid benefit were mixed using heterogenous regimens, ARDS clinical trials network showed 60 day mortality was not different compare to

placebo, a greater incidence of serious adverse events associated with myopathy/neuropathy, and those randomized after 13 days of ARDS onset had increased mortality(8% vs 35 % p=0.002)[20]

Annane and colleagues completed a post hoc analysis of their trial using hydrocortisone 50 mg iv every 6 h and enteral fludrocortisone 50 ug daily in patients with septic shock and relative adrenal insufficiency to assess the primary outcome of 28 d mortality, the study population included 59 % patient with mild ARDS (mean PaO_2/FiO_2 270 mmHg) . Non responders (cortisol responders ≦ 9 ug/dl) with ARDS, 28 day mortality was 75% in the placebo compared to 53 % on the corticosteroid group (RR 0,71(0,54-0,94) p=0.011) Hospital and ICU mortality were lower in corticosteroid group compared to placebo group. In responders with ARDS and patient without ARDS there was no difference in mortality, days alive and MV free.[21]

Sepsis associated ARDS confers higher mortality rate compared to sepsis without ARDS or in non sepsis related ARDS. Tongyoo and colleagues conducted a prospective RCT studying hydrocortisone 50 mg iv every 6 h for 7 days on 28 day mortality. There was no difference in 28 day mortality, 22,5 % vs 27,3 % and 60 day , 34,3% vs 40,4%. By day 7 of treatment the corticosteroid group has a higher PaO_2/FiO_2 319 vs 266 (p=0.0001) and lower LIS score 1,1 vs 1,4 (p=0.001) compared to placebo[22]

The DEXA-ARDS study is the largest, randomized, multicenter study assessing the efficacy of dexamethasone (20mg iv daily for 5 days followed by 10 mg iv daily for 5 days) compared to routine care in patients with moderate to severe non Covid-19 ARDS defined by the Berlin criteria to assess a primary outcome MV-free days.The Dexamethasone group had more MV-free days than the control group: mean difference 4,8 days. More patients in the dexamethasone group developed extubation failure in the 28 day period (8,6 % vs 5,1 %) [23]

From several clinical trial the benefit for giving corticosteroid have different result especially for survival , this difference result may be different in timing intervention, selection of corticosteroid, difference dosing and duration treatment , difference clinical setting.

SHOULD CORTICOSTEROIDS BE ROUTINE TREATMENT IN EARLY ARDS ?

From Meduri and colleagues they said YES because on their point of view that corticosteroid can switching production from proinflammatory to proresolving mediators while producing antifibrotic and antioxidant proteins that limit tissue damage and fibrosis and on from systematic review and meta-analysis that either methylprednisolone or hydrocortisone treatment in patients with ARDS and were used for a duration of at least 7 days found moderate certainty evidence that demonstrated a reduction in the duration of MV (mean difference 7.1 d less; 95 % CI, 3,2-10.9 d less) with corticosteroid and moderate certainty evidence that demonstrated survival (relative risk, 0,64;95% CI, 0,46-0,89) with corticosteroid. In 2017 the Corticosteroid Guidelines Task Force of the Society of Critical Care Medicine and the European Society of Intensive Care

Medicine related guidelines for corticosteroid in critically ill patients focus on ARDS, the task force reviewed clinical and experimental evidence on the central role played by critical illness related corticosteroid insufficiency (CIRCI) syndrome in the pathobiologic structure of ARDS and how increasing glucocorticoid receptor alpha (GR a) activation with quantitatively adequate and prolonged corticosteroid can reverse CIRCI and accelerate resolution of pulmonary and systemic inflammation and the result from Spanish investigators recently completed a the Efficacy study of Dexamethasone to treat the ARDS (DEXA-ARDS) RCT showed early administration dexamethasone for a duration of 10 d led to a reduction in the duration of MV and all cause death at 60 days without increasing rates for hyperglycemia, nosocomial infection or barotrauma [24]

Contrary to Meduri and colleagues , Hensley and colleagues said NO on their point of view, ARDS is a heterogenous clinical syndrome that may result from a variety of underling diseases. Despite it seemingly straightforward definition there is poor agreement on ARDS diagnosis across clinicians, and only 45% of patients whose condition meets the clinical criteria for ARDS have diffuse alveolar damage on autopsy, so it is difficult to identify ARDS with consistency, difficult to study ARDS and difficult to interpret and apply the findings of ARDS clinical trials to the bedsite. However early steroid therapy given within 14 days of ARDS onset has remained of continued interest. The first randomized trials of glucocorticoid for ARDS occurred in 1980s, at this time mechanical ventilation practices have changed drastically. Randomized trial of 180 patients ARDS using methylprednisolone for 7 to 28 days duration showing patients enrolled earlier (day 7-13) steroid therapy was associated with increase ventilator free days but no difference in 60 days hospital mortality rate and adverse effect neuromyopathy was more common in the steroid arm. Which led Steinberg et al to conclude that although earlier steroid use improves some outcome (ventilator free, ICU LOS) they cannot be recommended routinely. In DEXA-ARDS trial Villar et al using dexamethasone showing a better outcome and ventilator free on dexamethasone arm which led the authors conclude that steroid therapy is beneficial in ARDS, but the majority of trial population (77%) had sepsis and pneumonia , diagnosis for which other trials indicate benefit from steroid therapy. Recently in the RECOVERY trial showed benefit from dexamethasone therapy In COVID-19, but the benefit was concentrated among patients on mechanical ventilation and those with symptoms > 7 d prior randomization.

We can see from small individual trials that steroid therapy may benefit patients with ARDS, however there remains significant heterogeneity in patient with ARDS, which raises the question of whether steroid therapy should be used in all patients with early disease. Trial results favoring steroid therapy in patients with ARDS could mean a robust improvement in some patients while others may be harmed depending in some etiology. Several guidelines address the use of steroid therapy in ARDS, the surviving sepsis champaign's COVID-19 include a weak recommendation for corticosteroids in patients with COVID-19 and ARDS. A weak recommendation indicates that the desirable effects do not clearly outweigh the undesirable effects in all patients, Overall there is some evidence of not only benefit among heterogenous patients with ARDS but also clear risk of harms with steroid therapy. Although one could give steroid

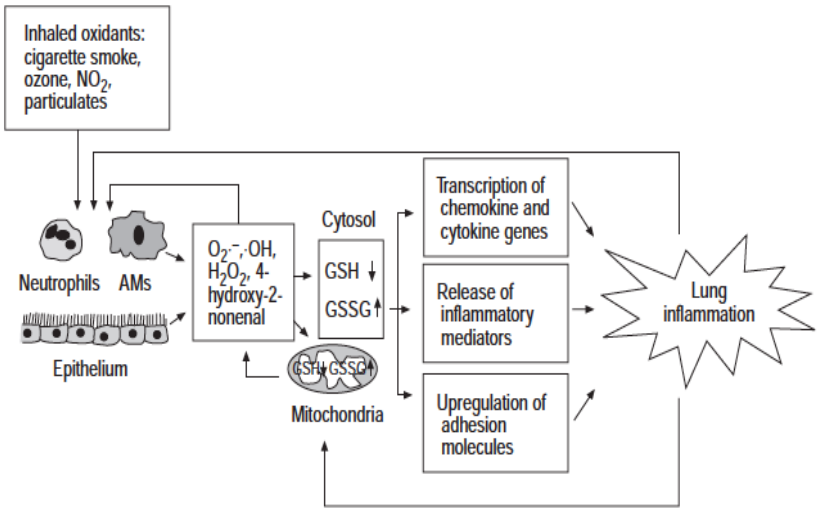
therapy to all patients with ARDS we believe that a more personalized approach is superior, in which steroid therapy are given selectively to patients based on the undelying etiology rather than for ARDS itself. We suggest routine use of steroid therapy for certain subgroups of patients with ARDS but avoid steroid therapy in other subgroups for whom benefit is less clear or risks of harm or greater.[25]

Recommendation from Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically ill patient: SCCM and ESICM 2017, we suggest use of corticosteroid in patients with early moderate to severe acute respiratory distress syndrome ($PaO_2/FiO_2 < 200$ and within 14 days of onset) (conditional recommendation moderate quality of evidence) , the task force suggested that methylprednisolone be considered in patients with early (up to day 7 onset ; $PaO2/FiO_2 < 200$) in adose of 1mg/kg/day and late (after day 6 of onset) persistent ARDS in a dose 2 mg/kg/day followed by slow tapering over 13 days[13]

ROLE OF ANTIOXIDANT

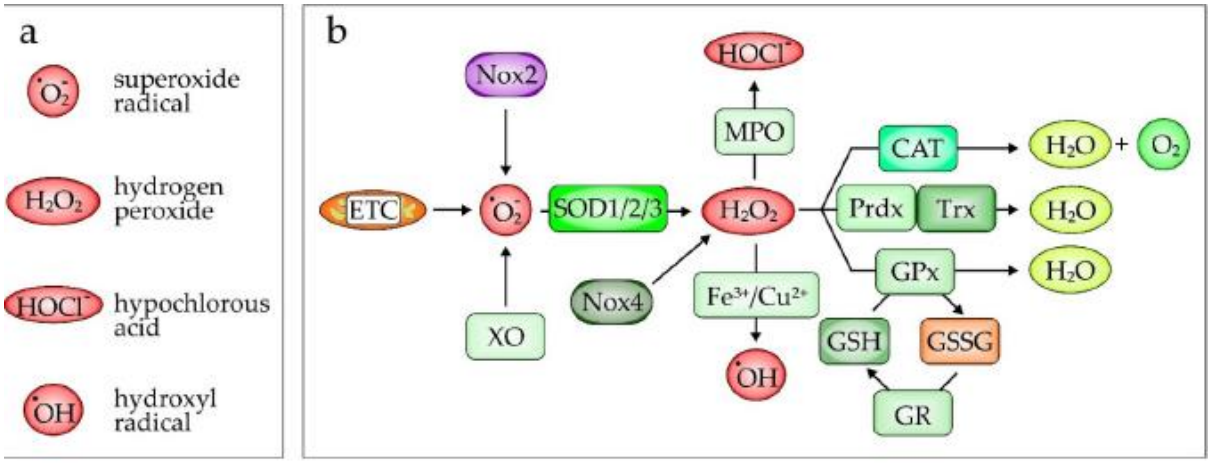
MECHANISMS OF OXIDANT MEDIATED LUNG INFLAMATION

The inflammatory response is mediated by oxidants which are inhaled and/or released by the activated neutrophils, alveolar macrophages (AMs) and epithelial cells leading to depletion of antioxidant reduced glutathione (GSH), Activation of transcription of th pro inflammatory cytokines and chemokine genes, upregulation of adhesion molecules and increase released of proinflammatory mediators are involved in the inflammatory responses[26],(see figure below)



Adapted from I Rachman[26]

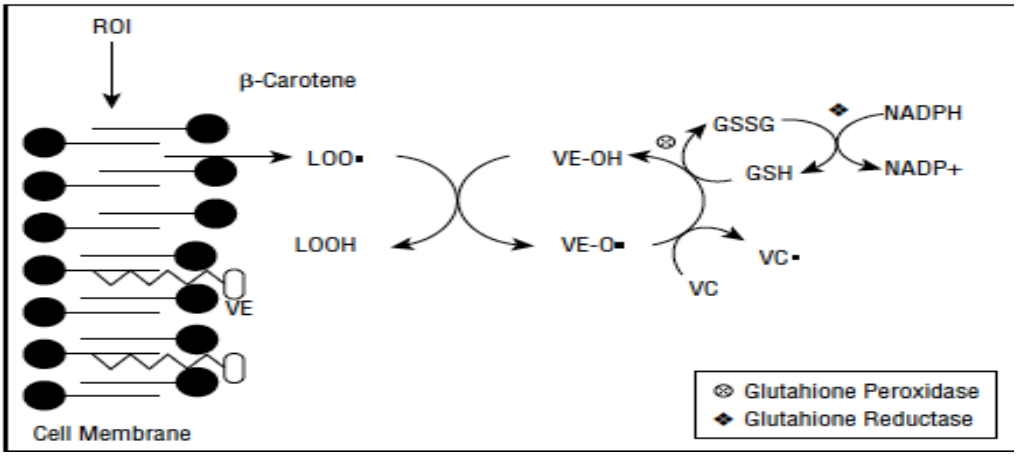
There are some Reactive Oxygen species (ROS) like superoxide radical , hydrogegen proxide, hypochlorous acid and hydroxyl radical involved in ARDS. The superodide radical O_2^- is generated by the NADPH oxidase2 (Nox 2), the xanthine oxidase (XO) and the electron transfer chain (ETC) located in mitochondria. O_2^- is dismutated to hydrogen peroxide (H_2O_2) by one of three superoxide dismutases (SOD_s), which are located in the cytosol (SOD1= CuZnSOD) on mitochondria (SOD2=MnSOD) or extracellularly often associated with the extracellular matrix (SOD3 = EC-SOD), one further source of H_2O_2 is Nox4, which is located in mitochondria or endoplasmic reticulum (ER) of endothelial as well as epithelial cell. H_2O_2 is the substrate for the myeloperoxidase (MPO) derived oxidant hypochlorous acid ($HOCl^-$) known to cause tissue injury. Stored in neutrophil granules, MPO is released following neutrophil activation. In Fenton reaction H_2O_2 is further metabolized to the highly antimicrobial hydroxyl radical ($^{\cdot}OH$) . ROS-scavenging enzymes, such as catalase (CAT) Or Glutathione peroxidase (GPx) detoxify H_2O_2 to H_2O and O_2. To achieve this GPx oxidizes GSH to GSSG which in return is reduced via the glutathione reductase to GSH,Similary peroxiredoxin (Or) belonging to a small family of peroxidases reduces H_2O_2 by oxidizing thioredoxin (Trx) which then is restored to the reduced form by thioredoxin reductase (see figure below)[27]



Adapted from von Knethen [27]

INTERACTIONS AMONG ANTIOXIDANT (see figure below)

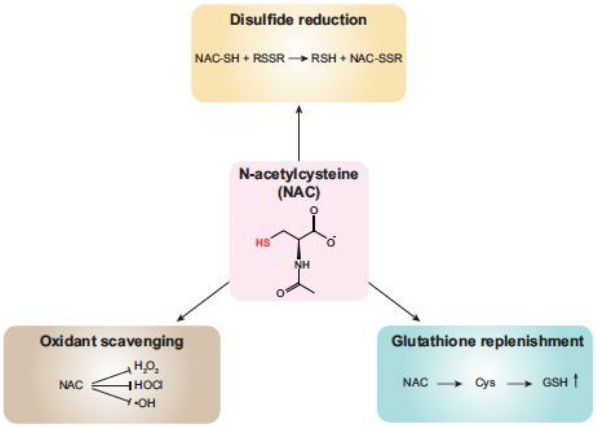
Reactive oxygen intermediates (ROI) induce membrane lipid peroxidation, resulting in a chain reaction that can be interrupted by the direct scavenging of lipid peroxyl radicals by vitamin E (VE) and beta carotene, Both vitamin C (VC) and glutathione (GSH) can then recycle vitamin E. The reducing ability of GSH catalyzed by the enzyme glutathione peroxidase, Glutathione is then recycled by NADPH, which is facilitated by glutathione reductase[28]



Adapted from Bulger [28]

ROLE OF N-ACETYLCYSTEINE (NAC)

NAC is a thiol and mucolytic agents, a precursor of L-csyteine and reduced glutathione (GSH). The characteristic of NAC of being a precursor of GSH represents the most important pharmacological property of this drug. NAC acts an an antioxidant by restoring the pool intracellular reduced GSH, which is often depleted in conditions associated with increased oxidative stress and inflammation. Due to its free sulfhydryl group, which confers NAC with the ability to reduce viscosity and elasticity of the mucus, and NAC can also act as direct scavenger off free radicals such as OH, H_2O_2 and O_2^-.



