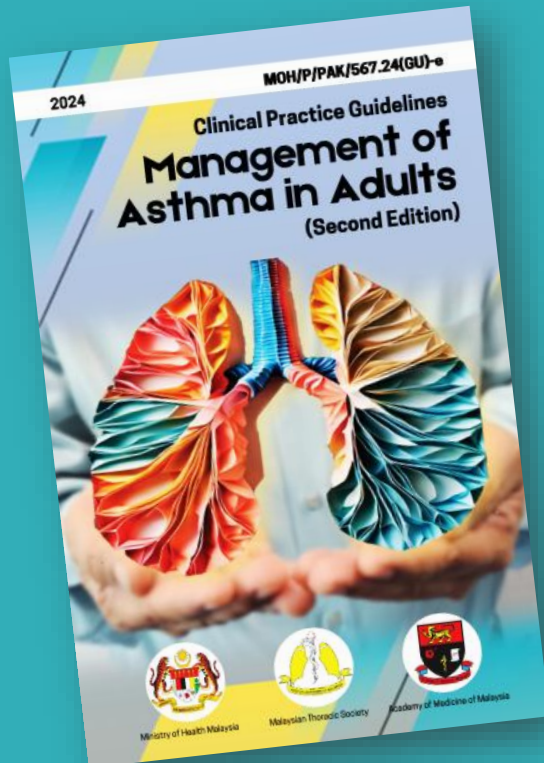


TRAINING OF CORE TRAINERS ON CPG

MANAGEMENT OF ASTHMA IN ADULTS (SECOND EDITION)



LECTURE 6

Severe Asthma & Special Groups

Dr. Azza Omar
Consultant Respiratory Physician
Hospital Raja Perempuan Zainab II

Dr. Hema Yamini Devi Ramarmuty
Respiratory Physician
Hospital Queen Elizabeth



Learning Objectives

- Recognize severe asthma, perform appropriate investigations to confirm the diagnosis and phenotype, and understand the latest management strategies, including biologic therapy.
- Manage asthma in pregnancy with safe medications, regular monitoring, and prevention of exacerbations.
- Recognize the risk factors, diagnosis and management of occupational asthma
- Understand the diagnostic criteria and management of exercise-induced bronchoconstriction
- Detect and treat asthma comorbidities to improve overall asthma control.

Special Population



- **Severe Asthma**
- Asthma in Pregnancy
- Occupational Asthma
- Exercise-induces Bronchoconstriction
- Asthma with Co-Morbidities



Severe Asthma

- Severe asthma affects about 5 - 10% of asthma patients.
- Asthma is heterogeneous, with various clinical phenotypes driven by complex biologic endotypes including type-2 (T2) high, T2 low and mixed endotypes.
- T2 inflammation is present in 95% of patients with severe asthma and can be readily identified using biomarkers. (Eosinophils, FeNO, IgE)
- It reflects the underlying pathobiology of asthma, which is directly involved in the causal pathway of asthma exacerbations.
- Biomarker-guided therapies (ICS, OCS, biologics) target core mechanisms and can enable steroid dose reduction

