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Editorial

Pleural disease in 2024

R K Panchal[1]

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Introduction

The pleura may be affected by over 50 systemic conditions and the burden of pleural diseases continues to rise globally[1,2]. Over the last decade there has been a growing interest in pleural disease, which has become firmly established as a distinct subspecialty within respiratory medicine. In a survey of the career intentions of respiratory medicine specialty trainees in the UK, pleural disease (38%) was the most popular subspecialty area of interest followed by lung cancer (34%) and interstitial lung disease (34%)[3]. High-quality, practice changing multi-centre randomised controlled trials coupled with an expanding repertoire of procedures has transformed pleural care and makes it an attractive subspecialty. In the UK, this unprecedented demand is demonstrated by the British Thoracic Society (BTS) who have a pleural specialist advisory group (SAG), the creation of the UK Pleural Society (UKPS) and the increasing development of NHS consultant respiratory posts with an interest in pleural disease.

Globally, a number of societies have published guidelines on management of pleural disease to standardise practice and improve care[4,5,6]. The most comprehensive remain the BTS guidelines which were first published in 2010 and updated in 2023 and are accompanied by a BTS Clinical Statement on Pleural Procedures which focuses on safe clinical practice[7]. This editorial aims to provide insight on the current evidence base which has helped to shape pleural disease practice.

Pneumothorax – 'less is more'

Over the past few decades pneumothorax management has increasingly become more interventional, which in part may be due use of smaller gauge Seldinger/pigtail drains that are deemed less invasive. However, there remains wide variation in pneumothorax management and a focus on pneumothorax size. A UK survey of respiratory clinicians reported that only 50% would manage a large primary spontaneous pneumothorax (PSP) with minimal symptoms conservatively, compared to 3% with symptoms[8]. There is no international consensus on the size of a pneumothorax[9]. In the new BTS guidelines, size alone is no longer an indication for intervention but is guided by the patient's symptoms and a focus on the patient's priority with less onus on distinguishing a primary from secondary pneumothorax[7]. Provided there are no high-risk characteristics and the patient is haemodynamically stable, if the preference is for procedure avoidance, conservative management with close follow-up may be an option as reported by Brown et al[10]. If the patient is seeking rapid symptom relief then needle aspiration or depending on expertise and resource availability, ambulatory management using Heimlich devices (e.g Pleural Vent) with close follow-up as reported by the Hallifax et al in the RAMPP trial are options[11]. Chest drain insertion should be reserved for patients that are symptomatic and fail needle aspiration or those with high-risk characteristics such as haemodynamic compromise, significant hypoxia, bilateral pneumothorax, underlying lung disease, >50 years with a significant smoking history or haemopneumothorax[7]. The UK continues to lead on pneumothorax research, with a number of ongoing studies, CONSEPT (conservative vs standard care in PSP), PRINCE-SSP (needle aspiration vs chest drain in secondary spontaneous pneumothorax), RASPER (early resolution of primary pneumothorax with suction vs standard care) and CoMiTED (conservative management in traumatic pneumothoraces). In the new world of pneumothorax management perhaps 'less is more'.

Thoracic ultrasound – 'the new stethoscope'

The last 10-15 years have seen an upsurge in thoracic ultrasound (TUS) performed by respiratory physicians. Point of care TUS offers many advantages; it is widely available, cheap, mobile, lacks radiation, allows real-time safe procedures (aspiration, chest drain, thoracoscopy) and is more sensitive than computed tomography (CT) in pleural fluid charac-

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terisation (e.g. echogenicity and septation)[12]. B-(brightness) mode TUS is the most widely used and can be useful in identifying pleural infection, malignancy, pleurodesis success whilst M-(motion) mode TUS is useful in pneumothorax ['lung-point sign'] and non-expandable lung[12]. TUS also allows image guided pleural biopsy in pleural infection (increases micro-biological yield by 25% compared to pleural fluid and blood culture) and pleural thickening/nodularity (easier when >1cm)[13,14]. The BTS has compiled training standards for TUS which provide a structured and comprehensive approach to managing pleural pathologies with guidance on what is required to become an emergency, primary, advanced or expert operator[15]. In the UK, TUS for pleural intervention is mandatory and is now advocated in many parts of the world and has evolved to become 'the new stethoscope' in guiding clinical decision making in pleural disease.

Malignant pleural effusion – 'streamlining plumbing'

Malignant pleural effusions (MPE) have a global incidence of 70 per 100,000/year and have been associated with protracted inpatient stays and lend themselves to ambulatory outpatient pathways[7]. The sensitivity of pleural fluid cytology varies depending on the likely primary cancer. With mesothelioma (6%) and haematological malignancy (40%) being less than adenocarcinomas (79%)[16]. Therefore, thoracoscopic or image-guided pleural biopsy remains important in the work-up of MPE and blind biopsies should be avoided[7]. Definitive management of MPE has largely revolved around talc slurry pleurodesis with indwelling pleural catheters (IPC) being reserved for patients with non-expansile lung or failed pleurodesis. However, IPC's are increasingly used in the first line management of MPE[17,18]. If IPC removal is favoured, aggressive daily drainage followed by talc in expansile lung has been shown to double the chances of successful pleurodesis (IPC-Plus)[19]. But if the intent is palliation then symptomatic drainage may suffice[20]. Historically, thoracoscopic talc poudrage was deemed to be more effective than talc slurry pleurodesis, however the TAPPS study demonstrated that there was no difference[21]. Thoracoscopic talc poudrage should therefore be reserved for patients undergoing first line diagnostic thoracoscopy where malignancy is suspected. There has been interest in accelerated pleurodesis regimes (e.g. thoracoscopy, IPC + talc) which 'streamline the plumbing' pathway and the recent TACTIC trial which has completed recruitment will be to provide insight into this soon[22]. IPC's also provide a conduit to the pleural space in MPE and there is keen interest in intra-pleural treatments to not only treat the underlying malignancy but provide MPE control[23].