The three classical narratives of how NAC exist its biologic[29]

CLINICAL TRIAL RESULTS (N-acetylcysteine and Vitamin)

Soltan-Sharifi and colleagues conducted a prospective RCT studying the benefit of the anti-oxidant compound N-acetylcysteine (NAC) in the management of ARDS by measuring patients intracellular glutathione (inside red blood cell) and extracellular (plasma) antioxidant defense biomarker and outcome. In group NAC received 150mg/kg day 1 followed by 50 mg/kg/day for three days. Treatment by NAC increased extracellular total anti-oxidant power and total thiol molecules and also improved intracellular glutathione and outcome of the patients.[30]

Moradi and colleagues investigated the effects of NAC treatment (IV NAC in 150mg/kg at the first day followed by 50 mg/kg/day for 3 days) on 27 ICU patient with ALI/ARDS considering the glutathione S-transferase genetic variations, as an important enzyme contributing in oxidative stress pathways. The result indicated that NAC improved oxygenation (increase in PaO_2/FiO_2) and decreased mortality rate in treated patients compared to control group ($p < 0.05$). Evaluation of three isoforms of glutathione-S-transferase (GST M1,P1 and T1) in these patients showed an association between GST M1 null, and GST M1 and T1 double null polymorphism with increased mortality in control group.[31]

In 2020 Taher A and colleagues designed a single centre clinical trial to assess the potential benefits of NAC in patients with COVID-19 associated ARDS. In group treated with NAC (47 patients) were given IV NAC 40 mg/kg/day for three consecutive days compared to placebo group (45 patients). The efficacy outcomes were overall mortality over 28 day, clinical status on day 28, the proportion of patients requiring mechanical ventilation, change on PaO_2/FiO_2 ratio, SOFA scores 48 and 96 h after intervention. They found no differences int 28 day mortality, clinical status day 28 shifted toward better outcome in NAC treated group but with p value =0,83, similar result were achieved in terms of proportion required invasive ventilator support, number

ventilator free days and median time of ICU and hospital stay , also changing in PaO_2/FiO_2 ration and SOFA score.[32]

In 41 ICU Switzerland Domenighetti and colleauges investigated using iV NAC may be beneficial on improve systemic oxygenation and reduce the need for ventilatory support in patients with ARDS. 22 patients on NAC group receiving NAC 190 mg/kg/day for 3 day compared to placebo group 20 patients. They found in this trial iv treatment NAC 72 hour neither improved systemic oxygenation nor reduced the need for Mechanical ventilation [33]

Another study from Ghorbi and colleagues reported effect of NAC on treatment of ARDS in mechanically ventilated patients admitted to icu, in NAC group receiving 150 mg/kg on day 1 followed 50 mg/kg on day 2-4, showed no difference on mortality, length of stay and duration on mechanical ventilation[34]

Bernard GR and colleagues investigated treatment with NAC and Procysteine (OTZ) increase the levels of glutathione and cysteine in patient with ARDS and common physiologic abnormalities and organ dysfunction associated with ARDS. NAC group receiving NAC (70 mg/kg,n =14) , OTZ (63 mg/kg, n=17) every 8 h for 10 days. Both anti oxidants effectively repleted RBC glutathione gradually over the 10 day treatment period, no difference in mortality and number of days of acute lung injury decreased and significant increase cardiac index in both treatment group[35]

Zhang and colleagues on their meta analysis effect of N-acetycysteine treatment in ARDS showed NAC did not contribute to reduce short term mortality (RR=0.73; 95% confidence interval 0.5-1.07 p=0.10) when compared to control group. However duration of ICU stay in NAC group was shortened (weighted mean difference -.56; 95% CI (7,32 to – 1,80) p=0.0001. There was no significant difference in ratio PaO_2/FiO_2.[36]

Another metaanalysis from Lu and colleagues showed compared to control group , th N-acetylcysteine group did not lower the overall mortality (RR 0,83; 95% CI 0,62to 1,11 p=0,21), but significantly shortened ICU (mean difference -4,47 days 95% CI -8,79 to -0;14 p =0.04)[37]

From The CITRIS-ALI Randomized Clinical Trial, Fowler and colleagues investigated the effect of IV vitamin C infusion on organ failure score and biological markers of inflammation and vascular injury in patient with sepsis and ARDS. The CITRIS ALI trial was a randomized, double blind placebo controlled, multicentre trial conducted in 7 medical intensive care unit in USA, in treatment group receive iv Vitamin C (50mg/kg in D5% in water every 6 hours for 96 hours. The Result from this trial were no significant differences in SOFA score, CRP levels and thrombomodulin level between placebo group[38]

Zhang and colleagues investigated high dose vitamin C in critically ill COVID-19 patients. This RCT was performed at 3 hospital in Hubei China, patients confirmed severe

C-ARDS, in treatment group receiving high dose intravenous vitamin C (HDIVC) 12 g of vitamin C/ 50 mg ml every 12 h for 7 days at a rate of 12 ml/hour. The primary outcome was invasive mechanical ventilation free days in 28 days,(IMVFD28) secondary outcomes were 28-day mortality, organ failure (SOFA) score and inflammation progression (IL-6), with the result no difference in IMVFD28, better rise in PaO_2/FiO_2 and lower IL-6 in HDIVC group.[39]

James and colleagues using combination diet low carbohydrate, high fat diet combining the anti inflammatory and vasodilatory properties of eicosapentaenoic acid (EPA; fish oil), gamma-linolenic acid (GLA;borage oil) and antioxidants may reduce pulmonary inflammation and may improve oxygenation and clinical outcome in patients with ARDS compared to isocaloric standard diet. Result in this trial combination EPA + GLA and antioxidants significant improvements in oxygenation (PaO_2/FIO_2 ratio), ventilator free support and decrease of icu stay[40]

In another report from Pontes-Arruda and colleagues using the same enteral nutrition enriched with EPA +GLA + vitamin antioxidant on 165 patients severe sepsis and septic shock with mechanical ventilator support compare to standard nutrition showed significant reductioin in mortality rate compared with patients fed with control diet, the absolute mortality reduction amounting to 19,4% (p=0.37). the treatment group also experienced significant improvemenst in oxygenation status, more ventilator free days, more icu free days, and lesser development of new organ dysfunction.[41]

CONCLUSION

Although corticosteroid and antioxidant theorical have some properties on reduced inflammation and radical oxygen species on pathophysiology ARDS but in clinical trial showed conflicting result in term of mortality, although some clinical condition improved like mechanical ventilation free days, icu free days, some reported improve of oxygenation. From the CIRCI guideline recommended to use methylprednisolone for early ARDS but not for late ARDS. No guideline for using antioxidant for treatment ARDS.

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CURRENT CHOICES OF ANTIBIOTIC TREATMENT FOR PSEUDOMONAS AERUGINOSA INFECTION

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Pneumonia is diagnosed by infiltrate or development of new infiltrate on chest radiograph with sign and symptom which suggest that the infiltrate is caused by infection. Sign and symptoms suggest infection, including: new onset fever, purulence sputum, and WBC (leucocytosis or leucopenia). Pneumonia can be classified into :

Type of Pneumonia	**Definition**
Community acquired Pnenumonia (CAP)	Pneumonia that is acquired outside of the hospital setting
Hospital Acquired Pneumonia (HAP)	A pneumonia that occurs 48 hours or more after admission; which was not incubating at the time of admission; not associated with mechanical ventilation
Ventilator-Associated Pneumonia (VAP)	A pneumonia that arises more than 48 hours after mechanical ventilation
Ventilated HAP (vHAP)	A pneumonia that occurs 48 hours or more after admission; which was not incubating at the time of admission; not associated with mechanical ventilation or Patients with severe HAP who require mechanical ventilation
ICU HAP	A pneumonia that occurs 48 hours or more after ICU admission

Table 1. Pneumonia Classification

Pseudomonas aeruginosa (PA) is a complex gram-negative facultative aerobe. This microbe is a common cause nosocomial infections and an antibiotic-resistant priority pathogen. *P.aeruginosa* is known impact lung infection with opportunistically colonize patient with cystic fibrosis, COPD and tuberculosis. In United States, *P.aeruginosa* is the most common gram-negative pathogen causing nosocomial pneumonia. *P.aeruginosa* is an uncommon cause of community-acquired pneumonia (CAP), but common cause of ventilator-associated pneumonia (VAP) and it is a significant cause of morbidity and mortality in critically ill patients and associated with worse clinical outcomes. It is an independent risk factor associated with high 30-day mortality, prolonged hospitalization in the ICU and extra cost. Pneumonia due to *P.aeruginosa* occurs in several distinct syndrome, such as hospital-acquired pneumonia (HAP) usually occurring in the ICU and prior intravenous antibiotic use within 90 day. Patient with *P.aeruginosa*-CAP, in general, initial empirical treatment required for initial treatment while waiting 48-72h for specific pathogen identification and antibiotic susceptibilities. The risk factor listed in IDSA/ATS pneumonia guideline are ICU admission, structural lung disease such as bronchiectasis or COPD with multiple exacerbation, tracheostomy and IRVS (intensive respiratory or vasopressor support).

The 2019 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guideline recommends initiating antipseudomonal drugs after considering the local epidemiology and validated risk factors for culture-positive PA pneumonia, such as prior infection (prior isolation) especially from respiratory tract, recent hospitalization, and the use of parenteral antibiotics in the last 90 days. For HAP/VAP with suspected *P.aeruginosa* (Table 2) or CAP, according to ATS/IDSA 2019 recommend clinician only cover empiric treatment options include piperacillin-tazobactam (4.5 g every 6 h), cefepime (2 g every 8 h), ceftazidime (2 g every 8 h), aztreonam (2 g every 8 h), meropenem (1 g every 8 h), or imipenem (500 mg every 6 h).

Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam-Based Agents
Antipseudomonal penicillins
Piperacilin-tazobactam 4.5 g IV q6h
OR
Cephalosporin
Cefepime 2 g IV q8h
Ceftazidime 2 g IV q8h
OR
Carbapenem
Imipenem 500 mg IV q6h
Meropenem 1 g IV q8h
OR
Monobactam
Aztreonam 2 g IV q8h

Table 2. Suggested Empiric Treatment Options for Clinically Suspected *P.aeruginosa*-VAP

In CAP cases, important to maintain the distinction between severe and non severe pneumonia, because the risk of inadequate empiric antibiotic therapy is much greater in severe CAP (Table 1). Therefore, we have highlighted these individual risk factors to help guide initial microbiological testing and empiric coverage for *P.aeruginosa.* Routine cultures in patients with pneumonia who treated for PA allow de-escalation of antibiotic therapy at 48 hours or back to standard CAP therapy if cultures do not reveal the pathogen

Minor Criteria	–	Respiratory rate of 30 breaths or more per minute
	–	Ratio of PaO_2 to fraction of inspired oxygen (ie, PaO_2/FiO_2) of 250 or less
	–	Multilobar infiltrates
	–	Confusion/disorientation
	–	Uremia (BUN 20 mg/dL or greater)
	–	Leukopenia (white blood cell [WBC] count less than 4000 cells/μL)
	–	Thrombocytopenia (platelet count less than 100,000/μL)
	–	Hypothermia (core temperature less than 36°C)
	–	Hypotension requiring aggressive fluid resuscitation
Major Criteria	–	Respiratory failure requiring mechanical ventilation
	–	Septic shock with need for vasopressor support

Table 3. 2007 IDSA/ATS for Defining Severe Community-acquired Pneumoni

For patients with HAP/VAP due to P. aeruginosa, IDSA/ATS 2016 recommend that the choice of an antibiotic for definitive (not empiric) therapy be based upon the results of antimicrobial susceptibility testing and against aminoglycoside monotherapy. The conventional treatments for PA infection are β-Lactam with antipseudomonal activity and fluoroquinolones, but novel antibiotic (**Table 4**) including ceftolozane/ tazobactam, ceftazidime-avibactam, imipenem/ relebactam, meropenem-vaborbactam and delafloxacin seem to be well tolerated and efficacious for the treatment of many infections caused by *P. aeruginosa* and this study have been recently introduced from Ibrahim D et al.

The treatment of PA infections in a clinical setting remains a notable challenge. Treatment with appropriate antibiotics, for empiric or definitive treatment, either combination therapy or the appropriate monotherapy. In cumulative meta-analysis of cohort studies from Tang, S.Y et al. who describe the result demonstrated no significant in mortality between patients administered with combined antibiotic or monotherapy treatment against *P.aeruginosa* bacteraemia.

Class	**Antibiotic agent**	**Dose recommended**	**Labeled indications for PA infections**
Novel β-lactams with β-lactamase inhibitors	Ceftazidime-avibactam	2.5 g every 8 h	HAP/VAP Complicated intraabdominal infections UTI including PNA
	Ceftolozone/tazobactam	1.5 g every 8 h	HAP/VAP Intraabdominal infections UTI including PNA
	Imipenem/Cilastatin-relebactam	1.25 g every 6 h	HAP/VAP Complicated intraabdominal infections UTI including PNA
	Meropenem-vaborbactam	4 g every 8 h	HAP/VAP UTI including PNA

Table 4. Novel antibiotic agents used for treatment *Pseudomonas aeruginosa* infections

Positioning of Piperacillin-tazobactam

Piperacillin-tazobactam is one of the broadest spectrum antimicrobial available, covering gram-positive, gram-negative, and anaerobic bacteria. It has been shown to be effective in the treatment of moderate and severe infections, such as pneumonia, complicated UTI, intrabdominal infections, soft-tissue infections, and gynecological infections. This drug is generally a well-tolerated antibiotic. The most common adverse affects include intestinal problems such as diarrhea, constipation, vomiting, and nausea followed by skin reactions. In the present study, no safety reports related to the use of the drug were found.

Piperacillin-tazobactam has been successfully used for the treatment in critically ill patient. Recently, continuous administration (continuous infusion) resulted in significantly: eradication and presumed of organism at the infection site, lower mortality rates, decreasing the length of hospital stay, and good outcome was defined as resolution of clinical signs and symptoms of infection in critically ill patients.

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MANAGEMENT OF SEVERE ASTHMA EXACERBATION

Understand the clinical approach and diagnosis of severe asthma exacerbation

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Introduction

Asthma is a chronic immunology disease and one of the main non-transmitted diseases which implies every age group but mostly starts in childhood.[1,2] From National Heart Institute, asthma is a chronic inflammatory airway disorder where a lot of cells roles specifically: mast cell, eosinophil, neutrophil (especially in sudden exacerbation, fatal exacerbation, work-induced asthma, smoking patient), T-lymphocyte, macrophage, and epitel cell.[3] Franjic et all stated that "Asthma is characterized by a variety of recurrent symptoms, reversible obstruction of the respiratory tract and bronchospasm. During seizures, there is cramping of the muscles in the lungs, the respiratory tract is narrowed and breathing is difficult. It is characterized by an inappropriately strong immune response and chronic inflammation of the tracheobronchial tree."[4]

The Global Burden of Disease Study reported in 2019, asthma has affected 262 million people around the world. In 2021, the cases were increasing to 300 million people with 1%-16% prevalence in some countries.[5] Most asthma-related deaths occur in low- and lower-middle-income countries, where under-diagnosis and under-treatment are challenging. Asthma is not commonly fatal but creates a vast direct and indirect economic burden including pharmacological treatment, health facilities, and lost of patient productivities.[6] Increasing diagnosis, treatment, and observation will reduce global non-transmitted disease load and make progress towards global health coverage.[2]

This chronic lower inflammatory disease is characterized by increased airway responsiveness which causes widespread narrowing of the lower airways that reverses either spontaneously or with treatment. Patient experiences often intermittent exacerbation and various bronchospasm levels, which often results in patient visits to the emergency room.[7,4] Patients accessing emergency care services can present with complaints that are extremely diverse. The most common symptoms are wheezing, dyspnea, and cough.[8]

Etiology

Some factors are linked to increased asthma risk probability, even though finding a single causing factor is quite hard. Asthma has a high probability to occur in a family member with asthma such as parents or siblings. Allergy histories (eczema, rhinitis) are also a higher risk of asthma prevalence. Urban lifestyle including housing complex, high air pollution, and more hygienic life style which reduce early exposure of allergen have higher risk of asthma.[9] Diseases in the early life stage (low birth weight, prematurity, tobacco exposure, air pollution, airway infection) affect lung development and increase the risk of asthma.[10] Babies fed with breastmilk show decreasing risk of wheezing disease than babies with formula or soymilk. [11]

Exposure to a variety of allergens and environmental irritants is also thought to increase the risk of asthma, including indoor and outdoor air pollution, house dust mites, mold, and exposure to chemicals, fumes or dust in the workplace. Children and adults who are overweight or obese have a greater risk of asthma. .[2,11] History of bronchiolitis in children is another risk of asthma. Around 40% of children with syncytial or parainfluenza virus will have persistent wheezing or asthma until the next stage of development. [9] Industrial countries tend to have plastic, farming, and chemical exposure in the working environment. The prevalence of asthma is higher in these countries. [11] Asthma occurs more often in the pre-pubertal boy but they have a higher possibility to recover from asthma in adolescence than girls. [9]

The phenotype of individuals contributes to asthma development and how their response to medical treatment. [12] Genomic variations coding beta-adrenoreceptor has been linked to the difference in responding beta-agonist cell response. In the future, specific therapy for specific individuals needs to be developed to reduce high-cost treatment for a patient with asthma. [11,12]

Pathophysiology

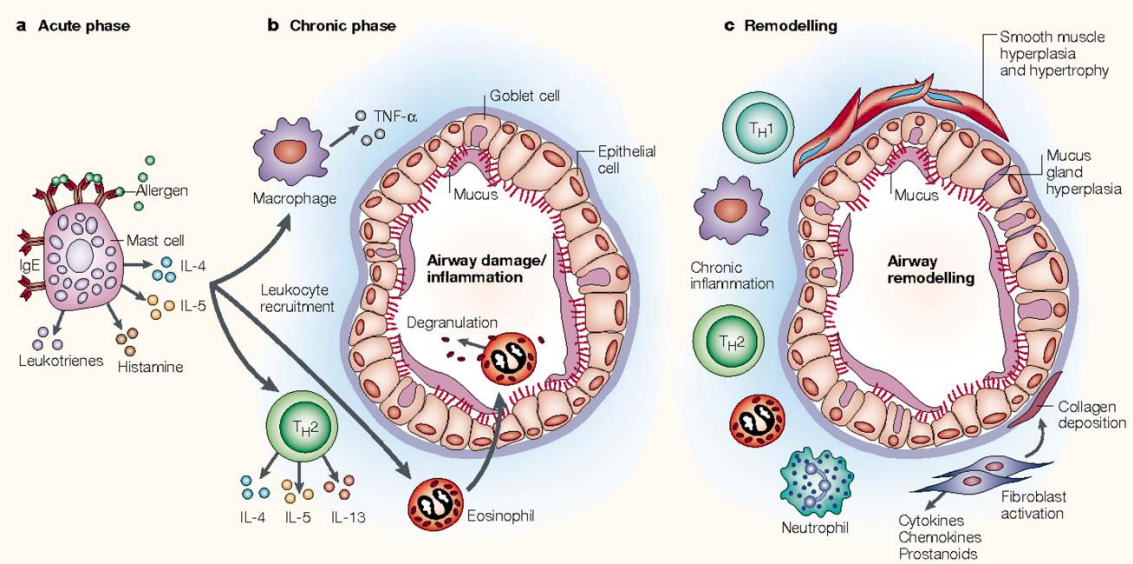


Image 1. Pathophysiology of Asthma. (Gern, J., & Busse, W. (2002). Relationship of viral infections to wheezing illnesses and asthma. Nature Reviews. Immunology, 2, 132 - 138.)