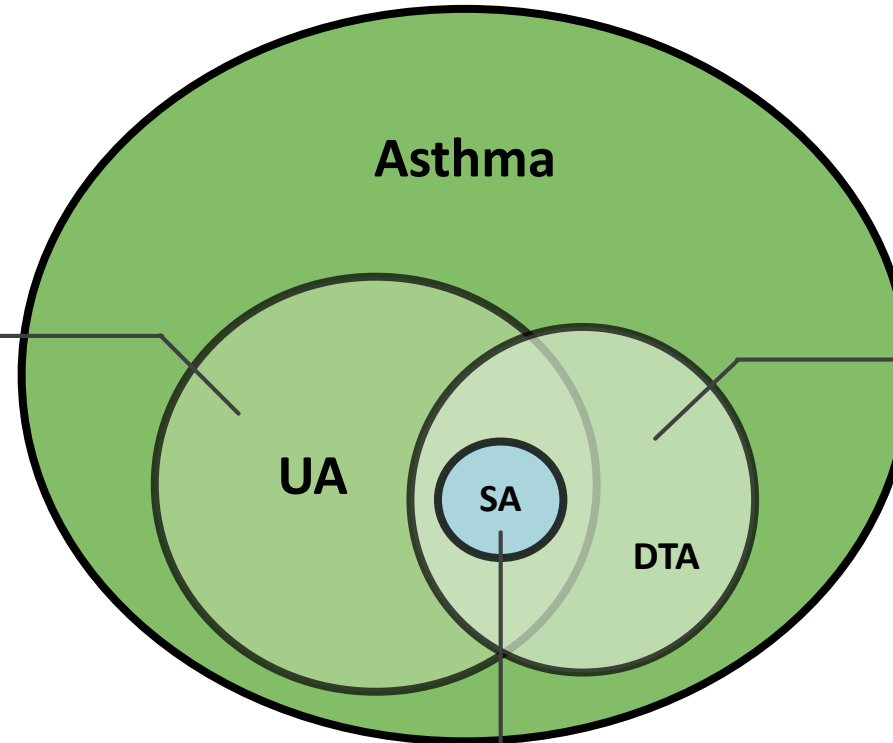
Relationship of Asthma, Uncontrolled Asthma, Difficult-to-Treat Asthma, and Severe Asthma



Uncontrolled asthma

includes one or both of the following:

- poor symptom control in the past four weeks (≥ 3 of the following)
 - daytime asthma symptoms ≥ 2 /week
 - reliever used ≥ 2 /week
 - activity limitation due to asthma
 - night waking due to asthma
- frequent exacerbations
 - ≥ 2 /year requiring OCS and/or
 - serious exacerbations (≥ 1 /year) requiring hospitalisation*



Difficult to treat Asthma

is defined by any of the following:

- uncontrolled asthma despite medium- or high-dose ICS with a second maintenance (usually LABA) or maintenance OCS
- requires high-dose treatment to maintain good symptom control and reduce exacerbation risk

The condition may be influenced by modifiable factors or may be due to an incorrect diagnosis or asthma mimickers.

Severe Asthma

is characterized either by:

- Uncontrolled asthma despite adherence to maximal optimized high-dose ICS-LABA and management of contributory factors **OR**
- Worsening asthma control when high-dose treatment is reduced

Inhaler technique and other modifiable factors should be addressed before considering the diagnosis of severe asthma.

Risk Factors



A large cohort study identified several factors significantly more common in patients with **severe asthma** compared to those with non-severe disease:

Airway & Disease-Related

- Incompletely reversible airflow limitation
- Frequent exacerbations
- Neutrophilic airway inflammation

Comorbidities

- Obesity
- Obstructive sleep apnoea (OSA)
- Gastroesophageal reflux disease (GERD)
- Depression
- Systemic inflammation

Other Contributors

- Vocal cord dysfunction
- Inhaler device polypharmacy
- Aspergillus sensitisation

Treatment of Severe Asthma



Systemic Corticosteroids

- OCS are adjunct therapy in uncontrolled asthma; considered the last-line option
- Use at the lowest effective dose and for the shortest possible duration
- >4 lifetime OCS courses linked to high risk of serious adverse events (AEs):
 - Osteoporosis and fractures
 - Pneumonia
 - Heart failure, cardiovascular and cerebrovascular disease
 - Type 2 diabetes mellitus
 - Depression and anxiety
 - Cataracts
 - Renal impairment
 - Weight gain
- Risks are amplified when combined with other corticosteroid therapies



Treatment of Severe Asthma-2

Macrolides

Azithromycin in Severe Asthma:

- Reduces exacerbations in severe asthma, especially with eosinophilic phenotype
 - IRR overall: 0.61; eosinophilic: 0.63)
- No added benefit when used in patients already on oral corticosteroids (OCS)
- Meta-analysis (5 RCTs) showed:
 - Slight FEV₁ improvement (MD: +0.06 L)
 - No significant reduction in exacerbations
- For non-T2 asthma, options include Azithromycin, Bronchial thermoplasty or Systemic steroids
- Recommended dosing:
 - 500 mg three times weekly or 250 mg daily
 - Duration: up to 1 year, extendable in specialist care
- Pre-treatment precautions:
 - Screen for NTM infection
 - Consider ECG (for QTc risk) and audiogram (if hearing loss risk)



Treatment of Severe Asthma-3

Biologics

Biologics are add-on therapy after optimizing standard asthma treatment. Phenotype assessment is essential before initiation.