Pleural infection – 'the sun should never set on a parapneumonic effusion'

The incidence of pleural infection continues to rise especially in those >65 years. Approximately, 40% of pneumonia patients develop a para-pneumonic effusion. The 1 year mortality remains around 20% with 15% requiring surgery[24]. Time to intervention is key to reducing adverse outcomes. The RAPID score [Renal (urea), Age, Purulence of fluid, Infection source (community/hospital), Dietary factor (albumin)] is a validated predictor of outcome in pleural infection and can be used to guide management[25]. When to intervene in suspected pleural infection in the absence of purulent fluid has remained challenging. The binary distinction between pH either < or >7.2 to determine drainage has been adapted[7]. Pleural fluid pH ≤7.2 still remains a high-risk predictor of infection but in the new 2023 BTS guidelines a pH ≤7.4 implies a low risk of pleural infection with no immediate need for drainage[7]. There is now a new 'intermediate risk' group with pH 7.21-7.39, where if the LDH is >900, coupled with clinical parameters of low pleural glucose, CT pleural enhancement or septation on TUS then prompt drainage should be considered[7]. In the majority, 12-14F small bore drains should suffice together with antibiotics for 2-6 week depending on the clinical response[7]. 40% of patients with pleural infection have negative microbiology[26]. Inoculating blood culture media with pleural fluid has been shown to increase micro-biological yield by 10-15% and image guided pleural biopsy increases this further[13,26]. Pleural fluid bio-markers (suPAR & PAI-1) have been shown to be associated with loculated pleural effusions and also increased mortality but require prospective validation [27, 28]. The Multi-centre Intrapleural Sepsis Trial (MIST) randomised controlled trials have provided the most robust evidence based on intra-pleural enzyme therapy (IET). MIST-1 was a negative study on the efficacy of streptokinase and MIST-2 demonstrated the synergistic benefit for tPA + DNAse with an overall bleeding risk of 4.1% in a recent study[29,30,31]. In patients where IET is not available or not suitable, the PIT trial demonstrated benefit with 250ml of saline irrigation three times per day[32]. The recent MIST-3 feasibility trial of early VATS (video-assisted thoracoscopic surgery) vs IET showed shorter length of stay with surgery and earlier resolution of pain and shortened recovery with IET, paving the way for hopefully a phase III study in the near future (MIST-4)[33]. A few studies have highlighted the benefit of early medical thoracoscopy (MT) in pleural infection. MT allows clearance of septations but cannot decorticate the parietal pleural and is thus still not recommended in international guidelines. The BTS 2023 guidelines advocate more aggressive treatment of pleural infection, with review at 48 hours after initial drainage and

antibiotics and if there is no improvement, to consider early surgical referral or IET[7]. The old adage of 'the sun should never set on a parapneumonic effusion' coined by Sahn and Light in 1989 still holds true in 2024[34].

Conclusion

Pleural disease remains a very satisfying branch of respiratory medicine with a broad range of conditions; interventions that keep clinicians enthused and make a difference to patients coupled with close multi-disciplinary team working and high-quality research outputs. Clinical practice will ultimately be determined by the local health economy, expertise and access to resources. The future of pleural disease research is bright and we are slowly unravelling the answers to questions that continue to challenge us. But as Gary Lee has highlighted, the holy grail of pleural disease management remains prevention of fluid development in the first place[35].

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Review

Multidisciplinary approach to sleep disordered breathing

S Withana[1]

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Abstract

Sleep Disordered Breathing (SDB) is a spectrum of disorders causing airflow obstruction, cessation, hypoxia and hypoventilation. Causative mechanisms involve structural, endocrine, metabolic, neurological, cardiovascular and psychological abnormalities. Prevalence of SDB is rapidly increasing with obesity and diabetes. Although CPAP/Mask based treatment is the gold standard, it is not always acceptable, tolerable or affordable for many patients.

Respiratory physicians should increase public awareness of other treatment modalities and assess patients with a view to develop a personalised care plan depending on patient s pathophysiology. Mandibular Repositioning Device therapy provided by orthodontists is increasingly utilised globally. Introduction of Drug Induced Sleep Naso Endoscopy (DISE) has transformed ENT interventions for SDB. Thoracic surgery for chest wall disorders, Diaphragm plication, Bariatric surgery, Maxillary Mandibular Advancement, Hypopharyngeal surgery and Hypoglossal Nerve Stimulation (HNS) are some of the recognised interventions.

Hypoventilation Syndromes are an important SDB contributing to both acute and chronic respiratory failure. In addition to obesity, drug s such as opiates, chest wall disorders such as kyphoscoliosis, neuromuscular diseases such as myopathies and diaphragm dysfunction should be evaluated. All SDB patients will benefit from screening for metabolic complications such as hypertension, dyslipidaemia, prediabetes , microalbuminuria and non-alcoholic steatohepatitis.

Respiratory Physicians need to play a key role in engaging other specialists such as Dentists, Surgical experts in ENT, Max Fax, Bariatric and Thoracic surgery and Neurologists, Psychiatrists, Stroke Specialists, Endocrinologists, General Physicians, Cardiologists, Anaesthetists and Nutritionists together with Sleep technicians/physiologists to provide a comprehensive individualised care plan.

Sleep Disordered Breathing (SDB) is a rapidly evolving area in Respiratory medicine with recent advancements in therapeutic interventions and the understanding of pathophysiology. SDB is a spectrum of disorders with disruption of sleep architecture due to airflow obstruction or cessation and hypoventilation. This spectrum covers Obstructive Sleep Apnoea (OSA), Central Sleep Apnoea (CSA), Upper Airway Resistance Syndrome (UARS), Obesity Hypoventilation Syndrome (OHS), Nocturnal Hypoventilation, Nocturnal Hypoxaemia, Overlap syndromes associated with other respiratory diseases such as COPD and ILD causing respiratory failure[1,2]. The most widely recognised disorder is Obstructive Sleep Apnoea and Hypopnoea Syndrome (OSAHS), with cessation of air flow (>5/hr of >10sec) or reduction of air flow (>30% reduction for >10sec) and intermittent hypoxia (>3% or 4% Desaturation) causing arousals, sleep fragmentation with daytime somnolence[3,4]. The causative mechanisms and complications of SDB involves a complex interaction of structural, physiological, metabolic, neurological, cardiovascular and psychological abnormalities[5]. SDB is a treatable but markedly under diagnosed condition linked to cardiovascular morbidity and mortality[6]. This highlights the need for a multidisciplinary approach to disease management.