Symptoms are modulated by immunoglobulin (IgE) and triggered by allergic responses toward allergens such as pollens or animal fur. Sensitization happens in the first encounter producing specific IgE antibodies sticking to mast cells' surface. In the next exposure, allergen bond to specific IgE on mast cells which release inflammatory mediators such as leukotriene, histamine, and prostaglandin. These mediators induce asthma attacks via bronchospasm.[13]

Exacerbation is influenced by external and internal factors. Allergen is the most common external factor related to allergy reactions. Inflammatory response by immune cells and the substance they produce are internal factors of exacerbation. These factors induce bronchial wall muscle contraction, bronchial mucous swelling, and increasing mucous production. The mechanism will lead to increased airway resistance and bronchial lumen narrowing. The narrowing creates symptoms such as dyspnea, cough, and wheezing. This condition is really important to recognize in a short time and begin treatment as soon as possible.[4]

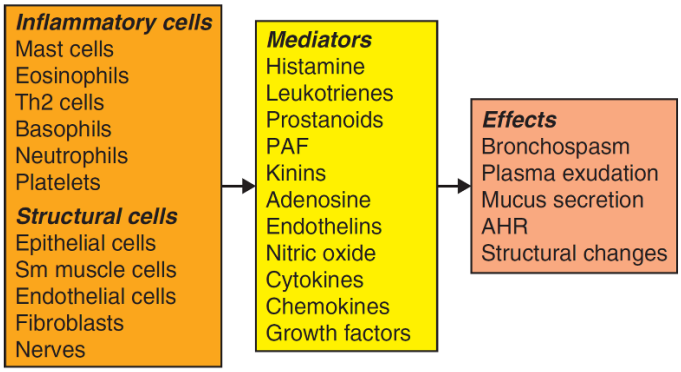


Image 2. Asthma mediator's summary. (Barnes, P. J., & Drazen, J. M. (2009). Pathophysiology of Asthma. Asthma and COPD, 399–423. doi:10.1016/b978-0-12-374001-4.00033-x)

If the symptoms were not well treated in a few years, there will be airway remodeling. Eosinophils, T-helper cells, and mast cells will migrate into the airway. Chronic inflammation causes hypertrophy of bronchial muscle, new vessel formation, and interstitial collagen deposition. Overproduction of mucous from goblet cells, increasing airway tonus, and hyperresponsive of the airway narrow the airway lumen, therefore worsening the symptoms. [9] The persistent obstruction is similarly seen in chronic obstructive pulmonary disease (COPD).[14]

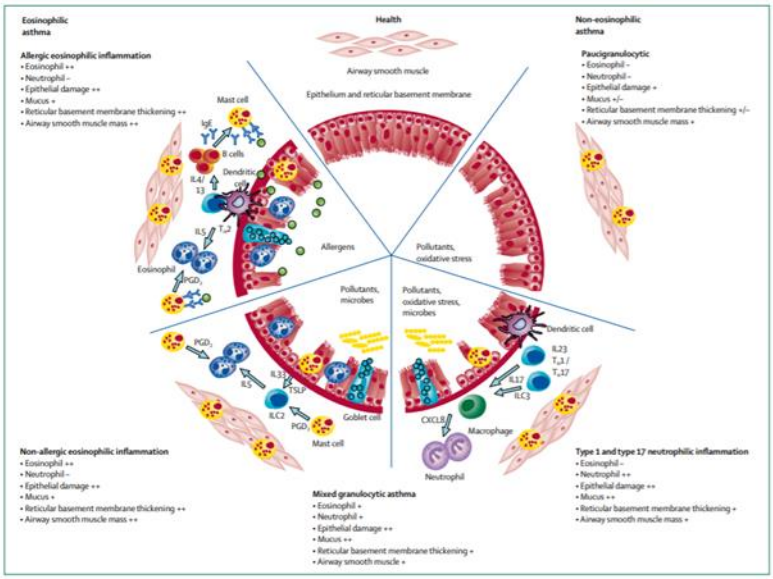
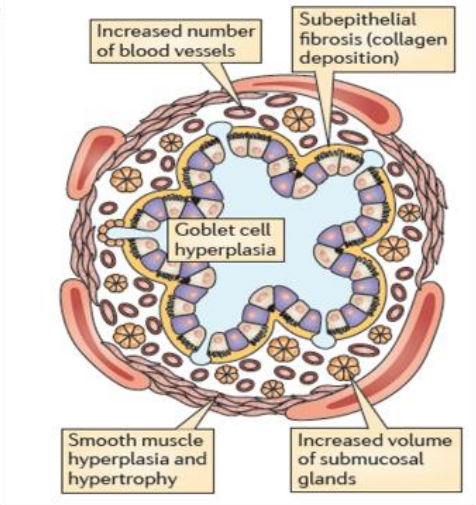


Image 3. Immunopathology of asthma. (Papi, A., Brightling, C., Pedersen, S. E., & Reddel, H. K. (2018). Asthma. The Lancet, 391(10122), 783–800. doi:10.1016/s0140-6736(17)33311-1)

Pathologic findings in patients with chronic asthma include bronchial wall thickening due to inflammation and edema, bronchial narrowing or obstruction, and the presence of mucus plugs that at times may be large and thick. This airway narrowing leads to alveolar hyperinflation and, in a subset of patients, may lead to the formation of bullae, the potential for bullae rupture, and the development of pneumothoraxes [4]



Airway From Patient with Asthma

Image 4. Airway from patient with asthma. (Fahy, J. Type 2 inflammation in asthma — present in most, absent in many. Nat Rev Immunol 15, 57–65 (2015). https://doi.org/10.1038/nri3786)

ASTHMA EXACERBATION MANAGEMENT IN THE EMERGENCY UNIT

Asthma management guidelines are based on a phased approach with progressively increased medication to achieve control of asthma symptoms and reduce the risk of exacerbations, with the option of reducing the dose of medication after a period of symptom control. While asthma is recognized as consisting of various disease subtypes, it is now often categorized into high (T2-high) and low (T2-low) type 2 asthma based on the predominance of cytokines and their cellular sources. Most asthma treatments target inflammatory pathways within the lungs to help improve symptoms, reduce the risk of exacerbations and avoid long-term complications. However, it is increasingly recognized that other treatable traits overlap with asthma and may contribute to poor symptom control in asthma. [6]

Short-acting bronchodilator. Short-activng bronchodilators are best administered via an oxygen-powered nebulizer. If a nebulizer is not available, a pMDI with a spacer is the preferred delivery method. Dosage of SABA should be 2.5 to 5 mg of salbutamol via a nebulizer (consider continuous nebulization at 10 mg/h or up to 10 doses administered every 20 minutes via a pMDI + spacer). Dosage of short-acting muscarinic antagonist should be 0.5 to 0.75 mg of ipratropium bromide via a nebulizer or up to 10 doses administered via a pMDI with a spacer.[17]

Inhaled corticosteroids. Inhaled corticosteroids (ICS) remain the mainstay of asthma management but their use earlier in the course of the disease is suggested. Recent evidence suggests a potential role for ICS in combination with a long-acting beta-agonist (LABA) for use as needed in mild asthma while maintenance and reliever therapy regimens are widely accepted. Other anti-inflammatory strategies including ultra-fine particle ICS, leukotriene receptor antagonists and macrolide antibiotics may show efficacy in certain phenotypes as well.[6] A study conducted by Edmonds et.al with a total of 1403 subjects, with symptoms of asthma exacerbation in the ED to compare inhaled corticosteroids with placebo. Administration of inhaled corticosteroids reduces hospital admission rates.[15] A study conducted by Ito et.al with a total of 98 subjects, with severe asthma symptoms were given additional inhalation therapy with Budesonide Suspension compared to without Budesonide. Administration of Budesonide inhalation therapy accelerates recovery time by 2X faster and shortens hospital time by 2 days. Therapy with the addition of inhaled Budesonide Suspension in cases of severe asthma reduces hospital stays and accelerates recovery time. [I6]

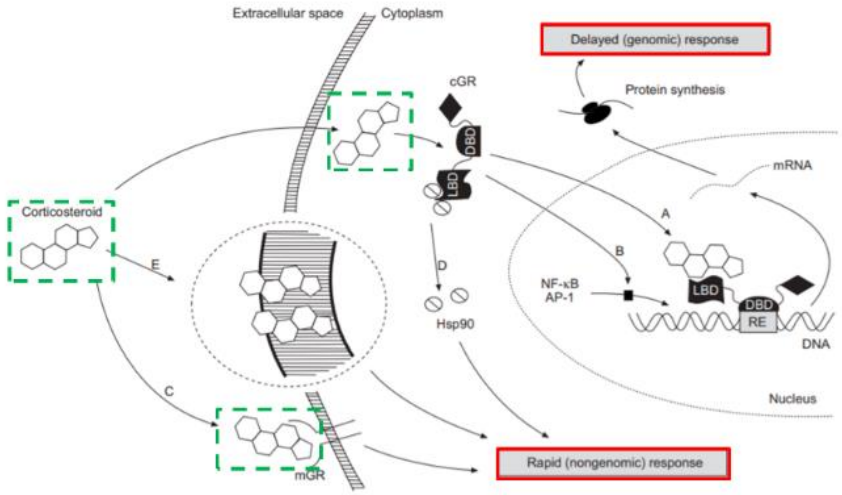


Image 5. Action of inhaled corticosteroid (G. Horvath, A. Wanner, Inhaled corticosteroids: effects on the airway vasculature in bronchial asthma, European Respiratory Journal Jan 2006, 27 (1) 172-187; DOI: 10.1183/09031936.06.00048605)

Oxygen therapy. Oxygen therapy should be used, if available, and titrated to maintain SpO2 at 93% to 95%. Such modality gives better clinical outcomes and is safer than high-flow 100% oxygen therapy. The unavailability of pulse oximeter is not a contraindication for oxygen therapy.[17]

Systemic corticosteroids. Prompt administration of systemic corticosteroids (oral or intravenous) improves clinical outcomes in patients with asthma exacerbation. Systemic corticosteroids should be administered within 1 hour of presentation, followed by a 5- to 7-day course with once a day

(a.m.) administration. Oral administration is as effective as intravenous. Systemic corticosteroids enhance resolution of exacerbations and prevent relapse. Dosage of prednisolone should be 1 mg/kg/d (maximum dose is 50 mg/d) or an equivalent dose of another OCS.[17]

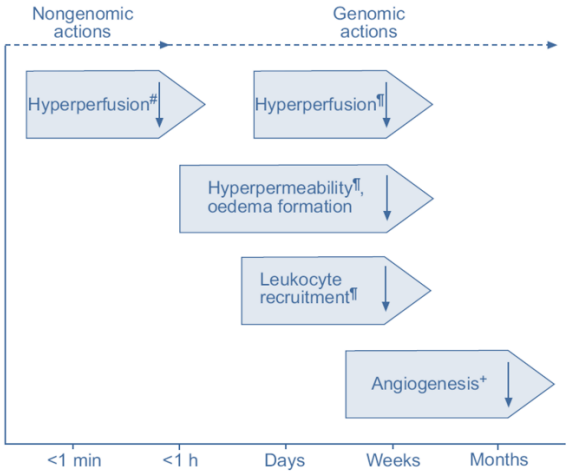


Image 6. Vascular Effects of Inhaled Corticosteroid. Inhaled corticosteroids have rapid, delayed, and long-term effects on airway vasculature in patients with asthma. (G. Horvath, A. Wanner, Inhaled corticosteroids: effects on the airway vasculature in bronchial asthma, European Respiratory Journal Jan 2006, 27 (1) 172-187; DOI: 10.1183/09031936.06.00048605)

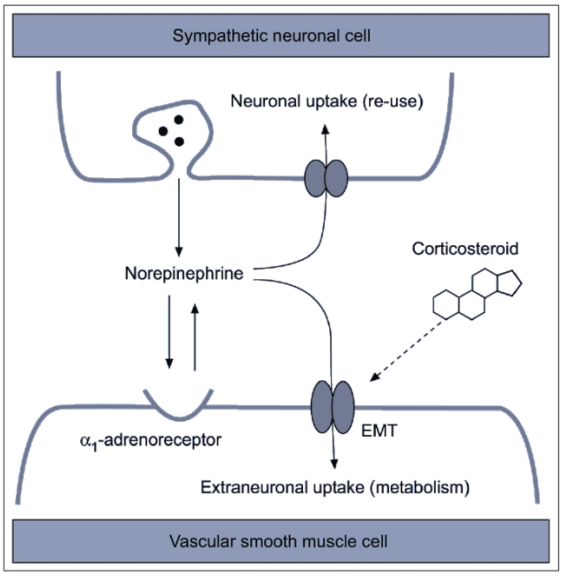


Image 7. Vascular Effects of Inhaled Corticosteroid. Glucocorticoids facilitate the noradrenergic neuromuscular signal transmission by rapidly (within 5 minutes) inhibiting the extraneuronal monoamine transporter (EMT) in vascular smooth muscle cells.G. Horvath, A. Wanner, Inhaled

corticosteroids: effects on the airway vasculature in bronchial asthma, European Respiratory Journal Jan 2006, 27 (1) 172-187; DOI: 10.1183/09031936.06.00048605

Noninvasive positive ressure ventilation—including biphasic positive airway pressure and continuous positive airway pressure—may be considered for patients who have severe asthma exacerbations but do not require immediate intubation although its role in treating asthma exacerbation remains unclear. In a 2012 Cochrane systematic review of 2 RCTs involving 96 patients with asthma exacerbation, there was no significant difference in the rate of tracheal intubation between the noninvasive positive pressure ventilation and usual medical care groups. In contrast, in a recent large observational study of 53,654 intensive care unit patients with asthma exacerbation, Althoff et al applied robust causal inference approaches and found an association between the use of noninvasive positive pressure ventilation and lower risk of receiving invasive mechanical ventilation and in-hospital mortality. Failure of noninvasive positive pressure ventilation may be an indication for intubation and invasive mechanical ventilation.[18]

Invasive mechanical ventilation. Of adult patients hospitalized with asthma exacerbation, 3% to 5% develop respiratory failure requiring mechanical ventilation. The decision to intubate and initiate mechanical ventilation is based on clinical judgment, and is guided by signs of respiratory failure (ie, inadequate oxygenation or ventilation), clinical symptoms (eg, altered mental status and respiratory fatigue), comorbidities, and the clinical trajectory. The primary goals of mechanical ventilation include providing sufficient oxygenation and ventilation while minimizing the risk of dynamic hyperinflation secondary to expiratory airflow limitation and alveolar air trapping.[18]

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UPDATE TUBERCULOSIS PREVENTIVE TREATMENT

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Indonesia is one of the countries with the highest burden of Tuberculosis, currently ranked third among in the world with incedence of 845.000 cases(1). WHO has agreed and reaffirmed the 2030 SDGs to reduce TB mortality and reduce TB incidence. In addition, four global goals have been set to reach the goals of SDGs, one of which is to provide Tuberculosis Prevention Therapy (TPT). The goals of the 2035 TB Eradication Strategy show that effective and aggressive TB treatment and prevention efforts can only be achieved when combined with the provision of TPT in cases of latent Tb (fig. 1).

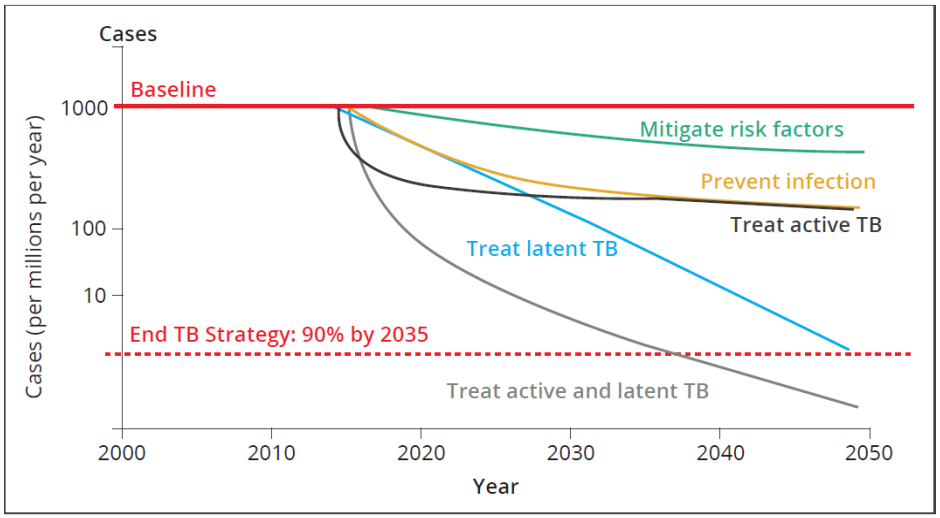

Fig 1. Model of Tuberculosis Control

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *M.tuberculosis* antigens with no evidence of clinically manifest active TB(2). LTBI's characteristics include has positive IGRA (*interferon-gamma release assay)* and TST *(tuberculin skin test)* and normal chest x-ray. In several studies, an average of 5-10% of infected people develop active tuberculosis during their lifetime, usually within the first 5 years after the first infection(3) mainly an individual with impaired immune response. After an individual is infected with *Mycobacterium tuberculosis*, the innate immune response will fully eliminate the infection without detecting in the body or lead to a state persistent where the immune system can not completely eliminate M.Tb from the body, but it controls the M.Tb and symptoms do not appear. In person with LTBI, several factors increase the risk of developing active TB, particularly related to an impaired immune response such as HIV infection, cancer on therapy, organ transplant, hemodialysis. People who living with HIV has higher risk than other for possibility 30% for developing active TB.

Not all individuals infected *M. tuberculosis* develop active TB. Based on WHO guideline, there is selecting at-risk population for identification of LTBI and consideration should be given the treatment,include :

- People living with HIV
- HIV-negative household contacts of person with pulmonary TB
- Other HIV-negative at-risk groups (patient with immunocompromised and prisoners, health workers, homeless people, and people who use drugs)

Increased risk of progressing from latent TB to active TB for vulnerable populations include people living with HIV and children under the age of 5 years. For people with HIV or children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on appropriate clinical evaluation should be given TB preventive treatment even if LTBI testing is unavailable. Meanwhile, for children aged $\geq$ 5 years, adolescent, adult and other HIV-negative at-risk groups should be systemically tested to consider for preventive treatment.

Identification for Latent TB Infection

There is no gold standard for identification or diagnosis of LTBI. *Interferon-gamma release assay* (IGRA) and and *Tuberkulin skin test* (TST) still in use to identificatoin of LTBI. WHO recommend a symptom-screening rule of a combination of current cough, weight loss, night sweats, and fever to exclude active TB in adults and adolescent(2) and confirmation of LTBI using IGRA or TST would be desirable before starting TB preventive treatment. Addition of chest radiographic finding to rule out active TB disease.