Approved Biologics

- Anti-IgE: Omalizumab
- Anti-IL-5/5R: Mepolizumab, Reslizumab, Benralizumab
- Anti-IL-4R α : Dupilumab
- Anti-TSLP: Tezepelumab

A recent local Health Technology Assessment indicated that mepolizumab, benralizumab, dupilumab, and tezepelumab significantly reduced exacerbations and hospital visits, improved lung function and asthma control, enhanced quality of life, and decreased the need for oral corticosteroids, especially in patients with high eosinophil counts (≥ 300 cells/ μ L) unresponsive to optimal treatment, while showing an acceptable safety profile.

Biologics



Agent	Effects	Safety Profile
Omalizumab (Real-World Evidence)	↑ FEV ₁ (12.4% at 1 year; up to 48% at 9 years), ↓ OCS use (70.8% reduced/stopped by 1 year, 100% stopped by 9 years)	
Dupilumab (Cochrane Review)	↑ FEV ₁ at 12 & 24 weeks, ↓ ACQ score, ↓ FeNO and IgE, ↑ Blood eosinophils (not clinically significant)	No excess adverse events
Anti-IL-5/5R Agents (Cochrane Review)	↓ Clinically significant exacerbations (Mepolizumab SC: RR=0.45, Mepolizumab IV: RR=0.53, Reslizumab IV: RR=0.43, Benralizumab SC: RR=0.59), Limited improvement in lung function or QoL	No increase in serious AEs
Anti-IL-13/IL-4 Agent	↓ Hospital/ED visits (e.g., Tralokinumab: RR=0.68), Small, non-clinically relevant QoL improvement	No excess serious adverse events

Colombo GL, et al. Ther Adv Respir Dis. 2019;13:1753466619841350.

Zaazouee MS, et al. Front Pharmacol. 2022;13:992731.

Farne HA, et al. Cochrane Database Syst Rev. 2022;7(7):CD010834.

Gallagher A, et al. The Cochrane Database Syst Rev. 2021;10(10):CD012929.

ALGORITHM FOR BIOLOGIC THERAPY SELECTION IN SEVERE ASTHMA

Patient with uncontrolled asthma with/without severe exacerbations (≥ 2 /year) receiving high doses of ICS-containing therapy and/or systemic corticosteroids

Assess patients' asthma phenotype

Type 2 inflammation markers
1. Blood Eosinophils 2. FeNO
3. Total and specific serum IgE

Requiring OCS maintenance

NO

YES

Type 2 Inflammation

Non - Type 2

LAMA
Azithromycin
Anti TSLP

Baseline blood Eos
(Pre-steroids)

No baseline blood Eos
Current serum Eos
<150 cells/ μ L

Anti-IL4/13
Anti-IgE

Blood Eos
<150
cells/ μ L

Blood
Eos
 ≥ 150
cells/ μ L

Anti-IL4/13
Anti-IgE

Anti-IL4/13 (if <1500 cells/ μ L)
Anti-IL5/IL5R*
Anti-IgE

Blood Eos <150 cells/ μ L

Blood Eos 150 - 1500 cells/ μ L[#]

Blood Eos >1500
cells/ μ L[#]