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Respiratory Physicians need to play a key role in engaging other specialists such as Dentists, Surgical experts in ENT, Max Fax, Bariatric and Thoracic surgery, Neurologists, Psychiatrists , Endocrinologists, General Physicians, Cardiologists, Stroke Specialists, Anaesthetists and Nutritionists together with Sleep technicians/physiologists to provide personalised care for each individual patient.

Patients with clinically significant SDB would generally seek help due to daytime hypersomnolence, fatigue, poor sleep hygiene, loud snoring affecting social life, concerns regarding stopping breathing or witnessed apnoeas and headache[1]. Degree of somnolence appears to be the best predictor of response to treatment[4]. However, due to the lack of awareness of the role of Respiratory physician in SDB, a large proportion of these patients would present to other specialities such as Neurologists, ENT surgeons and General physicians. Additionally, many patients with comorbid obesity with other respiratory disorders would present to the respiratory clinic with non-sleep related symptoms; and the contribution of obesity or nocturnal hypoventilation to their symptom burden is often overlooked. Respiratory physicians should have a low threshold to offer screening tools for SDB for more patients as a routine measure.

Respiratory assessment for a patient with SDB should include a thorough general examination starting from the moment the patient walks in. As CPAP therapy remains the gold standard for SDB[1], the assessment should include factors that could compound patients tolerance to CPAP. General examination should be aimed at identifying causative factors, including the distribution of obesity, neck circumference, features of endocrinopathies such as Hypothyroidism, Cushing's, Acromegaly and Craniofacial abnormalities such as prognathism, short neck, micrognathia and retrognathia[1].

There is increasing evidence base for Mandibular Repositioning Device (MRD) or Oral Appliance Therapy (OAT) as an effective treatment modality across all severity groups of OSAHS[7]. In addition to the health of dentition, jaw position and stability of temporo-mandibular joints is relevant for a dental referral. Respiratory physicians could increase the awareness of MRD therapy that could be provided by a registered dentist interested in SDB[8]. There are many types of custom made, semi bespoke and boil and bite devices available with non-inferior results compared to CPAP with long term safety data compared to surgical interventions and certainly superior to non-treatment or placebo9. MRDs could also be used as a combination therapy if a single approach fails to achieve symptom control. With increasing experience of individual centres, long term use of MRDs with supervision under Dental and Respiratory physicians, could become a cost effective treatment option for SDB[10]. MRDs are increasingly useful for patients opting for a non-PAP based treatment plan or for those who are PAP intolerant. Sri Lanka has many national level dental institutions and teaching hospitals that could potentially initiate MRD services and provide training. Many private dental services could also be educated and promoted towards providing these services through appropriate diagnostic and referral pathways.

Oropharyngeal and upper airway examination should include assessments relevant for an ENT referral. These include palato-pharyngeal abnormalities such as adeno tonsillomegaly, bulky uvula, macroglossia[1], Mallampati classification or Friedman tongue position scoring adopted by each service. Symptoms that should receive an ENT assessment include nasal voice, chronic nasal obstruction and chronic mouth breathing to search for conditions such as septal deviation, turbinate hypertrophy, previous nasal bone injury or nasal polyps. Although surgical interventions for upper nasal obstruction has not yet shown to be curative for OSA, there has been improvement in snoring, sleep quality and CPAP tolerance[11]. Over the last few years, Sleep ENT interventions have rapidly evolved with increasing availability of evidence for ENT interventions with large multicentre RCTs[12]. Since the introduction of Drug Induced Sleep NasoEndoscopy (DISE), patient selection for appropriate interventions has become more objective[13]. Developments in surgical tools such as lasers, radiofrequency technology and robotic surgery have added to a new dimension to the surgical options1. Generic approach to UVPPP is increasingly replaced by these modern techniques, although in selected patients Tonsillectomy with Uvulopalatopharygoplasty (TE-UVPPP) is still very cost effective[14]. Trans Oral Robotic Surgery (TORS) multi-level palato-pharyngeal interventions such as Laser assisted Uvulopalatoplasty (LAUP), Laser assisted Pharyngoplasty and Tonsillectomy and Reduction of tongue base are increasingly become popular[15]. ENT interventions are particularly important in the paediatric SDB cohort where adeno tonsillectomy has much success as a curative measure[16]. With the recent NICE approval of Hypoglossal Nerve Stimulation (HNS) as a recognised intervention for moderate to severe OSA patients with CPAP Intolerance[17], the need for managing SDB combined with a dedicated specialist ENT team has become even more interesting and rewarding. ENT surgery will continue to remain a vital part of providing personalised care for SBD especially for non-obese patients high nasal symptom burden,

for patients with CPAP intolerance seeking alternative therapies and to facilitate better quality CPAP[18].

Patient s with retrognathia, prognathism, malocclusion and certain cephalometric abnormalities causing narrowing of the upper airway would benefit from other surgical interventions such as Maxillary Mandibular Advancement (MMA)[8], and Hypopharyngeal surgery.19 Patients with OSA who were treated with MMA maintained improvements in AHI, sleepiness, oxygen desaturation, diastolic BP, and subjective sleepiness with concomitant significant improvements in QOL in the long term[19]. Maxillomandibular advancement is increasingly utilised for patients with initial CPAP failure for the treatment of moderate to severe obstructive sleep apnea (OSA)[20]. In the experienced centres there has been success in palatal implants in mild to moderate OSA[21].

Obese patients with a larger neck circumference are more at risk of supine sleep apnoea, with a unique subgroup that may respond to Position Sleep Apnoea therapy[22]. Obtaining history regarding sleep position in conjunction with the Supine Sleep apnoea index and degree of nocturnal hypoventilation is important in managing Position Sleep Apnoea (POSA). At least twice as many events occurring in Supine position with supine time >20% of total sleep time , defines clinically significant Supine OSA. Although many POSA devices using vibratory techniques are increasingly available, a pragmatic approach with appropriate advice would be beneficial in the correct clinical context, particularly in combination with other modalities.