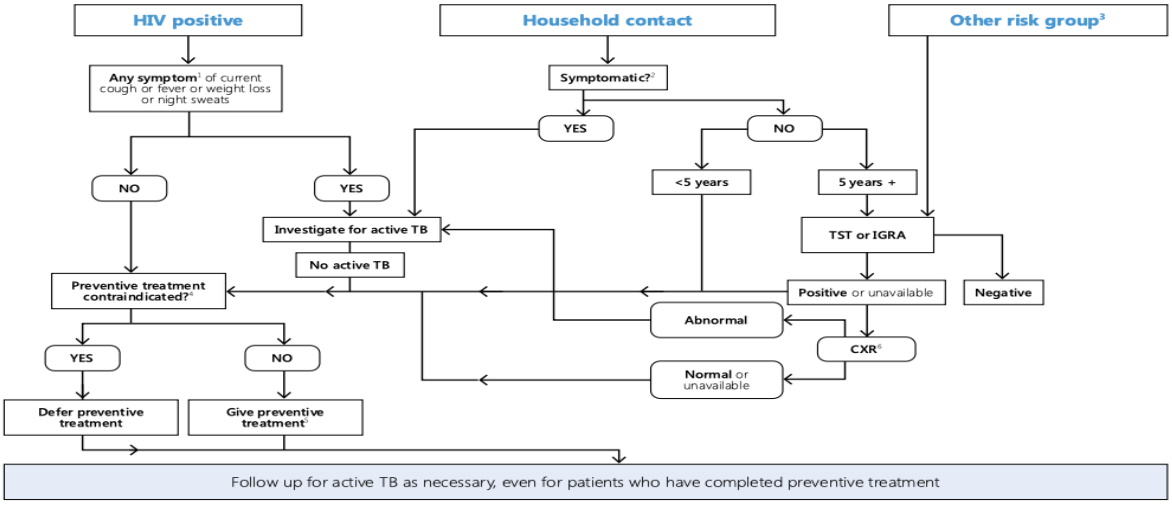

Fig 2. Algorithm for LTBI and TB preventive treatment in individuals at risk

Either TST or IGRA can be used to test for LTBI. Both available test – are indirect and require a competent immune response to identify people infected with TB. A positive test result by either method is not itself a reliable indicator of the risk of progression to active disease.

Tuberculosis Preventive Treatment Options

The following options are recommended for the treatment of LTBI (2):

- Daily isoniazid (6H)
- Weekly rifapentine plus isoniazid (3HP)
- Daily isoniazid plus rifampicin (3HR)

And may also be offered as alternatives : daily rifapentine plus isoniazid (1HP) or daily rifampicin alone (4R).

- Daily isoniazid (6H)

For people living with HIV showed isoniazid monotherapy reduces the overall risk for TB by 33% (2) and the that preventive efficacy reached 64% for people with a positive TST. The 6H should be given daily as monotherapy for six months (1 month = 30 day or given in 182 doses).

Isoniazid monotherapy for 6 months is recommended for treatment of LTBI in both adults and children in countries with high and low TB incidence.

Special precaution for patient with peripheral neuropathy, risk factor for peripheral neuropathy (e.g HIV infection, malnutrition, alcoholism, renal impairment, DM, pregnancy or lactation). Coadministration with pyridoxine is recommended in all patient at start therapy (25 mg daily)

- Weekly rifapentine plus isoniazid (3HP)

Compare the effectiveness of a 3-month weekly regimen of rifapentine plus isoniazid (#HP) with that of isoniazid monotherapy. There is no significant difference was found in the incidence of active TB between 3HP regimen and 6H or 9H(2). But, for the risk of hepatotoxicity was significantly lower with 3HP in adult PLHIV (people living with HIV) (RR 0.26, 95% CI 0.12; 0.55) and in those without HIV (RR 0.16, 95% CI 0.10; 0.27) .

Rifapentine and isoniazid weekly for 3 months may be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for both adults and children in countries with a high TB incidence(2). Should be given once a week at the same time, in 12 doses.

For Rifampicin- and rifapentine- containing regimens should be prescribed with caution to PLHIV who are on ART because of potential drug interaction (nevirapine and protease inhibitor group).

In the National Program, this regimen is already available in fix dose compact (FDC). Given in 3 tablet once a week.

- Daily isoniazid plus rifampicin (3HR)

Rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for children and adolescents aged < 15 years in countries with a high TB incidence(2).

Combination therapy of rifampicin plus isoniazid for three months (1 month= 28 day) for 3-month or given in 84 doses.

- Daily rifapentine plus isoniazid (1HP)

In 2019, the GDG published study of the 1HP regimen comparing the efficacy and safety with 9H alone. But this regimen will be in The National Program in the future. Restricted to individuals ≥ 13 years. The 1 HP regimen can not yet be used in The National Program because there is still need more scientific evidence to ensure the safety.

No	Sasaran	Pilihan paduan TPT		
		3HP	3HR	6H
1	Kontak serumah usia < 2 tahun *)		√	√
2	Kontak serumah usia 2 – 4 tahun	√		
3	Kontak serumah usia ≥ 5 tahun	√		
4	ODHA usia < 2 tahun *)		√	√
5	ODHA usia ≥ 2 tahun **)	√		√
6	Kelompok risiko lainnya	√		

Fig 3. Treatment choices for TPT based on The National Program

Drug regimen	Dose per kg body weight	Maximum dose
Isoniazid alone, daily (6H)	5 mg	300 mg
Isoniazid plus rifampicin, daily (3HR)	Isoniazid 5 mg Rifampicin 10 mg	Isoniazid 300 mg Rifampicin 600 mg
Rifapentine plus idoniazid, weekly (3HP)	-	-

Table 1. Recommended dosages of drugs for the treatment of LTBI

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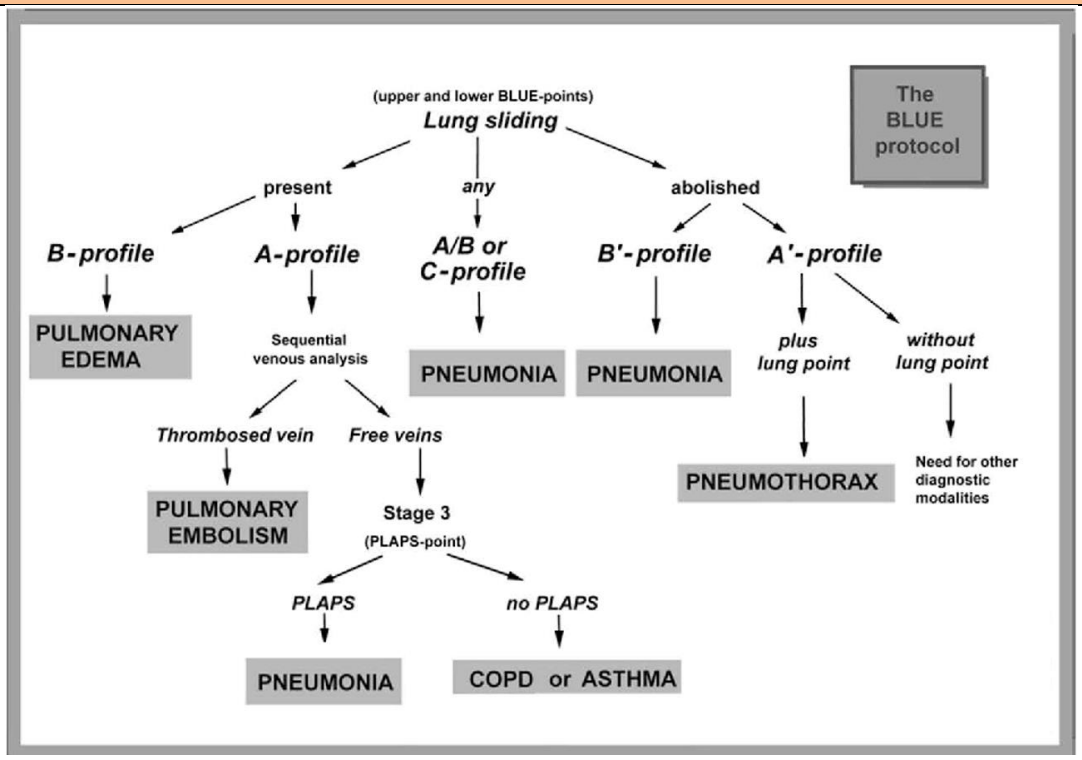
WORKSHOP

THE 10th JAKARTA INTERNATIONAL CHEST
AND CRITICAL CARE INTERNAL MEDICINE 2022

LUNG ULTRASOUND

No	Melakukan Keterampilan	Checklist	
1	Mengucapkan salam, memperkenalkan diri, memastikan identitas pasien, menjelaskan dan meminta persetujuan tindakan yang dilakukan		
2	Memeriksa ketersediaan alat		
3	Meminta pasien berada dalam posisi berbaring USG juga bisa dilakukan dalam posisi duduk/berbaring		
4	Menentukan lokasi peletakan *probe* secara anterior, lateral, atau PLAPS (Posterior/Lateral Alveolar/Pleural Syndrome)		
5	Pengenalan Alat USG		
	Pengenalan layar		
	Pengenalan tombol (cara memasukkan data pasien, freeze, measurement, penulisan teks, M-Mode)		
	Pengenalan Probe		
6	Melakukan Evaluasi Pencitraan Normal di Toraks Kanan dan Kiri	Toraks Kiri	Toraks Kanan
	Mengevaluasi adanya *Lung sliding*		
	Mengevaluasi adanya *seashore sign*		
	Mengevaluasi *A sign*		
	Mengevaluasi *B sign*		
7	Melakukan Evaluasi Pencitraan Abnormal di Toraks kanan dan Kiri	Toraks Kiri	Toraks Kanan
	Mengevaluasi penebalan pleura		
	Mengevaluasi *Barcode Sign*		
	Mengevaluasi *Lung Point*		
	Mengevaluasi *air bronchogram*		

	Mengevaluasi adanya massa dan mengukur volume		
	Mengevaluasi adanya efusi pleura,jenis dan volumenya		
Pengenalan BLUE Protocol			



THORACOCENTESIS

No	Melakukan Keterampilan	Checklist
A	Menerangkan prosedur tindakan yang akan dilakukan kepada pasien dan keluarga, indikasi dan komplikasi yang mungkin timbul, serta kemungkinan yang akan terjadi bila tidak dilakukan prosedur tersebut.	
B	Menerangkan prosedur tindakan yang akan dilakukan kepada pasien dan keluarga, indikasi dan komplikasi yang mungkin timbul, serta kemungkinan yang akan terjadi bila tidak dilakukan prosedur tersebut.	
C	Mempersiapkan Alat dan Bahan yang Dibutuhkan	
	Alat: - IV Catether no 14 dan 16 - Spuit 5cc 2 buah - Spuit 20cc 1 buah - Jarum 23 G - Infus Set atau Transfusi Set 1 Set Bahan: - Lidocaine 2% 1-2 ampul - Povidone Iodine - Spuit 5 cc 2 buah - Kassa Steril - Micropore	
D	Prosedur Tindakan	
1	Meminta pasien berada dalam posisi duduk tegak, kedua lengan pasien diletakkan diatas penangga di depan dada.	

2	Menentukan lokasi dan memberikan tanda pada lokasi torakosentesis (lokasi adalah satu sela iga di bawah perubahan suara sonor menjadi redup pada perkusi) atau ditentukan dengan USG.	
3	Mencuci tangan dan menggunakan sarung tangan steril.	
4	Melakukan tindakan asepsis dan antisepsis menggunakan povidon iodin pada daerah kulit yang ditentukan.	
5	Melakukan anestesi lokal dengan infiltrasi kulit dengan lidokain 1-2% dengan jarum 23 G hingga membentuk *wheal* intradermal.	
6	Menusuk jarum tegak lurus terhadap dinding dada (di bagian atas costae), sambil menyuntikkan lidokain sampai mencapai pleura parietalis.	
7	Tarik sedikit jarum sampai sudah tidak keluar cairan efusi, kemudian masukkan sisa lidocaine yang ada (2-3ml) di tempat tersebut (pleura parietalis). Setelah mencapai pleura parietal, lakukan aspirasi secara lembut sampai mendapatkan cairan efusi.	
8	Setelah tercapai anestesi (5-10 menit), lakukan pungsi pleura dengan IV Cath no 14/16 pada daerah yang dianestesi.	
9	Aspirasi cairan dengan spuit 20cc untuk pemeriksaan yang dibutuhkan seperti analisis cairan pleura, sitology, kultur ataupun ADA.	
10	Memasang set infus atau set transfusi (bo leh menggunakan *threeway*), lalu mengalirkan cairan keluar.	
11	Mencabut kateter secara lege artis di awal inspirasi.	
12	Menutup bekas luka tusukan jarum dengan kasa steril dan micropore.	
13	Merapikan alat dan membuang bahan medis habis pakai ke tempat sampah medis.	
14	Membuka sarung tangan, lalu mencuci tangan.	
E	Penanganan Pasca Tindakan	
1	Menilai hemodinamik pasca prosedur (tekanan darah, nadi, dan frekuensi nafas).	

2	Pemantauan hemodinamik pasien dalam 30 menit pertama pasca tindakan di ruang prosedur.	
3	Dokumentasikan perkembangan hemodinamik. Jika kondisi membaik, pasien dikembalikan ke ruang perawatan	

PLEURAL DRAINAGE (SELDINGER'S TECHNIQUE)

No	Melakukan Keterampilan	Checklist
A	Menerangkan kepada pasien dan keluarga pasien terkait indikasi dan komplikasi yang mungkin timbul, serta kemungkinan yang akan terjadi bila tidak dilakukan prosedur tersebut.	
B	Setelah mengerti dan setuju, pasien dan keluarga menandatangani surat persetujuan tindakan medis dan *site marking*	
C	Mempersiapkan alat dan bahan yang dibutuhkan:	
	Alat: - Gunting non bedah 1 buah - Meja steril berisi 1 set minor - Duk bolong steril - Rocket Pleural Drain nomor 12 dan 18 Bahan: - Kasa Steril - Plester - Alkohol 70% dan povidone iodine - Spuit 5ml 1-2 buah - Lidocaine 2% 2-4 ampul - Jarum dan benang jahit (Silk 2.0)	
D	Evaluasi hemodinamik dan konfirmasi dengan hasil pemeriksaan lab	
E	Prosedur Tindakan	
1	Tentukan lokasi insersi dengan bantuan USG	
2	Memposisikan pasien dengan sisi yang sakit menghadap ke arah dokter, tangan sisi paru yang sakit diangkat keatas kepala.	

3	Melakukan tindakan antisepstik dengan menggunakan betadine dialnjutkan dengan menggunakan alkohol 70% dengan gerakan berputar ke arah luar.	
4	Melakukan anestesi local lapis demi lapis dari kulit hingga pleura parietalis menggunakan lidocaine. Aspirasi sebelum infiltrasi obat suntik pada tiap lapisan. Anestesi dilakukan pada daerah yang akan dipasang mini pleural drain atau pada sela iga 5-6 axilaris posterior	
5	Melakukan pungsi percobaan menggunakan syringe anestesi tersebut	
6	Memasukkan mandrain/jarum pleural drain secara tegak lurus sampai menembus masuk rongga pleura, masukkan guide wire melalui catheter tab, lalu mandrain dikeluarkan	
7	Membuat sayatan ± 0,5 cm pada kulit, tepat diatas guide wire	
8	Melakukan insersi dilator sampai masuk ke rongga pleura, lalu dilator dicabut, guide wire tidak boleh tercabut.	
9	Melakukan insersi pleural catheter sampai masuk ke rongga pleura dengan bantuan guide wire, lalu guide wire dicabut dilanjutkan dengan aspirasi.	
10	Kateter/pleural drain kemudian difiksasi menggunakan jahitan tabbac, lalu ditutup dengan kassa steril yang telah diberi betadine dan difiksasi pada dinding dada menggunakan plester.	
F	Penanganan Pasca Tindakan	
1	Jika tindakan sudah selesai, pantau kelancaran aliran drain, monitor tanda vital pasca tindakan dan observasi ada tidaknya komplikasi pasca tindakan.	
2	Pemantauan hemodinamik pasien dalam 30 menit pertama pasca tindakan di ruang prosedur.	