Co-morbidities

FeNO <25 ppb

FeNO ≥ 25 ppb

Yes

No

High
IgE

CRSwNP
Or
Chronic
Urticaria

Non
CRSwNP
Or
Chronic
Urticaria

Anti-TSLP
Anti-IgE

Anti-IgE

Anti-IgE
Anti-TSLP

CRSwNP
Or
Chronic
Urticaria

Non
CRSwNP
Or
Chronic
Urticaria

Anti-IL4/13,
Anti-IgE
Anti-TSLP

Anti-IL4/13
Anti-TSLP

CRSwNP

Allergic
Dermatitis

FeNO
<25 ppb

FeNO
 ≥ 25 ppb

Anti-IL4/13
Anti-IL5/IL5R*
Anti-TSLP

Anti-IL4/13,
Anti-TSLP

Anti-IL5/IL5R*
Anti-TSLP

Anti-IL4/13
Anti-TSLP
Anti-IgE

[#]Rule out:
• Haematological malignancy
• Allergic bronchopulmonary aspergillosis
• Eosinophilic granulomatosis with polyangiitis
• Parasitic infection

Assess response, side effects and patient satisfaction at 4 months

Good response:

- Decrease OCS by $\geq 50\%$
- Decrease exacerbation rate by $\geq 50\%$
- Decrease symptoms
- Improved asthma control

Poor response:

- Reassess differential diagnosis, adherence, coexisting conditions, phenotypes and biomarkers
- Stop ineffective biologic agent
- Consider switching to a different biologic agent
- Share decision making

*In local setting, blood Eos >300 cells/ μ L is needed to start anti-IL5/IL5R

Abbreviations: CRSwNP=chronic rhinosinusitis with nasal polyps; Eos=eosinophils; FeNO= fractional exhaled nitric oxide; ICS=inhaled corticosteroid; IgE=immunoglobulin E; IL=interleukin; LAMA= long-acting muscarinic antagonists; OCS=oral corticosteroids; ppb=parts per billion; TSLP=thymic stromal lymphopoietin

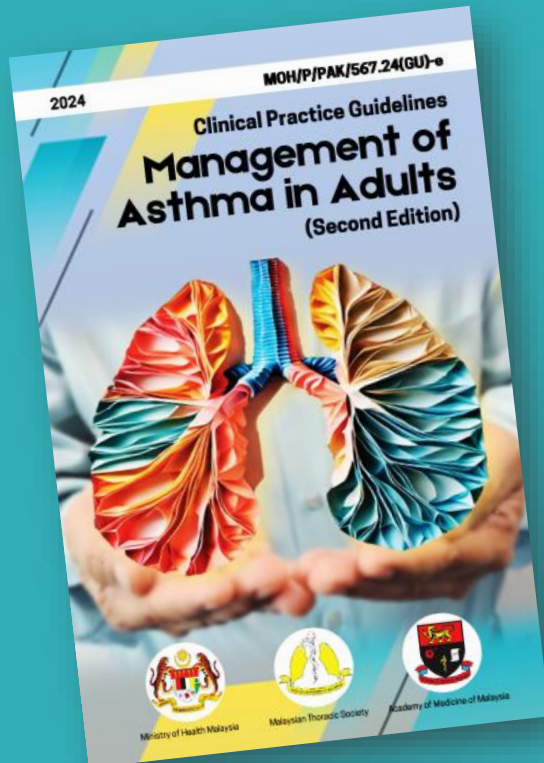


Recommendation 15

- Biologics should be considered as add-on treatment for severe asthma after optimising therapy. Phenotype assessment should be conducted prior to this.
- Long-term oral corticosteroids should be reserved for severe asthma when no alternative treatments are available. They should be tapered off or to the lowest effective dose with side effects closely monitored.
- Azithromycin may be considered as an add-on treatment in asthma patients who remained uncontrolled on high-dose inhaled corticosteroids.

TRAINING OF CORE TRAINERS ON CPG

MANAGEMENT OF ASTHMA IN ADULTS (SECOND EDITION)



LECTURE 6

Special Groups

Dr. Hema Yamini Devi Ramarmuty
Consultant Respiratory Physician
Hospital Queen Elizabeth

Special Population



- Severe Asthma
- **Asthma in Pregnancy**
- Occupational Asthma
- Exercise-induced
Bronchoconstriction
- Asthma with Co-Morbidities



Asthma in Pregnancy

- Asthma may **worsen, improve, or remain unchanged** during pregnancy.
- Women with **pre-existing severe asthma** are more likely to experience worsening control.