Nocturnal Hypoventilation can occur as a primary pathology or in combination of OSA. Sleep related hypoventilation could be demonstrated at an early stage of any chronic hypoventilation disorder ($PaCO_2$ ≥45 mmHg or 6 kPa). Obesity (BMI>30) Hypoventilation Syndrome is by far the commonest cause, the ICD-10 classification also identifies central causes such as congenital, hypothalamic and idiopathic central hypoventilation syndromes, hypoventilation syndromes due to medical disorders and drugs[24]. Drugs such as opiates, alcohol, methadone, benzodiazepines, antidepressants, anxiolytics, baclofen and dopamine antagonists are known contributing factors[1,24]. Another area of interest is Chest wall disorders such as kyphoscoliosis[25], pigeon chest[26], bony ankylosis and other skeletal and soft tissue abnormalities such as Achondroplasia[27], Downs syndrome[28] and other forms of Dwarfism ,Osteogenesis imperfecta[29], Marfans[30], Ehlers-Danlos Syndrome. Many causative mechanisms are attributable including upper airway narrowing, collapsibility, reduced muscle function and chest expansion[23]. SDB associated with chronic ventilatory failure due to restrictive lung diseases and overlap syndromes could be reversed with Non-Invasive Ventilation (NIV)[31].

Neuromuscular disease or Myopathies is another important group causing SDB/ Nocturnal hypoventilation[32]. These include Muscular dystrophies, Metabolic myopathies, Genetic causes such as Pompe Disease, Phrenic Nerve Palsy, Diaphragm dysfunction, Myotonia Dystrophica, Myasthenia, Spinal Muscular Dystrophy, Guillain-Barré syndrome, Charcot-Marie-Tooth disease, Multiple Sclerosis[33], Spinal cord trauma[34] and Motor Neurone disease (MND)[35]. NIV has improved prognosis and quality of life of patients with MND for the last two decades under the supervision of a Respiratory physician[36]. Other Neuropsychiatric conditions where screening for SDB is recommended include Parkinson's Disease and Progressive supra nuclear palsy[37], poorly controlled epilepsy, nocturnal seizure disorders[38], young onset cognitive impairment, Alzheimer's dementia[39]. In Depressive disorder, Schizophrenia and Bipolar disorder, treating comorbid SDB could improve patients' symptoms significantly[40]. Most of these neurological conditions cause a combination of nocturnal hypoventilation, obstructive and central sleep apnoea and nocturnal hypoxia[31] and, if untreated will lead to chronic ventilatory failure with pulmonary hypertension. Apart from CPAP and NIV, other modalities of treatment such as medication guided by a Neurologist or psychiatrist, Chest physiotherapy, Cough Assistant Devices and Inspiratory Muscle training[41] provided under a multidisciplinary team improves prognosis. Chronic Diaphragm palsy or paresis may benefit from Diaphragm-plication, Phrenic Nerve Stimulation and Unilateral or Bilateral Diaphragm pacing[42]. Respiratory physicians should develop a referral pathway particularly in collaboration with the neurology, psychology and general medical services to ensure patients are referred early for a comprehensive assessment, as many of these risk factors could overlap and coexist.

Respiratory physicians should be vigilant about SDB in their general respiratory clinics. Steroid induced muscle dysfunction and kyphosis related to osteoporosis is common in many chronic lung diseases. Chronic muscle wasting following long term illnesses such as post ITU myopathy, post stroke or age and deconditioning related muscle wasting are contributory factors for nocturnal hypoventilation[43,44]. Nocturnal and obesity hypoventilation are common overlapping conditions that would contribute to delayed recovery from acute respiratory exacerbations such as COPD and ILD[45,46]. SDB is also a known association with severe Asthma due to multiple risk factors including upper air way inflammation, collapsibility and obesity[47].

Obese patients and patients with SDB can also be at high risk of developing anaesthetic complications such as difficult intubation and difficulty in weaning post general anaesthesia with high risk of re-intubation[48]. Preoperative diagnosis of SDB is shown to improve perioperative mortality and cardiovascular complications[49]. Hence use of preoperative screening tools and increasing awareness among anaesthetic colleagues about screening for SDB and weaning to Non-Invasive Ventilation would improve post-operative recovery. As Domiciliary Oxygen, CPAP and BiPAP Ventilation services are increasingly becoming available across the country, Respiratory physicians should enable an appropriate referral structure with the use of correct screening tools.

Identifying comorbidities is an important aspect of managing patients with SDB, which should not be overlooked. Obesity (BMI>30) is the commonest risk factor for developing SDB (60-90%)[50]. Prevalence of SDB range between 30%-98% in the Obesity increasing with age and BMI[51]. SDB is associated with cardiovascular and metabolic abnormalities including sympathetic dysregulation, altered adipokines, inflammatory cytokines, insulin resistance, and glucose intolerance [5,52]. Risk of Diabetes is very high in patients with SDB[53], with increasing severity of SDB at a higher BMI, this relationship appears to be bidirectional[54]. Advice on weight loss, lifestyle measures, reducing alcohol intake and smoking cession should be part of routine care for all patients with SDB[1]. SDB patients will also benefit from screening for metabolic syndrome related complications such as dyslipidaemia, non-alcoholic steatohepatitis (NASH)[55], microalbuminuria and Chronic Renal Failure[56]. Treatment of Obesity and SDB improves metabolic and cardiovascular risk factors[57]. For those patients with resistant obesity (BMI>35) , Bariatric Surgery in conjunction with nutrition interventions can be curative for metabolic syndrome with evidence of improvement in AHI and nocturnal hypoxemia, but more evidence is needed for the long term impact on SDB[58].

SDB is associated with increased cardiovascular and all cause mortality59 with a strong association with resistant hypertension (>3 drugs); treating SDB with CPAP has proven to reduce hypertension.60 SDB is identified as an independent risk factor for Atrial fibrillation[61]. Patients with heart failure should be screened and treated for SDB[62] with monitoring for central sleep apnoea. SDB is a known risk factor for coronary artery disease particularly in patients with higher hypoxic burden, and screening for coronary artery disease can be recommended to patients with SDB[63]. Although CPAP therapy has not yet been proven to improve cardiovascular mortality, there is benefit seen in stroke prevention[64]. SDB is a definite risk factor for TIA s and stroke, particularly wake up stroke[65]. Respiratory physicians should work together with Cardiologists and Stroke specialists to improve patients' cardiovascular risk.