3	Dokumentasikan perkembangan hemodinamik. Jika kondisi membaik, pasien dikembalikan ke ruang perawatan.	

DIAGNOSTIC BRONCHOSCOPY

No	Melakukan Keterampilan	Checklist
A	Menerangkan prosedur tindakan yang akan dilakukan kepada pasien dan keluarga, indikasi, dan komplikasi yang mungkin timbul, serta kemungkinan yang akan terjadi bila tidak dilakukan prosedur tersebut.	
B	Setelah mengerti dan setuju, pasien dan keluarga menandatangani surat ijin tindakan.	
C	Memastikan pasien memahami bahwa pasien perlu menjalani *one day care*	
D	Mempersiapkan Alat dan Bahan yang diperlukan	
	Alat: - Satu set peralatanBronkoskopi - Sumber oksigen dan aparatusnya - *Mouth piece* - Kassa Steril - Kain penutup mata - Monitor tanda vital (termasuk *pulse oximetry*) - *Mucous Collector* dan wadah penampung bilasan - Untuk Sikatan bronkus: sikat dengan selubung, sikat kateter ganda tertutup polietilenglikol, gelas obyek minimal 6 buah, alkohol 96 % - Untuk Biopsi forsep: alat biopsi forsep, wadah berisi formalin 40 % - Alat *Grasping set* untuk pengambilan benda asing Bahan: - Midazolam 5 mg, 1 ampul - Fentanyl 100 mcg, 1 ampul - Lidocaine 2 %, 1 ampul	

	- Syringe 5 cc, 3 buah - Syringe 20 cc, 3 buah - Cairan NaCl 0,9 % - Xylocaine spray 10 % - Xylocaine PDF 40% - Obat resusitasi: Adrenalin ampul, dexamethason ampul, SA ampul, bicnat ampul, bronkodilator ampul)	
E	Prosedur Bronkoskopi dasar tanpa pendampingan anestesi	
1	Memasang monitor tanda vital dan saturasi oksigen, dilakukan pemeriksaan hemodinamik	
2	Anestesi local dan/atau topikal : - Inhalasi Xylocaine PDF 3cc dalam posisi duduk - Xylocaine spray 10 % 5 – 7 semprot daerah laringo-faring dan pita suara (menggunakan kaca laring) - Bila via hidung: semprotkan 30 mg lidocaine 4 % atau 10 % ke ostium nasal Injeksi lidocaine 2 % 2 mL ke trakea melalui cartilage cricothyroid	
3	Pasien diposisikan berbaring terlentang dan ditempatkan bantal di belakang bahu	
4	Bronkoskopi diinspeksi dan kejernihan gambar diperiksa	
6	Menutup kedua mata pasien dengan kain penutup untuk mencegah terkena larutan lidocaine/cairan pembilas.	
7	Meletakkan *mouth piece* di antara gigi atas dan bawah untuk melindungi bronkoskop.	
8	Melakukan premedikasi dengan pemberian injeksi Midazolam mulai dari 2 mg IV 5 menit dan/atau Fentanyl maksimal 200 mcg IV pada pemberian pertama sebelum insersi	
9	Bronkoskop mulai dimasukkan melalui celah *mouth piece*	
10	Melakukan inspeksi faring	

11	Instrument dimasukkan ke dorsal/epiglottis, mobilitas pita suara dilihat pada saat pasien menyebutkan “ii”	
12	Pita suara diinstilasi dengan Xylocaine PDF 40% yang telah diencerken dengan NaCl 0.9% (1:4) melalui saluran di bronkoskop. Sebelum diinstilasi, informasikan bahwa hal itu dapat merangsang batuk. Instilasi Xylocaine dengan jumlah yang sama dapat diulangi bila pasien terbatuk selama dilakukan tindakan. Xylocaine yang berlebihan diaspirasi dari sekitar laring	
13	Instrumen dimasukkan melalui bagian terlebar dari glottis pada saat inspirasi tanpa menyentuh pita suara. Pasien diberitahu bahwa hal ini dapat menimbulkan sensasi tercekik yang segera hilang	
14	Trakea, karina, dan percabangan bronkus dinilai dan dianestesi dengan instilasi Xylocaine PDF 40% yang telah diencerkan dengan NaCl 0,9% (1:4) maksimal 6 kali. Lobus superior paru kanan dan kiri dianestesi dengan injeksi langsung lidocaine (dosis maksimal instilasi lidocaine 400 mg)	
15	Inspeksi menyeluruh dilakukan pada semua percabangan bronkus sampai bronkus subsegmental.	
16	Bila visualisasi terrhalang sekret pada lensa distal, semprot dengan 5 mL NaCl 0,9 % yang diaspirasi kembali saat pasien batuk. Secara alternatif dilakukan fleksi ujung bronkoskop dan dengan hati-hati diusapkan pada mukosa trakea atau bronkus.	
F	Prosedur Sikatan/ Brushing untuk Sitologi	
1	Setelah bronkoskop berada pada daerah bronkus yang dicurigai terdapat kelainan, alat sikat dimasukkan melalui bronkoskop.	
2	Melakukan sikatan beberapa kali sampai dirasa cukup.	
3	Setelah selesai melakukan sikatan, alat sikat ditarik ke dalam kanal bronkoskop.	

4	Mengeluarkan sikat dari selubung sepanjang ± 5 cm, kemudian sikat dijentikkan pada gelas obyek untuk dibuat sediaan apus atau ujung sikat digunting dan dimasukkan ke dalam pot steril berisi media transpor / media kultur (sikat kateter ganda untuk pemeriksaan mikroorganisme).	
5	Sediaan apus untuk pemeriksaan sitologi dibagi menjadi sediaan basah (direndam dalam wadah berisi alkohol 96 %) dan sediaan kering.	
G	Prosedur *Forcep* Biopsi	
1	Setelah bronkoskop berada pada daerah bronkus yang dicurigai terdapat kelainan, ujung bronkoskop ditempatkan ± 4 cm di atas daerah tersebut.	
2	Forsep dibuka lalu didorong sampai terbenam di massa	
3	Forsep ditutup, lalu ditarik sambil melihat jaringan yang didapat (hindari jaringan nekrotik).	
4	Mengeluarkan forsep dan material yang didapat.	
5	Spesimen direndam dalam wadah berisi cairan formalin 40 %.	
6	Evaluasi perdarahan. Bila tidak ada perdarahan, bronkoskop dikeluarkan.	
H	Prosedur Ekstraksi Benda Asing	
1	Setelah bronkoskop masuk, memvisualisasi area yang dicurigai terdapat benda asing.	
2	Setelah benda asing ditemukan, melakukan evaluasi terhadap bentuk, jenis, sifat dan ukuran	
3	Memilih dan memasukkan instrumen yang sesuai: - *Grasping forceps* untuk mengeluarkan benda pipih atau tipis anorganik (pin/jarum), atau organik tapi keras (tulang) - *Basket* untuk benda berukuran besar dan tebal	
4	Mengeluarkan instrumen dan benda asing yang diekstraksi	

5	Evaluasi perdarahan atau benda asing lainnya yang mungkin masih tertinggal. Bila tidak ada, bronkoskop dikeluarkan.	
I	Penanganan Pasca Tindakan	
1	Jika tindakan sudah selesai, intrumen dikeluarkan. Skop ditarik sambil dilanjutkan memonitor tanda vital pasca bronkoskopi dan observasi ada tidaknya komplikasi pasca tindakan.	
2	Pemantauan hemodinamik pasien dalam 30 menit pertama pasca tindakan di ruang prosedur.	
3	Dokumentasikan perkembangan hemodinamik. Jika kondisi membaik, pasien dikembalikan ke ruang perawatan.	

ENDOBRONCHIAL ULTRASOUND

No	Melakukan Keterampilan	Checklist
A	Menerangkan prosedur tindakan yang akan dilakukan keapada pasien dan keluarga, indikasi dan komplikasi yang mungkin timbul serta kemungkinan yang akan terjadi bila tidak dilakukan prosedur tersebut.	
B	Setelah mengerti dan setuju, pasien atau keluarga menandatangani surat persetujuan tindakan medis.	
C	Mempersiapkan Alat dan Bahan yang Diperlukan	
	Alat - Satu set peralatan bronkoskopi dengan set EBUS - Sumber O_2 dengan aparatusnya - Mouth Piece - Kassa Steril - Kain penutup mata pasien - Pulse Oxymeter - Mucous Collector - Alat jarum TBNA, syringe - Gelas objek - Alkohol 96% Bahan - Sulfas Atropin (SA) 0.25 mg 1-2 ampul - Midazolam 5mg 1 ampul (opsional) - Xylocaine spray 10% - Obat resusitasi	
D	Evaluasi hemodinamik dan konfirmasi dengan hasil pemeriksaan lab	
E	Prosedur Tindakan	

1	Memastikan pasien telah teranestesi secara umum.	
2	Melakukan pemasangan ETT minimal ukuran 8 non-kinking dengan panduan flexible bronchoscopy.	
3	Melakukan instilasi anestesi di karina.	
4	Melakukan inspeksi umum pada kedua bronkus.	
5	Pengambilan sampel dengan TBNA dilakukan berdasarkan lokasi limfadenopati secara berurutan dimulai dari staging N tertinggi (dimulai dari N3, kemudian N2 dan N1).	
6	Sebelum melakukan pengambilan sampel dengan TBNA, lakukan evaluasi limfadenopati dengan ultrasound.	
7	Melakukan pengukuran diameter terbesar limfadenopati pada citra ultrasound.	
8	Memastikan lokasi TBNA serta landmark lainnya dapat dievaluasi; dan lokasi TBNA tidak dilalui oleh pembuluh darah dengan menggunakan Doppler.	
9	*Transbronchial needle system* (kateter fleksibel yang diujungnya terdapat jarum 21/22/19G dengan *internal sheath*) dimasukkan melalui kanal kerja bronkoskop sampai kateter keluar dari skop , tepat pada proksimal probe EBUS. Jarum harus tetap didalam kateter selama didorong melalui kanan bronkoskop untuk mencegah kerusakan pada skop bronkoskop.	
10	Mengintroduksi sheath hingga terlihat tip pada ujung skop.	
11	Memastikan jarum dalam posisi terkunci kemudian needle stopper dipindahkan sesuai dengan proyeksi kedalaman aspirasi (dapat dimulai dengan kedalaman 1 – 1.5 cm).	
12	Mengintroduksi needle sesuai kedalaman.	
13	Sampling dilakukan dengan cara *jabbing technique* diikuti dengan metode *slow pull* pada stilet.	

14	*Jabbing technique* dilakukan minimal 2x dan maksimal 4x pada setiap limfadenopati.	
15	Bila sampel tidak berhasil didapatkan pada pelaksanaan teknik tersebut maka perlu dilakukan aspirasi dengan tekanan negatif.	
16	Aspirasi dengan tekanan negatif dilakukan dengan menempatkan syringe pada ujung jarum setelah stilet dikeluarkan.	
17	Aspirasi dimulai setelah jarum menembus kelenjar getah bening dan selanjutnya keluarkan secara perlahan stilet dilanjutkan dengan penempatan syringe.	
18	Aspirasi dengan tekanan negatif dengan cara membuka stopper pada syringe diarahkan tegak lurus searah jam 12.	
19	Setelah dilakukan TBNA pada pembesaran KGB dilanjutkan dengan evaluasi dan kontrol perdarahan. Kemudian skop dikeluarkan.	
F	Persiapan Sediaan (*Slow Pull Method*)	
1	Setelah jarum TBNA dikeluarkan dari kanal kerja bronkoskopi, siapkan pot berisi formalin yang sudah ditandai lokasi KGB.	
2	Mengeluarkan jarum diarahkan ke dalam pot dan secara perlahan masukan stilet kembali ke tempatnya.	
3	Apabila tidak didapatkan jaringan dengan cara di atas, maka dapat diberikan tekanan negatif dengan syringe	
G	Penanganan Pasca Tindakan	
1	Jika tindakan sudah selesai, intrumen dikeluarkan. Skop ditarik sambil dilanjutkan memonitor tanda vital pasca bronkoskopi dan observasi ada tidaknya komplikasi pasca tindakan.	
2	Pemantauan hemodinamik pasien dalam 30 menit pertama pasca tindakan di ruang prosedur.	

3	Dokumentasikan perkembangan hemodinamik. Jika kondisi membaik, pasien dikembalikan ke ruang perawatan.	

ARGON PLASMA COAGULATION AND CRYOTHERAPY

No	Melakukan Keterampilan	Checklist
A	Menerangkan prosedur tindakan yang akan dilakukan kepada pasien dan keluarga indikasi dan komplikasi yang mungkin timbul serta kemungkinan yang akan terjadi bila tidak dilakukan prosedur tersebut.	
B	Setelah mengerti dan setuju, pasien diminta menandatangani surat persetujuan tindakan medis	
C	Mempersiapan alat yang dibutuhkan	
	Alat: - Satu set bronkoskopi, mesin dan *probe* APC (untuk prosedur APC) - Satu set bronkoskopi, mesin Cryo dan agen pendinging (untuk prosedur *cryotherapy*) - Sumber oksigen dan aparatusnya - *Mouth piece* - Kassa steril - Kain penutup mata pasien - Plat konduktor	
D	Prosedur Tindakan (APC)	
1	Memastikan sudah terpasang plat konduktor dan tertera indikator lampu hijau pada monitor APC	
2	Identifikasi lokasi lesi endobronkial dengan menggunakan bronkoskopi fleksibel	
3	Setelah lokasi teridentifikasi, *probe*-APC dimasukkan melalui *working channel* bronkoskopi fleksibel sampai terlihat penanda garis hitam diujung *probe*-APC, lalu diletakkan sekitar 1 cm diatas jaringan target.	
4	Memastikan pengaturan energi APC berkisar 25 ±20 W, fraksi O2 <	

	40%.	
5	Berkoordinasi dengan dokter Anestesi untuk tidak melakukan *bagging/* memberikan O2 pada saat prosedur APC akan dilakukan.	
6	Melakukan *continuous suction* agar area target bebas dari darah, mukus dan asap.	
7	Evaluasi ulang saluran napas bawah dengan bronkoskopi fleksibel pasca APC.	
E	Prosedur Tindakan (*Cryotherapy*)	
1	Mengidentifikasi lokasi lesi endobronkial dengan menggunakan bronkoskopi fleksibel	
2	Setelah lokasi lesi teridentifikasi, cryoprobe dimasukkan melalui working channel scope bronkoskop dan diletakkan diatas lesi. Proses pembekuan dilakukan hingga jaringan menempel ke ujung probe	
3	Durasi siklus pembekuan tergantung pada karakteristik jaringan dan dinilai oleh operator sesuai dengan ukuran jaringan beku yang terbentuk. ○ Lesi polipoid : ujung metal cryoprobe dapat diletakkan diatas atau didorong ke dalam jaringan. Cara ini dapat memaksimalkan volume pembekuan di sekitarnya. Aktivasi dilakukan selama 10-15 detik per kali . ○ Lesi infiltratif : cryoprobe diletakkan pada sudut tertentu di sisi lateral jaringan target, lalu dilakukan proses pembekuan dan pencairan. Probe lalu digeser 5 sampai 6 mm, dan proses pembekuan dan pencairan dilakukan kembali. Setiap zona pembekuan harus *overlap* dengan zona pembekuan sebelumnya. Prosedur dilanjutkan hingga seluruh lesi	

	endobronkial telah beku. Aktivasi dilakukan selama 10-15 detik per kali.	
4	Mengedukasi pasien untuk bronkoskopi ulang dalam 8-10 hari setelah *cryotherapy*. Materi yang telah luruh dikeluarkan dengan forcep, aspirasi atau *cryoadhesi*.	
F	Penanganan Pasca Tindakan	
1	Jika tindakan sudah selesai, intrumen dikeluarkan. Skop ditarik sambil dilanjutkan memonitor tanda vital pasca bronkoskopi dan observasi ada tidaknya komplikasi pasca tindakan.	
2	Pemantauan hemodinamik pasien dalam 30 menit pertama pasca tindakan di ruang prosedur.	
3	Dokumentasikan perkembangan hemodinamik. Jika kondisi membaik, pasien dikembalikan ke ruang perawatan.	

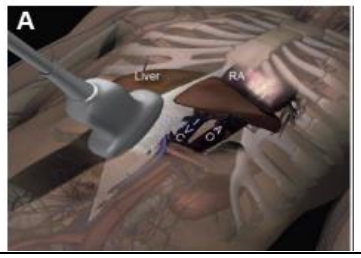
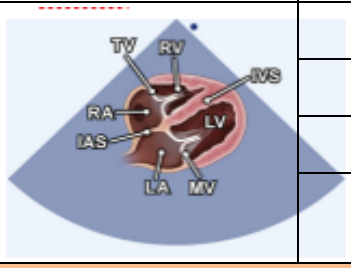
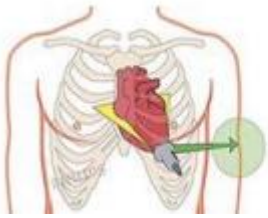
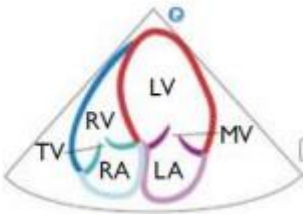
VASCULAR ACCESS PROCEDURE

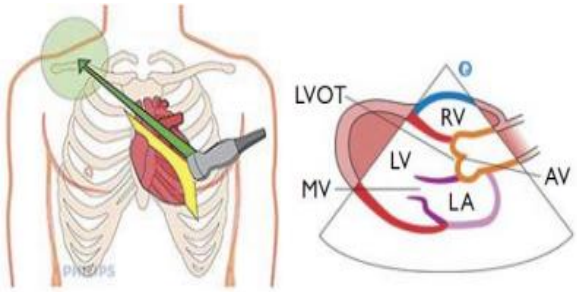
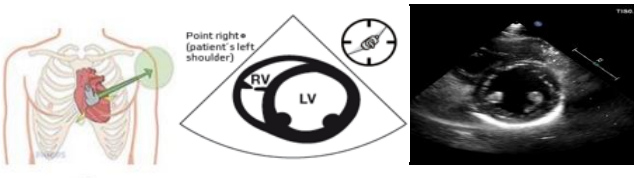
No	Melakukan Keterampilan	Checklist
A	Menerangkan prosedur tindakan yang akan dilakukan kepada pasien dan keluarga, indikasi dan komplikasi yang mungkin timbul, serta kemungkinan yang akan terjadi bila tidak dilakukan prosedur tersebut.	
B	Setelah mengerti dan setuju, pasien dan keluarga menandatangani surat persetujuan tindakan medis	
C	Dilakukan pemeriksaan hemodinamik dan periksaan darah	
D	Menentukan lokasi pemasangan kateter vena sentral : pada vena jugularis interna atau subklavia atau femoralis	
E	Menyediakan alat dan bahan yang diperlukan:	
	Alat: - Spuit 5ml 2 buah - Minor set steril - Set CVC - Sarung tangan steril - Duk bolong dan duk alas steril Bahan: - Benang jahit Mersilk 2.0 - Lidocaine 2% 5 ampul - Tegaderm - Gown steril - NaCl 0.9% 100ml 1 buah - NaCl 0.9% 500ml 1 buah - Transofix	

F	Prosedur Tindakan	
1	Memposisikan pasien ke posisi *tredelenberg*	
2	Mempelajari dan mengidentifikasi anatomi tempat prosedur akan dilakukan (bila perlu dibantu USG), dilanjutkan dengan tindakan sepsis dan antisepsis	
3	Jika akan dipasang di vena jugular interna kanan, minta pasien untuk sedikit memiringkan kepala ke sebelah kiri, hal ini akan memperluas lapangan pada leher sebelah kanan.	
4	Temukan 2 caput muskulus sternokleidomastoideus, yaitu kaput klavikula dan kaput sterna.Sisi sudut superior yang dibentuk oleh kedua kaput tersebut merupakan tempat kanulasi ke vena jugularis interna.	
5	Proyeksi arah jarum membentuk sudut 45 der ajat dan arahkan ke puting susu ipsilateral.	
6	Setelah terorientasi dengan lapangan tempat tindakan akan dilakukan, lanjutkan dengan prosedur a dan antisepsis.	
7	Setelah prosedur a dan antisepsis lakukan kembali pengenalan lokasi masuknya kanulasi menuju vena jugularis interna. Palpasi arteri karotis, yang terletak disisi medial dari tempat kanulasi akan dilakukan.	
8	Lakukan prosedur anestesi dengan lidokain. Dimulai dari daerah superficial hingga ke daerah lebih dalam.	
9	Melakukan tindakan dengan jarum 22G dihubungkan dengan syringe 5 ml. masukkan jarum dengan sudut 45 derajat ditempat yg tadi telah diidentifikasi. Tarik syringe setiap kali memasukkan jarum lebih dalam. Bila gagal, tarik kembali jarum, lakukan dengan posisi lebih ke lateral.	