Diagnosis

- Similar to diagnosis in **non-pregnant women**
- **Bronchoprovocation tests are contraindicated**
- If clinical history is **strongly suggestive** of asthma and no alternative cause is found:
 - **Start asthma treatment based on clinical judgement**
 - **May postpone confirmatory tests (e.g. spirometry or FeNO) until after delivery**

2. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention (2024 update). 2024

3. MoH, Malaysia. Clinical Practice Guidelines Management of Asthma in Adults. 2017.



Assessment and Monitoring

- **Monitoring frequency:**
 - Asthma patients should be reviewed **every 4 to 6 weeks** during pregnancy
- A cross-sectional study on asthma in pregnancy showed that both GINA classification and ACT had significant association with spirometry values (FEV1 and FVC) - these tools can be effectively used to assess asthma control⁷²

Treatment



Uncontrolled asthma in pregnancy poses **greater risks** to both mother and baby than the use of standard asthma medications- effective treatment is essential.

The treatment approach is the **same** as in non-pregnant patients



Maintenance Therapy

- Inhaled corticosteroids (ICS) are safe and preferred
- Inhaled β_2 -agonists and leukotriene receptor antagonists (LTRA) are safe
- Avoid step-down therapy during pregnancy
- Biologics: Use only if benefits outweigh risks, with specialist input



Asthma in Pregnancy

Exacerbations

- Higher risk during **2nd trimester**
- Treatment is the same as in non-pregnant patients

Labour

- In labour, continue maintenance and reliever inhalers

Breastfeeding

- Asthma patients should be encouraged to breastfeed, and their asthma medication can be safely continued during lactation

2. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention (2024 update). 2024

3. MoH, Malaysia. Clinical Practice Guidelines Management of Asthma in Adults. 2017.

26. SIGN & BTS. British guideline on the management of asthma. UK: SIGN-BTS; 2019.

Special Population

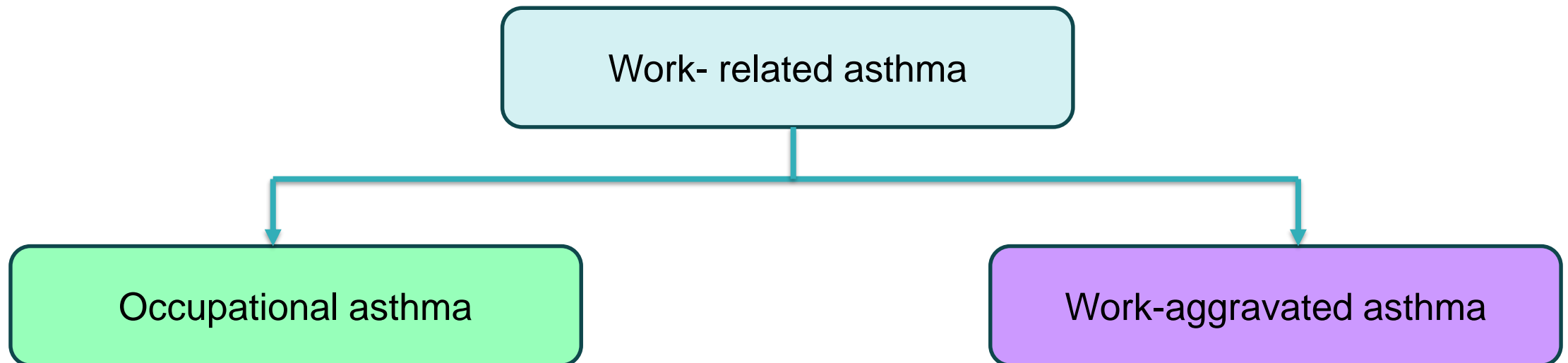


- Asthma in Pregnancy
- **Occupational Asthma**
- Exercise-induced
Bronchoconstriction
- Asthma with Co-Morbidities



Occupational Asthma

- Occupational Asthma (OA) is different from **work-aggravated asthma**
- **Work-aggravated asthma:**
 - Pre-existing or new adult-onset asthma that worsens due to **non-specific** workplace factors
 - Not caused directly by workplace agents





Occupational Asthma-2

- A type of **work-related asthma** caused by specific **workplace exposures**
- Can be triggered by immunologic or nonimmunologic airborne stimuli present in the workplace.