Many Respiratory services in the government sector (National Health Service) lack access to Respiratory or Sleep physiology support in performing diagnostics such as Polysomnography or Polygraphy. There is still a long way to go until freely accessible National sleep and ventilation services with interventions such as CPAP; NIV and Home Oxygen therapy becomes available. However, risk factor modification with lifestyle advice and health education can be an effective first line therapy[66]. Free Dental interventions, ENT and other surgical services should become increasingly available for this group of patients . Thanks to the hard work of many dedicated respiratory physicians, these interventions have been introduced in the government sector and have become more affordable in the private sector. It is important that the Respiratory and Sleep physiology services in both government and private sector are guided by clinicians who are trained in managing SDB and overlapping conditions, so that the patients receive a comprehensive personalised care plan. Respiratory physicians need to educate the public regarding the importance of SDB and how to access appropriate service providers. Developing multimodality treatment pathways where possible under one roof will help clinicians to work effectively, develop research and grow as a multidisciplinary team to provide holistic patient care.

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Review

New discoveries in asthma pathophysiology and their impact on the management: A short review

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Key words: eosinophilic asthma, innate lymphoid cells, dendritic cells, pulmonary epithelial cells, asthma pathophysiology

Abstract

Asthma is among the most common chronic inflammatory diseases worldwide and has been a challenging management problem despite rapidly evolving diagnostics and therapeutics. The high degree of heterogeneity in pathophysiological mechanisms and complex genetic and environmental interactions seen among certain subsets of patients form the basis for difficult asthma. Some of such examples are the involvement of type 2 innate lymphoid cells (ILC2 cells) in T2 inflammation, TH17-mediated neutrophilic inflammation and the complex interaction of *Aspergillus fumigatus* with the airway epithelial cells, activating specific immune pathways. A thorough understanding of the exact molecular and immune basis is imperative in planning of personalized care for asthma patients. Aligning between clinical phenotypes, molecular endotypes, and endotype-specific therapies is key to future asthma care. In this short review, we discuss some of the discoveries on the pathophysiology of asthma and their implications in asthma diagnosis and management from a global and Sri Lankan perspective.

Introduction

Asthma is a chronic inflammatory disease that predominantly affects conducting airways in which the innate and adaptive immune systems interact with epithelial cells to cause bronchial hyper reactivity (BHR), mucus overproduction, airway obstruction, and airway wall remodeling. These key pathological changes lead to repeated cycles of shortness of breath, wheezing, chest tightness, etc., among susceptible patients, causing exacerbations. Asthma affects up to 300 million people worldwide. 20-year projected total direct costs associated with uncontrolled asthma are estimated to be $300.6 billion in the United States[1,2]. In Sri Lanka, the prevalence of wheezing or persistent nocturnal cough in preschool and school children was above 20%, as per the local arm of the International Study of Asthma and Allergy in Children in 2002[3]. Furthermore, in 2001 and 2013 the prevalence of exercise-induced wheeze, rhinitis and eczema, among the current wheezers, was, in 2001 and 2013, reported as 72.3%, 70.2%, 78.9% and 77.7%, 79.1%, 72.2%, respectively[4]. The rising problem of poor air quality and the gaps in asthma management are potential problems that need to be addressed in Sri Lanka[5].

In many patients, asthma can be controlled by a combination of an inhaled corticosteroid and a short- or long-acting β2-adrenergic agonist which acts to open the constricting bronchial smooth muscle. However, among 5-10% of patients, the disease is refractory to usual corticosteroid treatment and often leads to recurrent medical encounters. This subset of difficult asthma patients often causes challenges in the diagnosis and management as well as contributes significantly to the health care cost. Traditionally, asthma was classified as allergic (extrinsic) and non-allergic (intrinsic) asthma. Most children and around 50% of adults have allergic asthma, in which the cardinal feature is allergic sensitization defined by the presence of serum immunoglobulin E (IgE) antibodies and/or a positive skin-prick test to the (lipo) proteins of inhaled

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or ingested allergens[2,6]. In contrast, nonallergic asthma usually develops later in life. It has neither IgE reactivity to allergens nor any obvious involvement of the adaptive immune system, such as type 2 helper T cells (TH2 cells). This form of asthma is more common in women, is often associated with chronic rhinosinusitis as well as obesity, and is difficult to treat, requiring long-term systemic steroids.

Clinical asthma diagnosis and treatment have undergone great shifts due to the advent of genome-wide expression studies and the use of targeted therapies with biological agents. Clinicians now realise that the categorization of asthma only into two clinical forms is an oversimplification. Hence, different asthma phenotypes with a distinct pathophysiology, often with a unique underlying molecular or an immune basis, are now being defined as asthma endotypes. These endotypes determine genetic susceptibility, environmental risk factors, age of onset, clinical presentation, prognosis and response to standard and new therapies among patients[7-9]. In this short review, we will focus on the underlying immunological basis of various asthma endotypes and the immune elements involved, integrating results from both animal and human studies. It will greatly help to assess, diagnose and manage asthma patients, including difficult asthma.

Newly discovered mechanisms in asthma endotypes

Eosinophilic asthma

Role of CD4+ TH2 cells in eosinophilic asthma

In the field of respiratory immunology, asthma has been considered the hallmark TH2 disorder of the lungs. This was supported by the early findings of eosinophilic inflammation in the asthmatic airway[10]. It also showed increased numbers of CD4+ cells that produce interleukin 4 (IL-4) and IL-5, correlating with the degree of airway eosinophilia[11]. Subsequent studies have shown that the various asthma endotypes fall into TH2hi and TH2lo clusters based on the presence or absence of the cytokines IL-4, IL-5 and IL-13 and eosinophils in blood and tissues[7,12]. The presence of serum IgE (atopy) is the hallmark of adaptive TH2 immunity[13].

Both animal and human studies have proven that CD4+ TH2 cells are the key controllers of the disease, and animal studies have further shown that the absence of the key TH2 cytokines IL-4, IL-5 or IL-13 causes substantial reductions in asthma symptoms[14]. IL-4 is necessary for the development of adaptive TH2 immunity, the induction of IgE and IgG1 antibodies against antigens, and for priming the vessel wall for eosinophil extravasation[14,15]. IL-13 was found to be necessary for mounting bronchial hyperreactivity, goblet cell metaplasia and mucous production[16,17]. Treatment with an antibody to the α-chain of the receptor for IL-4 (dupilumab) effectively blocks downstream signalling via the receptor IL-13. It has been proven to improve lung function and reduce the frequency of exacerbation in people with moderate to severe asthma with high levels of eosinophils in the blood[18].