10	Saat jarum telah masuk ke dalam vena, masukkan jarum kateter 18G. Masukkan pada lokasi dan jalur yang sama dengan jarum terdahulu. Bila jarum telah masuk kedalam vena, jarum dengan hati hati dikeluarkan, dan kateter dapat dimasukkan. Tutup bagian belakang dari kateter (*catheter hub*) untuk mencegah emboli udara.	
11	Mengambil *guide wire* dengan tangan yang tidak digunakan untuk menutup *catheter hub*, dan dengan menggunakan ibu jari masukkan *wire* dengan hati hati hingga kedalam vena.	
12	Membuat insisi lebih lebar pada kulit dengan scalpel dan dilatasi secara tumpul, agar kateter vena dapat dimasukkan dengan panduan guidewire.	
13	Setelah kateter vena sentral berhasil dimasukkan, guide wire ditarik keluar.	
14	Lakukan aspirasi pada setiap lumen kateter hingga (+) darah vena lalu fiksasi dikulit dengan kuat.	
G	Penanganan Pasca Tindakan	
1	Jika tindakan sudah selesai, monitor tanda vital pasca tindakan dan observasi ada tidaknya komplikasi pasca tindakan.	
2	Pemantauan hemodinamik pasien dalam 30 menit pertama pasca tindakan di ruang prosedur.	
3	Dokumentasikan perkembangan hemodinamik. Jika kondisi membaik, pasien dikembalikan ke ruang perawatan.	

ULTRASOUND IN CRITICAL CARE

No	Melakukan Keterampilan	Checklist
	Mengucapkan salam, memperkenalkan diri, memastikan identitas pasien, menjelaskan dan meminta persetujuan tindakan yang dilakukan	
	Memeriksa ketersediaan alat	
	Meminta pasien berada dalam posisi berbaring.	
A	View Subcostal (4ch) 2D	
1	Memastikan pasien dalam posisi berbaring (*supine*)	
2	Meletakkan *transucer* diletaakkan di area sub xiphoid, diarahkan ke area bahu kiri 	
3	Meminta pasien untuk menahan inspirasi	
4	Melakukan identifikasi	
	RV (*Right Ventricle*) RA (*Right Atrium*) LV (*Left Ventricle*) LA (*Left Atrium*) MV (*Mitral Valve*) TV (*Tricuspid Valve*) 	
B	View Apical 4 Chamber (A4C) 2D	
1	Pasien diposisikan *supine*	
2	*Transducer* diposisikan pada apex dan diarahkan ke area bahu kiri  	

3	Melakukan Identifikasi	
	RV (*Right Ventricle*) RA (*Right Atrium*) LV (*Left Ventricle*) LA (*Left Atrium*) MV (*Mitral Valve*) TV (*Tricuspid Valve*)	
C	View Parasternal Long Axis (PLAX) 2D	
1	Pasien diposisikan *supine*	
2	*Transducer* diposisikan pada ujung kiri sternum pada ICS 2-4 kemudian diarahkan ke arah bahu kanan 	
3	Melakukan Identifikasi	
	- RV - LA - LV - Ao (Aorta) - MV - AV	
D	View Parasternal Short Axis (PSAX) 2 D	
1	Putar probe dari posisi PLAX 90’ searah jarum jam , miringkan ke arah bawah dari daerah Katup Mitral (tingkat muskulus papilaris) 	
2	Melakukan Identifikasi	
	- RV - LV - Muskulus Papilaris	

RESPIRATORY MONITORING AND OXYGEN THERAPY

No	Jenis Instrumen Terapi Oksigen	Indikasi	Langkah Prosedur
1	Nasal Kanul	- Pasien dengan kebutuhan oksigen kadar rendah-sedang (saturasi Oksigen 90%-95%) - Pasien dengan atau tanpa gawat nafas - Pemberian terapi oksigen jangka panjang - Pasien bernafas spontan	- Nasal Kanul dipasang - Mengalirkan oksigen sebanyak 1-4Lpm (tanpa sistem humidifikasi) atau 1-10 Lpm (dengan sistem humidifikasi) - Melakukan observasi saturasi oksigen pasien
2	*Simple Face Mask*	- Pasien dengan kebutuhan oksigen kadar sedang-tinggi (FiO_2 40-60% dengan aliran 6-10 Lpm) - Pasien bernafas spontan	- *Simple Face Mask* dipasang - Mengalirkan oksigen sebanyak 6-10 Lpm - Melakukan observasi saturasi oksigen pasien
3	*Non Rebreathing Oxygen Facemask* (NRM)	- Pasien kondisi akut dengan kebutuhan oksigen kadar tinggi (FiO_2 80-95% dengan aliran 15 Lpm) - Pasien sadar dan bernafas spontan	- Memeriksa dan memastikan identitas pasien - Menghubungkan selang oksigen ke NRM - Mengatur aliran volume yang dialirkan (15Lpm)

		- Dapat dipertimbangkan pada pasien yang penyakitnya berpeluang membaik dengan intervensi segera seperti : Penyakit Paru Obstruktif Kronis (PPOK), Edema Paru Akut, asma berat - Trauma fisik mayor	- Mengembangkan *reservoir bag* dengan menutup *valve* dan mencoba membuka *valve* dengan meremas *reservoir bag* . - Memasang NRM menutupi hidung dan mulut dengan *elastic strap* melewati telinga dan belakang kepala - Memastikan *Flap* terbuka saat pasien ekshalasi dan *bag* tidak kolaps. Bila terjadi, aliran volume oksigen perlu dinaikkan - Mendokumentasikan perubahan saturasi oksigen dan kondisi klinis pasien
4	*High Flow Nassal Canule* (HFNC)	- Penghantaran oksigen FiO_2 sampai dengan 100% dengan arus antaran sampai 60 Lpm. - Pasien dengan gagal nafas akut tipe 1 (hipoksemia). - Alternatif pada pasien gagal nafas tipe 2 (hiperkapnik) - Pemberian terapi inhalasi	- Memeriksa dan memastikan identitas pasien - Menghubungkan sumber Oksigen dengan HFNC - Pengaturan arus dimulai dari 20-40 Lpm sesuai kenyamanan pasien dan dapat dinaikkan higga 60 Lpm - Suhu diatur 31’C , 34’C atau 37’C sesuai kenyamanan pasien - Fraksi oksigen diatur 90-100% sebagai terapi inisial dan dapat disesuaikan dengan target saturasi.

		- Pasien post ekstubasi - Preoksigenasi saat akan dilakukan intubasi - Edema Paru kardiogenik - Pasien bernafas spontan	- Pemantauan klinis dilakukan selama 30 menit dalam 1 jam pertama,kemudian dilanjutkan setiap jam
5	*Non Invasive Ventilation* (NIV): Continuous Positive Airway Pressure (CPAP) Bilevel Airway Positive Pressure (BIPAP)	- PPOK - Edema Paru Akut - Penyakit paru kronik berat - Disfungsi diafragma - Gagal nafas akut - Pasien dangan kesulitan penyapihan (*weaning*) - Pasien sadar dan mampu bernafas spontan	**Persiapan** - Menjelaskan kepada pasien dan keluarga terkait manfaat prosedur manfaat NIV (CPAP/BIPAP) dan cenderung membuat rasa tidak nyaman. - Memilih ukuran *mask* yang tepat - Pertimbangkan pemerian antiemetic atau pemasangan NGT untuk menurunkan tekanan gaster. NIV cenderung menyebabkan kembung atau mual. - Mengatur tekanan pada *mask* saat belum terpasang - Memposisikan *mask* sedikit diatas wajah pasien dan beri waktu menyesuaikan, ketika sudah dibiasakan, ketatkan *strap* ke belakang kepala pasien. **Mengatur *setting* NIV:**

			CPAP: Inisiai tekanan 5, 7.5 atau 10 cm H_2O BIPAP: Inisiasi tekanan ekspirasi (EPAP)/tekanan Inspirasi (IPAP) = 12cmH_2O / 4 cmH_2O **Observasi:** • Evaluasi kondisi pasien minimal 5 menit • Mengukur AGD 1,4 dan 12 jam setelah pemasangan NIV • Kadar FiO_2 dititrasi sesuai target PaO_2 atau saturasi • Intubasi bila dalam 48 jam terjadi kegagalan NIV.
6	*Oxygen Concentrator*	Pasien yang membutuhkan Long Term Oxygen Therapy (LTOT) dengan indicator: - Pasien dengan $Pa0_2$ <55mmHg saat istirahat dengan terapi optimal kondisi yang dialami - Pasien dengan PaO_2 >55mmHg dengan tanda disfungsi sistem saraf pusat, cor	- Memposisikan *Oxygen Concentrator* 30-60cm dari dinding atau perabotan - Nyalakan mesin 15-20 menit sebelum digunakan untuk memastikan oksigen telah terkonsentrasi dengan baik - Isi bagian *humidifier* dengan air steril - Hubungkan *tube* ke *humidifier* - Menyesuaikan aliran oksigen 5 lpm

		pulmonale, hipertensi pulmonari, atau polisitemia - Pasien dengan bukti PaO_2 di bawah 55 mmHg saat tidur atau olahraga.	- Memakaikan *nasal canule* atau *mask* - Mengobservasi kadar saturasi
7	Ventilasi Mekanik (*Setting Ventilator)*	Gagal Nafas: - Laju nafas >35x menit atau <5x menit - SaO_2 <90% atau PaO_2 <60 mmHg - pCO_2 > 5 mmHg - Tidal Volume < 5mL/kg - Penurunan kesadaran (GCS<8) - Post operasi mayor - Post henti jant ung	Melakukan setting utama dari ventilator: - **Volume Tidal (Vt)** Mengatur jumlah volume tidal sesuai dengan berat badan. Volume tidal diset (8-10 ml/kg) - **Positive End Expirtory Pressure (PEEP)** Digunakan untuk menurunkan keperluan O_2 dengan memperbesar permukaan area difusidan mencegah kolaps jalan nafas. Set PEEP umumnya di set 5 cmH_2O, paling tinggi 20 cmH_2O. - **Mode (*Assisted* atau *Controlled*)** Mode *assisted* akan menginisiasi nafas saat laju nafas yang terdeteksi dibawah standard yang di set di mesin sehingga tidak terjadi apnea.

			Mode *controlled* memblokade semua nafas spontan. Umumnya digunakan pada pasien yang tersedasi atau di Kamar Operasi. - **Rate (Laju nafas per menit)** Menyesuaikan laju nafas sesuai dengan kebutuhan pasien (10-16x/menit). - **FiO_2 (Fraksi oksigen yang disalurkan)** Fraksi oksigen yang diberikan disesuaikan dengan kebutuhan pasien dan PEEP yang dipasang. FiO_2 > 50% berpotensi menyebabkan atelektasis

RESEARCH

AND

CASE REPORT

THE 10th JAKARTA INTERNATIONAL CHEST
AND CRITICAL CARE INTERNAL MEDICINE 2022

Recurrent Pneumothorax in Miliary Tuberculosis is Rare Complication: A Case Report

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Introduction: Miliary tuberculosis has a low prevalence rate. Pneumothorax is also a rare complication of tuberculosis. However, the incidence of pneumothorax in miliary tuberculosis is an emergency and life-threatening case.

Case Illustration: A 17-year-old boy came to the ER with complaints of left chest pain penetrating back since 11 hours ago. Complaints were accompanied by shortness of breath and cough. Patients in the third week anti-tuberculosis treatment. On the X-ray of the thorax (AP view) there was tuberculosis with left pneumothorax. Emergency chest tube thoracostomy was performed. Four days after the installation of the chest tube, based on the X-ray of the thorax, the left pneumothorax was no longer present. Chest tube is removed 5 days after installation. Approximately 7 hours after the chest tube removal, the patient complained of shortness of breath and there was a recurrent left pneumothorax based on a thorax X-ray. A Chest tube thoracostomy was performed for the second time. After that the patient was referred to higher-level hospital because an extensive pleural rupture is suspected.

Discussion: Beware of the occurrence of pneumothorax in miliary tuberculosis patients with complaints of shortness of breath, chest pain, and cough.

RIGHT LUNG ABSCESS WITH EMPYEMA IN PATIENT WITH UNCONTROLLED TYPE 2 DIABETES MELLITUS

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Introduction

Lung abscess defined as necrosis of the pulmonary tissue and formation of cavities containing necrotic debris or fluid that caused by microbial infection. Empyema is complication from lung abscess that penetrate lung pleura and uncontrolled diabetes is one of the risk factor to develop lung abscess.

Case Ilustration

A man, 57 y.o. with chief complain shortness of breath since 4 days. In physical examination was found tachypnoe, decreased of vesicular in right hemithorax and dull in percussion. Laboratorium examination was found Leucocytosis and high blood sugar. Fronm chest radiology found right pleural effusion. Chest radiology after Pluerocentesis was found pleural effusion and cavity with air fluid level. CT thorax we found TB lesion with abscess in segment 6 of the right lung lateral periphery and fluid density with air loculated in laterobasal. Clindamycin was given to patient and then switch to meropenem after pleural fluid culture. Insulin was given to patient for glycemic control. We consult with the department of surgery for abscess drainage. Intraoperative we found 1500 ml of abscess fluid and decortication thoracotomy was done to the patient. We also consult physiotherapy for deep breathing and chest wall expansion exercise.

Discussion

lung abscess that penetrate pleura can make complication of empyema that hide underlying abscess, and early recognition of lung abscess is needed to avoid unnecessary procedure such as tube drainage which have risk creating bronchopleural fistula and further extending the infection to the pleura. Early surgery intervention is effective in treatment for lung abscess with empyema.

P_{aO2}/F_{iO2} Ratio in Massive Pleural Effusion Patients at Kandou Hospital Manado with Optimal Drainage Volume

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RSUP Prof Dr R. D. Kandou Manado

Background

Massive pleural effusion often causes disruption of oxygen diffusion to the blood vessels and will affect the results of the PaO2/FiO2 (P/F) ratio. Pleural effusion index (PEI) as an indicator of the volume of pleural effusion. The optimal volume for drainage of the pleural effusion is determined by a thoracentesis procedure which is usually discontinued when no fluid is released and there are signs of complications, such as REPE (Reexpansion Pulmonary Edema).

Objectives

To determine the description of the P/F ratio in patients with massive pleural effusion predrainage and postdrainage based on the optimal volume drainage.

Methods

A cross sectional study was conducted. The samples used were 30 patients with massive pleural effusion at Kandou Hospital Manado. An predrainage PEI assessment with a chest X-ray, the blood gas analysis taken predrainage and postdrainage.

Result

The P/F ratio (mmHg) predrainage was obtained in 17 patients (56.7%) P/F ratio <100, 8 patients (26.7%) with P/F ratio 100-200, and 5 patients (16.7%) with P/F ratio 200-300. The mean baseline PEI was >78%, in 17 patients with P/F ratio <100. After drainage, there was a significant difference which showed an increase in the P/F ratio. The mean volume optimal drainage >959 cc at the predrainage PEI value >78% and at the predrainage PEI value <78%, the mean volume optimal drainage is <700 cc.

Conclusion

The (P/F) ratio was higher postdrainage than predrainage with the optimal volume drainage. The optimal volume of drainage can be estimated based on the initial PEI (Pleural Effusion Index) value to minimize complications.

Correlation Between Genexpert MTB/RIF Assay and Chest X Ray In Drug-Resistant Tuberculosis Patients

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Backgroud
Drug-resistant tuberculosis (TB) remains a threat to public health in the world, including Indonesia. The use of the GeneXpert MTB/RIF test is one of the modalities for diagnosing drug-resistant tuberculosis. Chest X-ray is still an adjunct in the diagnosis of tuberculosis. Studies assessing the relationship between the two are still very limited.

Objective: This study aims to see the relationship between GeneXpert results and the extent of chest X-ray lesions based on the American Tuberculosis Association

Methods
This research is a correlational observational study with a cross sectional design. GeneXpert MTB/RIF examination and chest X-ray in MDR TB patients treated at RSMH Palembang from 2021 to 2022 were collected.

Results
A total of 80 subjects surveyed, 33 (41.3%) with moderate MTB were found, 21 (26,3%) high, then very low and low were 15 and 11 respectively. On the other hand, based on lung lesions, 57 (71.4%) had extensive lesions, 14 (17.5%) had moderate lesions, and 3 (3.8%) had the minimal lesions. There was a positive correlation between the results of using the GeneXpert MTB / RIF assay and the extent of lesions on chest radiographs ($p < 0.01$, r 0.326).

Conclusions: There was a positive correlation between the results of using the GeneXpert MTB/RIF assay and the extent of lesions on chest X-ray

Keywords: Drug-resistant tuberculosis, GeneXpert MTB/RIF assay, chest X-ray

Association Between Antibiotic Appropiateness and Mortality in Elderly Patients with Pneumonia during Covid-19 Pandemic

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Abstract

Background : Elderly patients have a higher risk of developing pneumonia. In addition, elderly patients are also at a faster risk of developing antibiotic resistance. The increased prevalence of pneumonia is at risk for increased resistance and mortality in elderly patients with pneumonia

Objectives : This study aims to analyze the correlation between appropriateness of empirical antibiotics and mortality in elderly pneumonia patients.

Methods : The research subjects were taken from elderly patients with pneumonia at Mitra Keluarga Kalideres Hospital from January 2021 to March 2022. Data were collected secondarily through medical records.

Results : There were 57 elderly patients with pneumonia of which 29 (50.88%) were COVID-19 patients. Mostly, 51 (89.47%) received empirical antibiotics which were resistant based on the results of sensitivity tests. Resistant empirical antibiotics account for higher mortality rate than the sensitive ones (PR = 1.18), although there was no statistically significant relationship between the empirical antibiotics appropriateness and patients' mortality (Chi Square, p=0.679).