Clinical Features of Occupational Asthma



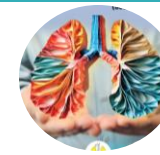
- Patients typically present with **common asthma symptoms**:
 - Cough, wheeze, chest tightness, and shortness of breath at work
- Often work in **high-risk jobs** with exposure to known asthma triggers
- Symptoms usually **improve significantly when away from work**, such as:
 - On weekends
 - During vacations or extended leave

Risk Factors of Occupational Asthma



- **Over 400 causes** of OA have been identified
- 2 key risk factors:
 - **Individual susceptibility** (e.g., genetic or allergic tendency)
 - **level of exposure** to workplace allergens

Risk Factors of Occupational Asthma-2



Occupational Groups

- | | | |
|--|--------------------------|---------------------------|
| - Animal handlers | - Farm workers | - Plastics/rubber workers |
| - Bakers | - Food processors | - Storage workers |
| - Carpenters | - Forestry workers | - Textile workers |
| - Chemical workers | - Hairdressers | - Waiters |
| - Cleaners | - Laboratory technicians | - Welders |
| - Dental workers | - Metal workers | |
| - Electrical/electronic production workers | - Painters | |

Workplace Agents

- | | | |
|--|-------------------------------|--|
| - Animal's and insects' protein (animal dander, urine, saliva, serum proteins) | - Colophony and fluxes | - Metals (e.g. chromium, cobalt, nickel, zinc) |
| - Chemicals and solvents (aldehydes, acids and alkalis) | - Drugs (antibiotics, others) | - Plant protein (flour and grain dust, latex) |
| | - Dyes (used in textile) | - Wood dust |
| | - Henna and persulphates | |
| | - Isocyanates | |

Diagnosis & Assessment of Occupational Asthma



- Diagnosis involves:
 - Recognizing **typical asthma symptoms**
 - **Ruling out** other potential causes
- Take a **detailed occupational history**:
 - Type of work and possible irritant exposures
 - Symptom pattern about work
 - Improvement during weekends or time off
- **Ask about occupation** in:
 - Adults with new or worsening asthma symptoms
 - Reappearance of childhood asthma
 - Unexplained airflow obstruction

Diagnosis of Occupational Asthma



- PEFR is essential for **diagnosing and monitoring OA**
- **Serial PEFR measurements:**
 - Minimum **4 readings/day**, 2 hours apart during waking hours
 - Record **before taking bronchodilators**
 - Continue for **at least 3 weeks**
 - Should include **3 periods of workdays** and **3 periods off work**
 - Document **work hours, tasks, exposures, medications** with timing
- **≥20% variability** between workdays and off days suggests OA

Treatment & Referral of Occupational Asthma



- **Early diagnosis** is essential
- Identify and eliminate **occupational sensitisers**
- Key strategies include:
 - **Relocation** of the worker away from the exposure
 - **Substitution** of the hazardous substance with a safer alternative
- Pharmacological treatment of OA is **similar** to non-OA asthma patients

- Patients with suspected OA should be referred to a specialist for further evaluation. Confirmed cases of OA should be notified using WEHU-L1 (JKKP7) form to the Department of Occupational Safety and Health.