Eosinophilia in lung tissue is driven by IL-5, which enhances the development of eosinophils in the bone marrow, and by the recruitment of eosinophils to the lung mucosa and interstitium via the production of eotaxins, including chemokine ligand (CCL11), CCL24 and CCL26. Eosinophil-derived mediators such as eosinophil peroxidase cause bronchial hyperreactivity directly and through effects on dendritic cells (DCs)[19,20]. Eosinophils also contribute to airway wall remodelling and subepithelial membrane thickening via the release of transforming growth factor-β (TGF-β)[21,22]. Eosinophils, once activated, undergo cytolysis and release eosinophilic granules containing eosinophilic toxins such as eosinophil-derived neurotoxin, eosinophil peroxidase and major basic protein, which damage pulmonary cells[23,24]. The elimination of eosinophils through the use of antibodies against IL-5 (mepolizumab) leads to a reduction in exacerbation frequency in a subset of patients with high levels of circulating eosinophils in blood with frequent exacerbations and among those receiving high-dose inhaled steroids[25]. An antibody to the receptor for IL-5 (benralizumab) has shown depletion of eosinophils for months after a single injection[26].

Role of ILCs in eosinophilic asthma

In human studies, blockade of the receptor for IL-4 or IL-5 has led to a favourable clinical response in patients with high eosinophil counts, regardless of their atopic status. Administration of allergens led to airway eosinophilia in mice deficient in T cells or B cells. Such findings suggest that there are other ways of generating type 2 cytokines and eosinophilia without the involvement of the adaptive immune system. Innate lymphoid cells (ILCs) were initially classified as non-T, non-B effector cells in different disease models, and the published reviews have described distinctive forms of ILCs (ILCs 1/2/3). Group 2 ILCs are known to produce TH2 cytokines. Although ILC2 cells lack antigen-specific receptors, they react to epithelium-derived cytokines such as IL-25, IL-33 and thymic stromal lymphopoietin (TSLP)[27-29]. The activation of ILC2 cells is induced by IL-25 and IL-33, produced by epithelial cells in response to injury and stimulation

via toll-like receptors (TLRs), and produces TH2 cytokines, including IL-5, IL-9 and IL-13[30]. Studies have suggested that protease-containing allergens activate ILC2 cells indirectly through lung epithelial cells[31,32]. ILC2 cells can also be activated in the lungs following allergen exposure via the expression of the cysteine leukotriene receptor (CysLT1R)[33]. This evidence suggests that ILC2 cells can be activated early after allergen exposure by multiple mechanisms and that their production of TH2 cytokines could cause allergic asthma symptoms in a T cell-independent manner. In addition to their role in allergy, ILC2 cells also contribute to BHR in response to respiratory viruses[34,35]. The role of ILC2 cells in viral infections helps to explain the exacerbation of asthma symptoms in some patients following viral exposure. However, the relative contributions of ILC2 cells versus that of TH2 cells in asthma remained inconclusive. ILC2 cells are shown to produce the TGF-β-like molecule amphiregulin, which contributes to airway remodelling by inducing epithelial repair processes (Figure 1)[36,37].

This sub form of the TH2hi endotype of asthma often seems to have associated chronic rhinosinusitis and nasal polyps and does not respond favourably to steroids. Some of these patients also seem to have colonization of the nasal sinuses and airways with filamentous fungi that might represent a chronic trigger for innate immune system activation[38]. The Cardinal feature of this subset is the production of IL-5 and IL-13, which is not effectively suppressed by steroids in ILC2 cells as it does in CD4+T cells. The ILC2 cells are stimulated by chronic epithelial activation, including by environmental pollutants, irritants, chronic airway mycosis or repetitive viral infections driving the expression of epithelial cytokines IL-25, IL-33 and TSLP. TSLP can induce this state of steroid refractoriness in ILC2 cells and if ILC2 cells are driving disease in this subset of patients. The predominant role of ILCs and their steroid refractoriness in a subset of people with severe, nonatopic asthma with a high eosinophil count in the blood and a TH2 signature is explained by the above mechanisms. This would also explain why they respond well to the blockade of the IL-4 receptor or IL-5[36].