Conclusions : Despite the result, research on a wider scale is needed to obtain more accurate results. In addition, it is necessary to re-assess the use of empirical antibiotics in accordance with the results of appropriateness and culture tests in patients with pneumonia, especially in elderly.

Keywords : antibiotic aprropiateness, mortality, pneumonia, elderly patients

Disseminated Tuberculosis of the Bone Marrow in Systemic Lupus Erythematosus : A Rare Case Report

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Abstract

Backgrounds: Patients with systemic lupus erythematosus (SLE) are susceptible to tuberculosis (TB), especially in endemic areas such as Indonesia. The variable and nonspecific clinical features of disseminated TB often leads to an erroneous or misdiagnosis.

Case Illustration: A 38-year-old female was admitted to the hospital in May of 2021 with a 1-month history of photosensitivity, malar rash and without respiratory symptoms. SLE was diagnosed based on the clinical symptoms and positive antinuclear antibodies (ANA, :1000) and the anti dsDNA antibody. She began and responded well to a treatment with 20 mg prednisone daily and 200 mg of hydroxychloroquine twice daily. Subsequently, the dosage of prednisone was gradually reduced to 10 mg per day. In August 2021, the the patient was referred to our hospital once again with fever, profound weakness of 5 kg, night sweats, and severe back pain. A physical examination revealed an enlarged lymph node on the left subclavian (up to 1 cm diameter). A chest radiograph was unremarkable but a noncontrast computed tomography (CT) demonstrated widespread miliary opacities. Spinal magnetic resonance imaging (MRI) showed contiguous lesions in the vertebral bodies, sacrum, and ilium. Because of the persistent fever, lymphadenopathy, abnormal spine MRI findings, and non response to the initial empirical therapy, the differential diagnosis included lymphoma and TB. A histological examination of a bone marrow biopsy was performed. The pathology results showed a diffuse infiltrate of large cells with slightly nuclear pleomorphism and focal necrosis. The acid fast stain and polymerase chain reaction (PCR) assays for Mycobacterium tuberculosis were both positive.

Discussion: SLE patients with accompanying TB have always beed a major concern in Indonesia. However, little is known about TB of the bone marrow in SLE patients. The propensity of lupus patients to develop TB remains controversial. One hypothesis is that high doses of corticosteroid or/and other immunosuppressive agents are main causes. Disseminated TB is a potentially lethal form of TB and can present with variable clinical features, thus, a diagnosus is difficult. Hematogenous disseminated miliary nodules in the lungs and bone marrow (spine, sacrum, and ilium) were the prominent features. In contrast to the good prognosis of pulmonary TB, the literature review of similar reported case of TB of the bone marrow revealed a high mortality rate near 50%.

Conclusion: TB of the bone marrow can manifest as pulmonary or spinal miliary TB lesions without hematologic involvements, and the prognosis was poor in patients with underlying diseases.

Keywords: Disseminated tuberculosis, Systemic Lupus erythematosus (SLE), Bone Marrow

Evidence Based Case Report: Perbandingan antara Pemeriksaan RT-PCR dengan Sampel Saliva dan Sampel Swab Tenggorok dalam Menegakkan Diagnosis COVID-19

dr. Fahry Hamka, dr. Mulia Destini, dr. Ni Made Hustrini, SpPD, K-GH

ABSTRAK

Latar belakang: COVID-19 merupakan suatu penyakit menular yang disebabkan oleh *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV2) dan menjadi pandemi di dunia. Jumlah penderita kasus COVID-19 di Indonesia setiap hari terus bertambah. Penegakkan diagnosis COVID-19 saat ini menggunakan baku emas, yaitu pemeriksaan RT-PCR dengan sampel swab tenggorok (nasofaring dan orofaring). Pemeriksaan ini memiliki beberapa kelemahan seperti membutuhkan tenaga ahli dan alat pelindung diri dalam pengambilan sampel, rasa tidak nyaman dan takut pasien, serta risiko penularan yang tinggi ke petugas. Salah satu alternatif non-invasif dalam penegakkan diagnosis COVID-19 adalah pemeriksaan RT-PCR dengan sampel saliva.

Tujuan: Mengetahui apakah pemeriksaan RT-PCR dengan sampel saliva sama baik dibandingkan dengan sampel swab tenggorok dalam menegakkan diagnosis COVID-19 pada pasien dewasa suspek COVID-19. **Metode:** Pencarian literatur dilakukan pada beberapa *database,* yaitu MEDLINE, Cochrane Library, ProQuest, dan Cochrane COVID-19 Study Registry pada tanggal 21-23 September 2020. Proses pencarian dan seleksi artikel dilakukan oleh 2 orang *reviewer*, dimulai dari judul dan abstrak, skrining sesuai kriteria inklusi dan eksklusi, pengecekan temuan ganda, serta asesmen pada naskah lengkap yang terjaring. Setiap artikel yang terpilih sesuai dengan kriteria eligibilitas ditelaah kritis untuk menjawab pertanyaan akan validitas, kegunaan, dan aplikabilitas menggunaan kriteria penilaian dari *Center of Evidence-based Medicine, University of Oxford*. **Hasil:** Pencarian menghasilkan temuan sebanyak 80 artikel di MEDLINE, 12 artikel di Cochrane Library, 96 artikel di ProQuest, dan 141 artikel di Cochrane COVID-19 Study Registry. Setelah melakukan seleksi artikel, didapatkan satu *systematic review* dan lima studi potong lintang yang sesuai dengan kriteria eligibilitas untuk selanjutnya ditelaah kritis. Keenam artikel memiliki validitas yang baik karena PICO-nya sesuai, penelitiannya dilakukan pada spektrum pasien yang sesuai, serta dilakukan juga pemeriksaan baku emas sebagai referensi. *Systematic review* yang terpilih memberikan kesimpulan kualitatif yang baik dari hasil sembilan artikel yang ditelaah dan tidak melakukan analisis statistik gabungan, empat studi potong lintang menunjukkan sensitivitas dan spesivisitas yang baik, dan satu studi yang lain hanya menggambarkan sensitivitas yang baik. Dengan karakteristik pasien yang serupa, termasuk situasi dan kondisi pandemi yang dihadapi saat ini, seluruh artikel dapat bermanfaat dan diterapkan dengan baik pada pasien.

Kesimpulan: Dari telaah yang telah dilakukan, dapat disimpulkan bahwa pemeriksaan RT-PCR dengan sampel saliva merupakan alternatif yang non-invasif dalam menegakkan diagnosis COVID-19. Pemeriksaan RT-PCR dengan sampel saliva menunjukkan hasil yang sama baik dibandingkan dengan sampel swab tenggorok dalam menegakkan diagnosis COVID-19.

Kata kunci: sampel saliva, sampel swab tenggorok, diagnosis COVID-19, dewasa

Late onset of Pleural Effusion: Unusual Manifestation during Tuberculosis Treatment

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Abstract

Introduction:
Pleural effusion is the build-up of fluid in the space between the lining of the lung and the pleural space which is a common manifestation in tuberculosis. The basic pathophysiology includes the type-IV hypersensitivity in which the clinical presentation usually manifest long after the infection initiated.

Case Report:
We describe two cases presenting with pleural effusion after intensive treatment of tuberculosis. The first case was a 22-year-old male with tuberculous spondylitis and lymphadenitis. Before intensive tuberculous treatment, we found no evidence of pulmonary involvement. However, after given the standard regiment for 3 months, the patient showed respiratory symptoms. Further evaluation showed massive left pleural effusion. Thoracocentesis was done twice and Adenosine deaminase test was found positive.
The second case was a 25-year-old female presenting with classic symptoms of pulmonary tuberculosis, diagnosed based on clinical and radiological findings. Following 7 weeks of standard regiment, chest radiograph revealed right pleural effusion. Thoracocentesis was performed and showed the laboratory features similar with the first case. Following the thoracocentesis and further radiographic analysis, the administration of tuberculous treatment for both patients was continued and there was no pleural effusion ever since.

Discussion:
As far as literature review, there was no reported case of late onset pleural effusion and the mechanism of this case has not been fully understood yet. It is possible that this is the clinical consequences of the type-IV hypersensitivity appearing after 2 months intensive treatment. These patients are currently closely monitored until completion of treatment.

Keywords : Pleural effusion, Tuberculosis

Asma Tidak Terkontrol Sebagai Manifestasi Long COVID-19 pada Pasien Geriatri

Uncontrolled Asthma as a Manifestation of Long COVID-19 in Geriatric Patients

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Abstrak

Pendahuluan

Asma merupakan penyakit saluran pernapasan yang tidak menular tersering di Indonesia. Berdasarkan RISKESDAS 2018, prevalensi penderita asma di Indonesia adalah 2.4% dari jumlah penduduk. Esaserbasi asma sering dihubungkan dengan adanya infeksi pada saluran pernapasan. WHO menjelaskan jika sampai saat ini belum didapatkan hubungan yang jelas terkait infeksi SARS-CoV-2 dengan asma.

Illustrasi Kasus

Pasien perempuan 62 tahun dikonsulkan ke bagian respirologi dengan kondisi sesak nafas yang hilang timbul sebelum operasi. Pasien sudah menderita asma sejak 5 tahun, terkontrol dengan menggunakan inhaler budesonide/formoterol (200/6) 2x1 hisap. Pasien mengaku menderita DM sejak 1 tahun SMRS, tidak mengkonsumsi obat karena dikatakan gula darah normal. Riwayat hipertensi juga diakui sejak 2 tahun SMRS, saat ini hanya mengkonsumsi amlodipine 1x5 mg, tetapi tidak rutin kontrol. Pada bulan Maret 2022 pasien menderita COVID-19, saat itu pasien menjalani isolasi mandiri dengan tetapi menggunakan obat asma secara mandiri. Dua minggu pasca terdiagnosis pasien mengeluh sesak disertai mengi semakin sering muncul, dan sering terbangun saat malam hari. Pada pemeriksaan fisik didapatkan RR 26x/menit, didapatkan wheezing pada kedua lapang paru. Atas kondisi tersebut pasien, dosis inhaler budesonide/formoterol ditingkatkan menjadi 2x2 hisap dan diberikan inhaler salbutamol 1x 1 puff (100mcg) setiap pasien merasa sesak semakin memberat.

Diskusi

Asma disebabkan oleh proses peradangan pada saluran pernapasan salah satunya infeksi virus. Saat ini belum terbukti dengan jelas bahwa infeksi COVID-19 merupakan faktor risiko eksaserbasi asma. Beberapa literatur menjelaskan SARS-CoV-2 dikaitkan dengan tingkat eksaserbasi asma yang rendah. Penggunaan steroid inhalasi diduga dapat menurunkan ekspresi dari reseptor ACE yang merupakan reseptor dari SARS-CoV-2. Kondisi ini berlawanan dengan komorbid lainnya pada pasien yaitu usia tua, hipertensi, dan DM yang bisa meningkatkan ekspresi reseptor ACE, sehingga dapat muncul gejala sisa pasca terinfeksi COVID-19 yang berupa tidak terkontrolnya asma pada pasien.

Kata kunci : Asma, COVID-19, Geriatri

Interstitial Lung Disease in Sjögren's Syndrome

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Abstract

Introduction: Sjögren's Syndrome (SS) is a systemic autoimmune disease of the exocrine gland.[1,2] Although most of the manifestations appear in mouth and eyes, lung involvement occurs in 9-20% of patients.[3] We presented a case of SS with Interstitial Lung Disease (ILD) as a presenting symptom.

Case Illustration and Discussion: 74 years old caucasian man, came with 3 days of dry cough, fever, and dyspnea. The symptoms were fluctuating and deteriorated in the following days, any precipitating factors were denied. Physical examination showed increased respiratory rate (26/minute), elevated temperature (38.2°C), dry eyes with hyperemia conjunctiva, and dry mouth. Laboratory results revealed normal WBC, elevated ESR, negative covid-19 PCR, negative IGRA, and negative sputum examination. ANA IF examination showed positive Anti-SSB/La that was strongly associated with Sjögren's Syndrome. Chest CT scan showed multifocal ground-glass opacities and fibrosis that predominated in the subpleural of both lungs. These findings support the condition of ILD with underlying SS. Steroid and hydroxychloroquine were started, and the symptoms improved in the following days. Serial chest x-ray examination in the outpatient clinic showed improvement of radiological ILD appearance.

Lung involvement could occur in 9-20% of the SS patients.[3] The pulmonary manifestations include airway abnormalities, lymphoproliferative disorders, and interstitial lung disease.[3-5] The first association between SS and ILD was described in 1973, the combination of immune response with local inflammation could cause bronchopulmonary damage that progresses into ILD.[3,6,7] The main symptoms of this ILD are dyspnea and cough.[3,8] Chest x-ray can show bilateral lung infiltrates with linear and reticular opacities (10–30%). Chest CT is the most sensitive method, it shows ground-glass opacities (92%), non-septal linear opacities (75%), interlobular septal thickening (55%), cysts (30%), reticulation, and fibrosis.[3,9] However, radiological abnormalities might not correlate with pulmonary function test and respiratory symptoms.[3]

In the global pandemic of covid-19 situation, presentation of respiratory symptoms and pulmonary GGO in imaging results could strongly support the covid-19 diagnosis.[10] This case showed another diagnosis of pulmonary symptoms and GGO that should be considered especially if the condition is accompanied by certain systemic-immunologic manifestations. The ACR 2012 criteria of SS were strongly featured in this case, the presentation of lung involvement with certain conformable ILD conditions in imaging results supporting the diagnosis of SS associated with

ILD. Suitable treatment based on precise diagnosis could help alleviate the symptoms, reduce medical costs, and improve quality of life.

Conclusion: ILD manifestation of SS should be considered in patients with pulmonary disorder and GGO, especially if the condition were accompanied by certain systemic-immunologic manifestations.

Keywords: *sjogren syndrome, interstitial lung disease, ILD, ground glass opacities, GGO*

Co-existence of Rifampicin-Sensitive Pulmonary Tuberculosis and Rifampicin-Resistant Tuberculous Lymphadenitis in HIV Patient: a Case Report

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Abstract

Introduction: Tuberculosis is the most common opportunistic infection in HIV patient. Clinical presentation varies according to degree of immunity ranging from pulmonary involvement to extrapulmonary site such as lymph node, bone, brain, meninges, spinal cord, and kidney. Risk of drug-resistant tuberculosis is higher in HIV positive patient.

Case Illustration: A 51-years old man admitted to emergency room with worsening shortness of breath since one day prior. He had been complaining of recurrent dyspnea, cough, and weight loss in the last 4 months. His physical examination showed oral thrush, multiple lymphadenopathies in right cervical region, diminished breath sound in right lower pulmonary lobe, and rhonchi in both lungs. He was tested positive for HIV and his absolute CD4 count was 12 cells/µl. Chest x-ray revealed right pleural effusion and opacities in both lungs. Rifampicin-sensitive *Mycobacterium tuberculosis* was detected from sputum Xpert-MTB/RIF assay. We performed fine needle aspiration biopsy (FNAB) to confirm the cause of lymphadenopathy. Rifampicin-resistant *Mycobacterium tuberculosis* was discovered from lymph nodes aspirates Xpert-MTB/Rif assay. Patient was then diagnosed as Rifampicin-resistant TB.

Discussion: Lymphadenopathy is one of the common presentations in HIV positive patient resulting from various causes. A prompt diagnosis procedure must be performed to initiate correct treatment. Tuberculous lymphadenitis was one of the most frequent causes of lymphadenopathy in HIV positive patient. FNAB has quite precise sensitivity and specificity in diagnosing tuberculous lymphadenitis. Xpert-MTB/Rif assay has been widely used to diagnosis tuberculosis and can confirm rifampicin resistance. Several reports stated Xpert-MTB/Rif assay using FNA specimen also has good sensitivity and specificity to detect extrapulmonary tuberculosis.

Conclusion: FNAB and Xpert-MTB/Rif assay should be performed in HIV patient presenting with lymphadenopathy to determine the etiology and guide treatment.

Keywords: tuberculosis, rifampicin-resistant, HIV

Early Vasopressor and De-resuscitation in Steven Johnson Syndrome with Septic Shock: A Case Report

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Abstract

Sepsis is a life-threatening medical emergency frequently observed in intensive care unit (ICU). Surviving Sepsis Campaign in 2021 has recommended the administration of early vasopressor in the first hour of sepsis or septic shock but has not yet included de-resuscitation protocol. De-resuscitation in acute management of septic shock is where patient received active removal of accumulated fluid. It has been proposed by some studies and ongoing clinical trials. Here we present a case with early vasopressor and de-resuscitation. Male, 27 years old presenting to the emergency room with shortness of breath, altered mental status, and widespread blisters on his body and lips started a few hours prior, after receiving non-steroidal anti-inflammatory drug through intravenous injection. Patient was hypotensive, tachycardic, and tachypneic at admission, diagnosed with Steven Johnson Syndrome with Septic Shock. Patient received fluid resuscitation, early vasopressor, and diuresis agent aimed to actively remove fluid after the initial phase of resuscitation. Patient was admitted to ICU and progressively recovering. At day-10, patient was stabilized and was transferred to general ward. Early vasopressor and de-resuscitation are beneficial for the patient.

Keywords: sepsis, shock, de-resuscitation, vasopressor, fluid, case report

Evidence Based Case Report:

"Hubungan antara Patogen Penyebab Infeksi terhadap Kejadian Eksaserbasi Akut pada Pasien Penyakit Paru Obstruktif Kronis"

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Pendahuluan: Kejadian eksaserbasi akut pada penyakit paru obstruktif kronis sering disebabkan oleh infeksi sekunder akibat patohen. Laporan kasus berbasis bukti ini bertujuan untuk mengetahui hubungan antara patogen penyebab infeksi dengan kejadian eksaserbasi akut pada pasien dewasa dengan PPOK.