Special Population



- Asthma in Pregnancy
- Occupational Asthma
- **Exercise-induced Bronchoconstriction**
- Asthma with Co-Morbidities



Exercise-Induced Bronchoconstriction (EIB)

- Defined as **transient, reversible airway narrowing** during or after exercise
- Can occur in:
 - Patients **with** or **without** chronic asthma



Diagnosis of EIB

- Based on:
 - **Typical clinical symptoms**
- **Reversible airflow limitation**, demonstrated through:
 - **Exercise challenge test**
 - **Indirect bronchoprovocation** (e.g. mannitol challenge)
- Diagnostic criteria:
 - **>10% drop in FEV1** within **30 minutes** post-exercise



Management of EIB

- A proper warm-up with progressively increasing intensity may reduce the severity of exercise-induced bronchoconstriction
- **Pharmacologic options:**
 - *Patients with EIB and asthma* should stay on their regular asthma treatment and use their reliever inhaler before exercising, as prescribed.
 - *EIB without asthma* is usually managed with pre-exercise SABA alone



Special Population

- Asthma in Pregnancy
- Occupational Asthma
- Exercise-induced Bronchoconstriction
- **Asthma with Co-Morbidities**
 - Obesity
 - Obstructive Sleep Apnoea
 - Allergic rhinitis
 - Chronic rhinosinusitis
 - Gastroesophageal Reflux Disease
 - Anxiety and Depression



Asthma with Co-morbidities

- **Co-morbidities are common in patients with asthma and are associated with:**
 - Higher risk of **adverse effects** from treatment
 - **Poorer quality of life**
 - Increased **healthcare utilisation** compared to those without co-morbidities
- Patients with **multiple co-morbidities** often have **difficult-to-treat** or **severe asthma**.
- Active identification and management of co-morbidities is essential to improve **asthma control** and **asthma-related outcomes**.



Asthma with Co-morbidities-2

1) Obesity

- Obese asthma patients:
 - Tend to have **poor asthma control**
 - Treatment approach: Similar to other asthma patients — **ICS remains the mainstay**
 - **Weight loss is important** and should be actively encouraged

2) Obstructive Sleep Apnoea(OSA)

- **Continuous positive airway pressure (CPAP)** therapy is the recommended treatment for OSA.
- CPAP has been shown to **reduce** the risk of asthma exacerbations



Asthma with Co-morbidities-3

3) Allergic rhinitis

- Most patients with asthma have **allergic rhinitis**
- Symptoms may vary with **environmental/occupational exposures** such as furred pets, house dust mites, molds and pollens.
- **Intranasal corticosteroids -most effective therapy** for allergic rhinitis
- LTRA may be useful as an **add-on therapy** in patients with **seasonal allergic rhinitis and asthma**

4) Chronic rhinosinusitis

- Symptoms present on **most days for ≥ 12 weeks**
- May be present with or without nasal polyps.
- Associated with **more severe asthma**, especially in patients with **nasal polyps**
- Presence of **nasal polyps** may help guide the choice of **biologic therapy** in severe asthma



Asthma with Co-morbidities-4

5) Gastroesophageal Reflux Disease (GERD)

- Symptoms include heartburn, epigastric or chest pain, dry cough
- Asthma patients - **more likely** to have GERD
- **Proton pump inhibitors** have shown benefit in asthma patients with symptomatic reflux and those with nocturnal respiratory symptoms

6) Anxiety and depression

- Are linked to
 - *poor asthma control*
 - *reduced medication adherence*
 - *Poor quality of life*
 - *Increased frequency of exacerbations*
- Referral to psychiatry- for proper assessment & effective Mx

TAKE HOME MESSAGES



- Biologics should be added for severe asthma only after optimising therapy and conducting **phenotype assessment**.
- Long-term oral corticosteroids should be used only when no alternatives exist and must be **tapered to the lowest effective dose** with close monitoring.
- Diagnosis and management of asthma during pregnancy are **similar** to non-pregnant patients.
- All suspected occupational asthma **should be referred** to a respiratory physician or a physician experienced in occupational health.
- **Co-morbidities** should be identified and treated appropriately in asthma.

Thank You!!



Training of Core Trainers on CPG
Management of Asthma in Adults
(Second Edition)