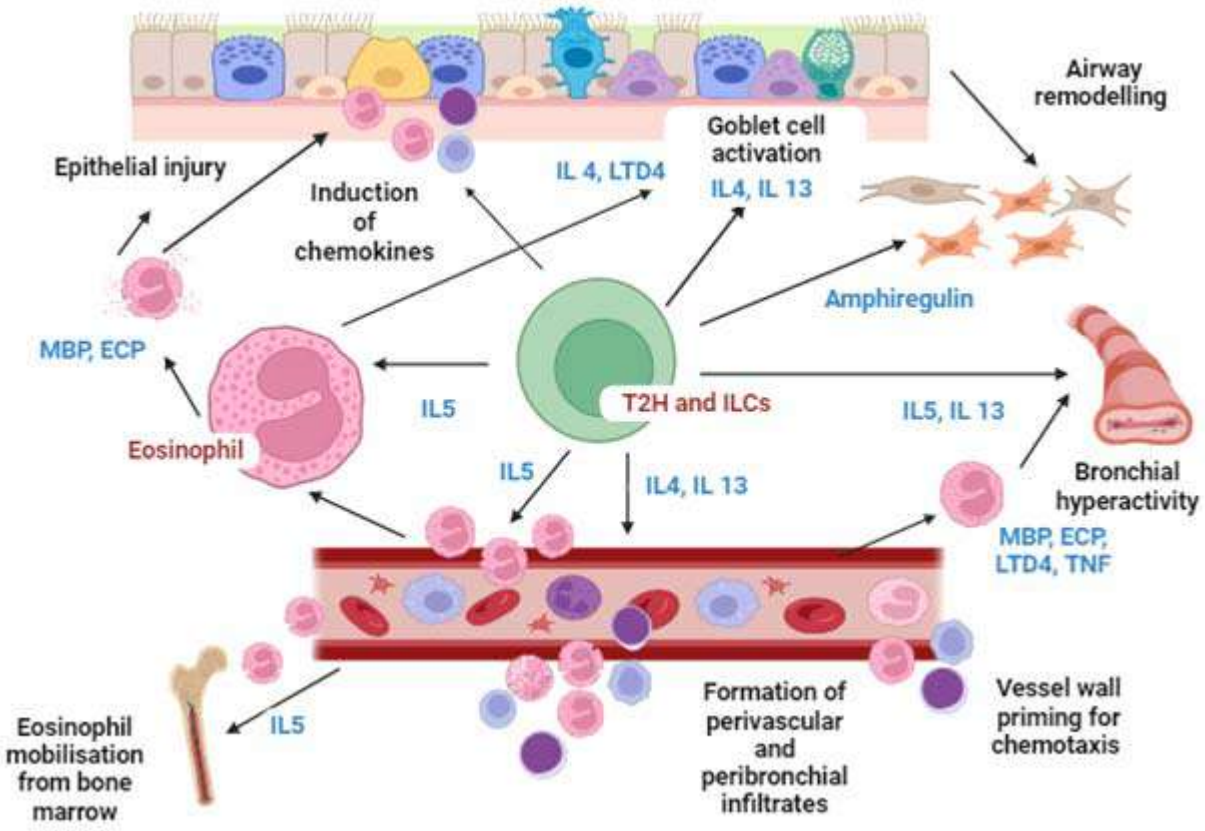

Figure 1. ***Summary of functions of TH2 cells and ILC2 cells in asthma****. TH2 cells and ILC2 cells share many features, such as the production of TH2 cytokines and the expression of the chemokine receptors. Through the production of IL-5, they control eosinophil development in the bone marrow. They cause goblet cell metaplasia and bronchial hyperreactivity and prime the vessel wall for eosinophil exit via IL-13. TH2 cells make more IL-4.* ***ECP****, eosinophil cationic protein;* ***MBP****, major basic protein;* ***LTD4****, leukotriene D4;* ***TNF****, tumor necrosis factor*

Role of TH9 cells in eosinophilic asthma

IL-9 was initially considered a TH2-specific cytokine induced by IL-2, IL-4 and TGF-β[39]. TH9 cells are now identified as a distinct helper T cell subset, and studies have shown that additional stimuli such as TSLP also contribute to the differentiation of TH9 cells[40]. IL-9 acts as a mast cell growth factor that promotes IL-4-driven antibody production by B cells, and they can also induce goblet cell metaplasia[41]. IL-9 has high expression levels in the lungs of patients with asthma[42]. In a chronic asthma model, antibodies to IL-9 suppressed the development of airway remodelling by reducing mast cell numbers[41]. Although T cells were initially considered the main source of IL-9, some studies have shown that ILC2 cells produce greater amounts of IL-9 than T cells. Furthermore, IL-9 derived from ILC2 cells has been shown to be an autocrine amplifier of ILC2 cell function by promoting their survival[42,43]. Trials have been initiated to target IL-9 in patients with asthma (MEDI-528), but they have produced disappointing clinical results[44].

Neutrophilic asthma

Role of TH17 in neutrophilic asthma

Although asthma is classically associated with TH2 signals and eosinophilia, some asthma patients show neutrophil-predominance. Especially, patients with late-onset and more severe asthma seem to have neutrophilic predominant inflammation with less reversible airway obstruction with a mixed TH1 and TH17 cytokine profile[45-47]. This severe form of asthma is also characterised by increased airway remodelling. In some experimental asthma models, IL-17A contributes to remodelling by triggering fibroblast proliferation and by opposing the anti-inflammatory role of regulatory T cells (Treg cells)[45,48]. In mice and humans, IL-17 can also cause direct contraction of bronchial smooth muscle cells, thus causing BHR directly[49]. The cytokine production by TH17 cells is resistant to inhibition by steroids, which explains why neutrophil-rich inflammation driven by TH17 cells pathologically correlates with steroid-refractory asthma. However, a clinical trial with an antibody against the human receptor for IL-17 (brodalumab), which blocks the activity of IL-17A, IL-17F and IL-25, has shown minimal effects on outcome measures of asthma in mild to moderate disease[50]. It is possible that the subset of patients, especially those with large numbers of sputum neutrophils or with a high degree of lung function reversibility, would respond more favourably[45]. There is also a complex interaction between TH17 cell-driven asthma and tumour necrosis factor (TNF). Pulmonary and systemic levels of TNF are increased in patients with severe steroid-resistant neutrophilic asthma despite some studies have not confirmed this[45,51]. In clinical trials, the results of TNF blockade in asthma have also been variable[52]. Therefore, it is still unclear if TNF blockade in IL-17-rich neutrophilic asthma would improve steroid responsiveness.

Role of regulatory T cells in asthma

For many years, it was believed that inflammatory responses in asthma develop because of the deficiency in natural or induced Treg cells. Animal studies have shown that Treg cells suppress asthma features through IL-10 and TGF-β, which suppress pulmonary dendritic cell activation and through direct interactions with endothelial cells, preventing angiogenesis[53,54]. As per preclinical data, another possible mechanism involves IL-35 production by Treg cells that can potentially suppress IL-17-induced BHR[55]. The exact role of Treg cells in patients with allergic diseases has been much debated. In severe asthmatics, the number of Treg cells present in the blood and sputum is lower, and their suppressive activities are impaired compared with cells from healthy subjects[56].

This impaired Treg cell function in allergic patients seems to affect the regulation of TH2 responses. In the blood of house dust mite (HDM)-sensitized children, a population of Treg cells could suppress the production of TH1 cytokines but not that of TH2 cytokines by peripheral blood mononuclear cells. This might explain that Treg cells in allergic patients might promote allergen-specific TH2 responses instead of controlling them. These Treg cells express the inhibitory molecule, T-cell immunoglobulin immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT) receptor and produce fibrinogen-like protein 2, which selectively spares TH2 responses while efficiently suppressing TH1 and TH17 responses[57]. TIGIT is potentially a therapeutic target in this context.

Overlap syndromes in asthma

The current evidence suggests that the consideration of eosinophilic asthma as an exclusive TH2 disorder and neutrophilic asthma as an exclusive TH17 disorder is an oversimplification and is seen only at the extremes of a continuous spectrum. In many cases, there is considerable overlap in the types of cytokines found in an asthma endotype in relation to the severity of asthma. Some studies have further shown immunophenotype switching from a predominant TH2 response to TH1 and/or TH17 response(s)[58]. Interestingly, some asthma features are induced by CD4+T cells that produce both TH17 cytokines and TH2 cytokines, adding to the complexity[59].