Metode: Penelusuran literatur dilakukan pada September 2020 di *database* Pubmed, Medline, CINAHL, Scopus, dan Cohchrane Library dengan menggunakan kombinasi keywords seperti COPD, pathogen, infection, secondary infection, pneumonia, acute exacerbation dengan menggunakan MeSH terms serta boolean operator. Penelitian yang menyajikan data analitik hubungan antara patogen penyebab infeksi dengan kejadian PPOK eksaserbasi akut dalam OR atau RR, systematic review, kohort, case report dan cross sectional diikutkan. Telaah kritis dilakukan berdasarkan *appraisal etiology worksheet (harm).*

Hasil: Didapatkan tiga penelitian kohort prospektif yang sesuai dengan kriteria eligibilitas yang dimasukkan ke dalam EBCR ini. Patogen penyebab infeksi yang konsisten memiliki hubungan dengan PPOK eksaserbasi akut adalah yaitu Human Rhinovirus, Moraxella catarhalis, dan Streptococcus pneumoniae yang diisolasi dari sampel sputum dengan OR dan RR yang signifikan. Ketiga studi yang didapatkan memiliki validitas yang baik, hasil yang cukup penting, serta dapat diaplikasikan dalam kasus.

Kesimpulan: Terdapat hubungan yang bermakna antara jenis virus dan bakteri penyebab infeksi dengan kejadian PPOK eksaserbasi akut.

Kata kunci: Eksaserbasi akut, infeksi, patogen, pneumonia, PPOK

Badai Sitokin pada Pasien COVID-19 Menyebabkan Gangguan Ginjal Akut?

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ABSTRAK

Latar belakang:
Coronavirus Disease 2019 (COVID-19) merupakan penyakit infeksi menular pernapasan akut yang parah disebabkan oleh *Severe Acute Respiratory Syndrome Coronavirus-2* (SARS CoV-2). COVID-19 menyebabkan kematian mencapai lebih dari 700 ribu. Hal ini sering dikaitkan dengan adanya peningkatan mediator inflamasi yang menyerang organ yang mengekspresikan reseptor *Angiotensin Converting Enzym-2* (ACE-2). Organ ginjal salah satu target mediator inflamasi tersebut. Meskipun beberapa studi menjelaskan badai sitokin terhadap kerusakan organ multipel. Namun, hubungan badai sitokin menyebabkan kerusakan organ ginjal belum banyak diketahui.
Tujuan:
Mengetahui apakah badai sitokin menyebabkan gangguan ginjal akut (*Acute Kidney Injury*/AKI)pada pasien COVID-19 derajat berat.
Metode:
Pencarian artikel dilakukan secara sistematis dengan pencarian elektronik melalui *Pubmed/MEDLINE, Cochrane, dan Cochrane COVID-19 Study Register*. Kata kunci yang dalam pencarian antara lain *"COVID-19", "Cytokine Storm", "C-Reactive Protein", "Interleukin-6", "Tumor Necrosis Factor", "Interferon", "Acute Kidney Injury".* Pencarian artikel dilakukan pada tanggal 21-23 September 2020. Artikel yang didapatkan lalu ditelaah secara kritis dengan menggunakan *appraisal etiology worksheet (harm)* dari Ebling Library dengan tujuan untuk mendapatkan hasil yang objektif.
Hasil:
Hasil pencarian artikel didapatkan 47 artikel *Pubmed* dan 11 artikel *Cochrane*, dan 2 artikel *Cochrane COVID-19 Study Register*. Setelah melewati seleksi, didapatkan tiga artikel yang ditelaah kritis. Dari telaah tiga artikel tersebut didapatkan hubungan *C-Reactive Protein* (CRP) ($p<0,05$), Interleukin 6 [p:0,03, HR 1,83 (1,299-2,725)] dan Interleukin 6 ($p =0,03$) terhadap gangguan ginjal akut (*Acute Kidney Injury*/AKI)/ derajat keparahannya secara berurutan pada masing-masing artikel.
Kesimpulan:
Ketiga penelitian yang didapat menunjukan hubungan namun tidak bersifat kausatif terhadap kejadian gangguan ginjal akut (*Acute Kidney Injury*/AKI) karena keterbatasan data untuk memastikan bahwa peningkatan mediator inflamasi (CRP atau IL-6) dapat secara independen menyebabkan gangguan ginjal akut (*Acute Kidney Injury*/AKI).

Kata kunci: COVID-19, *Cytokine, Acute Kidney Injury*

Pulmonary Embolism in Acute Dyspnea Patient

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Introduction: Pulmonary embolism (PE) is a form of venous thromboemebolism (VTE) that is common and sometimes fatal. The clinical presentation of PE is variable and often nonspesific, making the diagnosis challenging. Various resources are available, such as clinical scoring systems, laboratory data, and imaging studies which help guide clinicians in their workup of PE. The evaluation of patients with suspected PE should be efficient to that patients can be diagnosed and therapy administered quickly to reduce the associated morbidity and mortality.

Case: A 67-year-old man present to the hospital with shortness of breath since 2 days ago, hemiparesis of right side of the extremity and hemoptysis. Patient has a history of stroke. Upon physical examination, the patient's heart rate is 110 times per minute, respiration rate is 32 times per minute with nasal canule, and there are ronkhi and weakness in right extremity. Upon well's score assessment, patient's well score is 6 (high probabikity of PE). Laboratory data D dimer: 35.200; CRP-quantitative 65; Procalcitonin 0.84; Cr/eGFR 5.4/101; Blood gas analysis Alkalosis metabolic. CT Pulmonary Angiography: Thromboembolism in pulmonary trunk left and right; superior, posterobasal and laterobasal part of pulmonary artery. Consolidation in 6,9 and 10^{th} segment of right lung susp infarction; Thromboembolism in apicoposterior and anterior part of left pulmonary artery with cavity in 1,2 and 3^{rd} segment left lung susp infarction.

Discussion: Pulmonary embolism is a potentially deadly form of thromboembolism, occured due to a migration of thrombus from the venous into pulmonary circulation. Patients with PE may present without symptoms, yet some may experience immediate death. A history of strokealong with other illnesses are included in the risk factors of PE. While PE is often mistaken for pneumonia due to the similarity in their cardinal features, co-existence of both is also common. Pneumonia appeared to be a predisposing factor to PE, and those two can be found in stroke. The seriousness of PE highlighted the importance of thromboprophykaxis, The use of UFH and LMWH plays a role in reducing the incidence of PE and overall, thromboembolism after acute ischemic stroke

Keywords: *pulmonary embolism, pneumonia, stroke complications, thromboprophylaxis*

Embolization In case Pulmonary Arteriovenous Fistula Lobe Inferior Dextra

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ABSTRACT

Introduction: Pulmonary arteriovenous fistula (PAVF) in the lung is unusual. PAVF is described as abnormally dilated vessels that provide a right-to-left shunt between pulmonary artery and pulmonary vein.

Case Report: A 27-year-old male patient was admitted to hospital with the chief complaint of hemoptysis for 1 week in the last 1 month ago. from the results of the MSCT Angiography of the thoracic aorta, with contrast it was found that there were widening of the distal veins. Right pulmonic in right posterobasal segment clustered to form nidus and draining vein with ground glass and nodule with AVM impression with inflammation. After diagnostic angiography was found; There is a fistula between the right inferior pulmonary artery and the right inferior pulmonary vein. So in this patient, a diagnosis of pulmonary arteriovenous fistula inferios dextra.

Disccusion: PAVF is a rare case. PAVFs occur with an incidence of 2 to 3 per 100,000 population. Females are more often affected than male. Multiple lesions are found in 33% to 50% of patients. The majority of patients with multiple PAVFs have lesions confined to the lower lobes; 8% to 20% of patients have bilateral PAVFs. Management of PAVFs can be done by angiography embolization or by surgery. For at least the past decade, the standard of therapy for most PAVFs has been angiographic intervention. The fact that it is less invasive than surgery and can be repeated easily are two major advantages.. However, at or after the procedure, the patient had no complaints or indications that led to the risk of complications that were feared, and the patient went home in good condition and at the next follow-up to the Thoracic Cardiovascular Surgeon was also in good condition.

Conclusion: Management of PAVFs can be done by angiography embolization or by surgery. For at least the past decade, the standard of therapy for most PAVFs has been angiographic intervention. The fact that it is less invasive than surgery and can be repeated easily are two major advantages. But this procedure also has some risks of complications.

Keywords: **:** Pulmonary, arteriovenous fistula, hemoptysis, angiography embolization.

NTM Infection Incidental Finding in Immunocompromised Patient with Encephalitis: A Case Report

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Background

Non Tuberculous Mycobacterium (NTM) is an opportunistic pathogen in immunocompromised. It is known about 15% of AFB+ sputum samples turns out to be NTM based on bacteriological culture. The annual prevalence NTM infection each year worldwide. Besides lung, NTM infection may involve any organ but most commonly manifested as pulmonary disease (50.7%), followed by skin/soft tissue (15.3%), disseminated (11%), and lymphatic disease (7,7%). The purpose of this case report is to present a patient with NTM co-infection that incidentally found in CSF. This is the type of case that oftenly underdiagnosed by clinicians due to lack of awereness.

A Case illustration

A 37-year-old man, HIV-positive, with impaired level of consciousness due to traffic accident, complained of severe headache and weakness on left side several months prior to hospital admission. On physical examination, we found GCS score of 13, somnolence, stiff neck, positive babinsky and left motoric hemiparese. Chest X Ray revealed heterogen opacities in the lower lobe of the right lung, suggesting pneumonia. CT-brain showed multiple space occupying lession (SOL). Lumbar puncture was performed. This patient was admitted to inpatient ward with the preliminary diagnosis encephalitis toxoplasmosis dd/ SOL. On the third day of hospitalization, his condition deteriorated. The patient complained of difficulty breathing with respiratory rate of 32x/m & worsening chest x-ray. A diagnosis of respiratory distress e.c community-acquired pneumonia (CAP) was made. He was intubated and treated with empiric antibiotic for CAP; ceftriaxone and azitromycin. Sample of cerebrospinal fluid (CSF) was evaluated for AFB and tuberculosis PCR (polymerase chain reaction). The analysis revealed negative of M. Tuberculosis and positive of NTM. Patient then discharged and advised to continue the NTM therapy regiment through Internal Medicine Outpatient Department.

Discussion

Diagnosis and medication of NTM can be challenging. It is known that NTM infection cases are on the rise, considering these pathogen are often underdiagnosed. Prompt clinical evaluation for NTM should be executed whenever the patient's profile fit as a risky group. Immunocompromised patient subsequently infected with NTM, not always M.Tubeculosis. Early diagnosis of NTM improve the prognosis as well as the treatment outcome.

Recurrent Hydropneumothorax in Suspected Malignancy; a Case Report

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Hydropneumothorax is a clinical condition usually manifesting as a sign of underlying pulmonary illness, the management of which is usually an insertion of chest tube with negative pressure output to continuously reduce intrapleural pressure. However, the underlying disease must be addressed to eradicate the condition altogether. A 62-year old female was admitted for shortness of breath worsening in one month. The patient had been treated for tuberculosis for approximately a month from another hospital, after presenting with shortness of breath, non-specific fever, and significant weight loss. The patient had been diagnosed before with hydropneumothorax and had been installed a chest tube on her left chest due to repeated hydropneumothorax. The chest tube produced 200-300 cc of fluid per day and showed signs of exit site infection. Physical examination showed diminishing breath sounds on the left chest, with erythematous lesions around the exit site of the chest tube. Pleural fluid analysis showed exudative properties but was negative for bacterial culture. Blood work for inflammatory markers were elevated. Prior chest CT scan showed multiple nodules on the right lung lobes, and hydropneumothorax on the left lobe. Pleural ultrasound of the left chest showed loculated effusion and chest tube were extracted. A bronchoscopy was done to diagnose the cause of the repeated hydropneumothorax, and an endobronchial hemorrhagic nodule was found and biopsied. Bronchoalveolar lavage was also done to obtain samples for galactomannan, fungal culture, and cytology analysis.

Peak Inspiratory Flow Rate (PIFR) in Hospitalized COPD Patients and Risk of Early Readmission: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: *Chronic Obstructive Pulmonary Disease (COPD) is a prevalent lifelong disease which has become the third leading cause of death globally in 2019 according to World Health Organization (WHO) report. Patients hospitalized for acute exacerbation of COPD have high rates of early readmission: 9–26% within 30 days and 18–39% within 90 days of discharge according to one study. Identifying factors of readmission are useful to optimize efforts to reduce hospitalizations. Recent studies have reported that suboptimal levels of Peak Inspiratory Flow Rate (PIFR) in COPD patients may be associated with higher rates of early readmission due to reduced capacity to inspire inhaler medications.*

Objective: *To assess the association between PIFR category of hospitalized COPD patients and risk of early hospital readmission (within 30 and 90 days of discharge).*

Methods: *Cohort studies measuring the association between PIFR category in hospitalized COPD patients and rates of 30- and 90-day hospital readmission are included in this review**.** Literature searching was conducted in seven elextronic databases: Pubmed, Embase, Scopus, Cochrane Library, ProQuest, EbscoHost and ScienceDirect as of May 31th 2022.. Risk of bias assessment was conducted using the Newcastle Ottawa Scale (NOS) for cohort studies. Quantitative analysis was performed using Review Manager software 5.4.*

Results: *Four studies are included in the quantitative analysis. All studies are of high quality wtih low risk of bias. Mantel-Haenszel test with fixed model analysis showed suboptimal PIFR is associated with higher rates of hospital readmission in all groups; however, the results are not statistsically significant. The highest RR is found in 30-day all cause readmission group (pooled RR 1.40; 95%CI 0.86–2.28; p = 0.18; I^2 = 25%). Suboptimal PIFR is also associated with fewer number of days before all-cause readmission (65.5 vs 101.0 days; p = 0.009) according to Loh et al.*

Conclusion: *PIFR category is not significantly associated with risk of early hospital readmission. However, hospitalized COPD patients with suboptimal PIFR tends to have higher rates of early readmission in all groups. Therefore, further studies need to be conducted with a larger sample size to confirm its statistical significance.*

Keywords*: COPD, PIFR, readmission*

Non Hodgkin Lymphoma Mimicking Lung Cancer

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Background

The first possibility considered in the etiology of large lung masses is neoplastic lesion. The probability of the lesion being malignant increases with the increasing size, although some benigna lesion can reach large size. The usual differential of large neoplastic masses include bronchogenic carcinoma, sarcomas, primitive neuroectodermal tumours, blastomas, metastatic lesions, lymphomas, etc. Primary or secondary lymphoma which have similar radiological presentation but different treatment and prognosis.

Case Presentation

A smoking 62 year old male was admitted to emergency department with progressive dyspnoe, mild cough without sputum, fever and five kg weight loss. There was multiple right clavicula lymphadenopathy. Chest examination revealed dull percussion on right side and reduced breath sounds in the same region. There was no hepatosplenomegaly. Chest radiograph showed homogenous opacity in right hemithorax. Patient was diagnosed with right lung mass suggest malignant, right supraclavicular lymphadenopathy suggest metastasis, hospital acquired pneumonia, normocytic normochromic anemia and hypoalbuminemia. Bronchoscopy showed distal trachea mass (closed 70% distal trachea and right upper main bronchus) suggest infiltration from extraluminal mass. Chest CT revealed isohipodens mass in right superior, medial and inferior lobe with right mediastinal infiltration and endoluminal infiltration of distal trachea and right superior lobe. Right pleural effusion with atelectasis and multiple mediastinal lymphadenopathy. Pleural fluid cytology showed negative. Abdominal CT revealed negative of intraabdominal lymphadenopathy and intraabdominal metastatic lesion. Histopathology result from bronchoscopy biopsy suggest lymphoma with differential diagnosis was poorly differentiated carcinoma. Immunohistochemistry showed the cell to be positive for the CD20 and diagnostic was diffuse large B cell lymphoma subtype non germinal center B cell like. Patient was referred to medical oncology for chemotherapy with RCHOP regiment.

Conclusion

This case illustrates that lung involvement in lymphoma can mimic lung cancer clinically and radiographically, especially in large lung mass. Thus lymphoma should be considered as differential diagnosis in patients with pulmonary masses.

Keywords ; lymphoma, lung cancer

Miliary TB and elevated transaminase enzymes in an untreated human immunodeficiency virus patient.

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Abstract

Introduction Tuberculosis (TB) is closely related to Human Immunodeficiency Virus (HIV) and causes 25% death in HIV patients. Miliary TB is a complication of a focus of tuberculosis infection that is spread hematogenously, in the form of fine spots that are generally evenly distributed throughout the lung fields. Giving Anti Tuberculosis Drugs can have side effects in some TB patients including drug-induced hepatitis, therefore it is necessary to check liver function. Liver function tests that are commonly used are transaminase enzymes, namely SGOT and SGPT levels which will show an increase if there is damage or inflammation in liver tissue. In HIV positive patients, it is recommended to have liver function tests every month.

Case illustration Here we report a case of a male patient diagnosed with miliary TB and HIV who had an increase in the transaminases enzyme at the beginning of the diagnosis with chief complainnts of cough with phlegm, fluctuating fever, night sweats, weakness, nausea, vomiting, and weight loss 0f 14 kg since three months before being admitted to the hospital. The patient appeared moderately ill with composmentis consciousness, temperature 38,8C, saturation 98% with oxygen, BMI underweight (13,4kg.m2), anemic conjunctiva and sclera are not icteric. The laboratory finding anemia left shift hypochromic microytic with thrombocytopenia (Hb 9,8g/dl, Hematocrit 28,3%, leukocytes 2470/Ul, platelets 157000/uL MCV 87fl, MCH 28,7pg, MCHC 33,0g/dl), increase transaminase enzymes (SGOT:398U/L SGPT:90U/L), hypoalbuminemia (2,17g/dL), normal kidney function, hiponatremia (124), HbsAg and Anti HCV: non Sputum BTA I/II/II: +1/+2/+2, Gene Xpert: MTB detected, Rifampicin resistance was not detected. Reactive HIV test, CD4: 26 sel/UL. Ro Thorax examination: Inhomogeneous nodular opacity in both lung fields, suspected pneumonia, USG: Chronic liver disease. The patient received Co-trimoxazole therapy, modified Anti Tuberculosis Drugs and Antiretrovirals. After being given modified anti-tuberculosis and antiretroviral therapy, clinical and laboratory improvement occurred. Conclusion We report a case of miliary TB in an HIV patient with elevated transaminase enzymes before treatment with anti-tuberculosis drugs. The need for

monitoring of liver function in patients who show symptoms of hepatitis and examination of liver function.

Keywords: AIDS, HIV, Increased transaminase enzymes, TB.

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