It is also important to consider the impact of the TH1 cell-derived cytokine IFN-γ in eosinophilic and neutrophilic asthma. Mice have shown BHR in which IFN-γ acts together with IL-13 to cause smooth muscle contraction and activation of cells of the innate immune system. IFN-γ also seems to promote the chemotaxis of TH2 cells in the lungs[60-62]. The airways of asthmatics contain increased numbers of IFNγ-producing CD4+ T cells, and there is a rise in the serum levels of IFNγ during acute exacerbations of asthma[63,64]. This would explain the underlying role of IFNγ in viral-induced asthma exacerbations. However, no clinical trials have assessed the therapeutic effect of IFN-γ blockade.

Role of other immune elements in asthma

Epithelial cell-DC interactions in response to allergens

Whatever the endotype of asthma, the various T cells or ILCs that control airway inflammation must be activated and interact with each other. For T cell responses, this involves the activation of antigen-presenting dendritic cells that recognize the allergen and present it to T cells in the lymph nodes, draining the lungs. Previous studies have shown that dendritic cells are sufficient to induce TH2 and TH17 adaptive immunity against inhaled allergens in mice that have not encountered the allergens previously. Different subtypes of DCs in the lungs are broadly categorised as conventional DCs (cDCs) and plasmacytoid DCs (pDCs). It has been found that cDCs are necessary and sufficient to induce allergic sensitization, whereas some cDCs also induce tolerance to inhaled allergens. pDCs also induce tolerance to inhaled antigens[65-68].

It has also become clear that airway epithelial cells (ECs) are crucial in controlling DC activation[69]. Many allergens, such as *A. fumigatus* spores, cockroaches or house dust mites, have protease activity. Proteases (such as papain or Der p 1) act on ECs to decrease barrier integrity by cleaving tight junction proteins and induce an innate cytokine response via stimulation of protease-activated receptors. In this way, they stimulate airway epithelial cells to produce IL-33 and thymic stromal lymphopoietin, which activate dendritic cells, ILC2 cells and basophils[70]. Cat dander and house dust mites contain allergens (Fel d 1 and Der p 1) that directly stimulate Toll-like receptor 4 on epithelial cells to produce IL-1α, IL25, IL-33, TSLP and the cytokine, granulocyte-macrophage colony-stimulating factor[71-73].

Many of the human genome-wide association studies of asthma have found single-nucleotide polymorphisms in genes encoding molecules that control epithelial barrier function (for example, filaggrin) and control the production or responsiveness to epithelial cytokines, such as thymic stromal lymphopoietin, which further indicates a crucial role for ECs in asthma. Also, many of the environmental risk factors for asthma, such as cigarette smoking, viral infections and air pollution, seem to converge on the epithelial cell-DC interaction[69]. It has become increasingly clear that dendritic cells and ECs are important in sensitizing allergens and causing ongoing asthma. There is an increase in the numbers of activated DCs in the airways of people with asthma and in mice with ongoing inflammation, and these form clusters with activated T cells around the airways and blood vessels in the lung[74,75]. In ongoing disease, epithelial cells continue to feed airway inflammation by activating incoming monocytes to adopt an immunogenic phenotype and by producing chemokines and cytokines that activate eosinophils, neutrophils and other cells of the innate immune system. ECs that undergo repeated cycles of injury and repair also contribute to the process of airway wall remodelling via the release of repair cytokines[69]. In trials, AMG 157 is a human antibody to TSLP that has been shown to block the late asthmatic response and bronchoconstriction in response to allergen challenges in humans and reduces eosinophil counts[76].

Effects of IgE on mast cells, basophils and DCs

IgE has the lowest concentration of all antibodies, and IgE mainly has a role in allergic disease, in which it has the potential to activate mast cells and basophils via the high-affinity IgE receptor FcεRI. The expression of FcεRI is highly influenced by serum concentrations of IgE and also by the TH2 cytokine IL-4. The presence of antigen-specific IgE in the serum of patients with asthma leads to the sensitization of mast cells and basophils attached to high-affinity IgE receptors, which have an important role in the disease. Mast cells infiltrate the bronchial smooth muscle layer and contribute to BHR, possibly driven by the mast cell growth factor IL-9 and the release of leukotrienes[77]. In the TH2hi endotype of asthma, increased numbers of mast cells have also been found between airway ECs. Increased numbers of basophils have been found in the blood and tissues of patients with asthma and mice exposed to house dust mites. Basophils are an important source of IL-4 that leads to TH2-type sensitization by acting together with DCs[78,79]. Basophils could also have an important role as memory cells to allergens by producing lipid mediators and cytokines that prime the vessel wall for extravasation and stimulate CD4+ effector cells, and they could also be involved in tissue remodelling[80]. Basophils are armed with the high-affinity IgE receptor and, just like mast cells, could react immediately when there is re-exposure to the relevant allergen.

The drug omalizumab is a humanized monoclonal antibody that binds to the constant domain of IgE, inhibiting its interaction with the high-affinity receptor FcεRI. It has proven efficacy in a subset of patients with allergic asthma. The effect of triggering FcεRI on DCs has been studied in vivo only recently. DCs in mice carrying the FcεRI receptor are at least 50 times more potent in presenting antigens to CD4+ T cells when antigen-specific IgE is present[81]. Moreover, the presence of IgE on DCs prime naive T cells for TH2 differentiation and recall responses to antigens. It can also lead to the production of IL-10 and the tryptophan catabolizing enzyme indoleamine deoxygenase, which suggests that FcεRIα expression on DCs might also contribute to the switching off of inflammation[82].

Susceptibility to respiratory viral infection in asthma

In most patients with asthma, exacerbations are caused by relatively mild respiratory viruses, such as human rhinovirus, respiratory syncytial virus, adenovirus, or influenza virus. In some asthma endotypes, virus-induced exacerbations are a major problem despite adequate disease control. The increased susceptibility to viruses could be caused by a primary defect in innate antiviral immunity in some asthmatics, related to epithelial fragility and barrier dysfunction, or due to defects in the production of toll-like receptor 7 or interferons[83].

In the lung, antiviral immunity relies heavily on the production of type I interferons (IFN-α and IFN-β) and type III interferons (IFN-λ, IL-28A, IL-28B and IL-29)[84]. It has been unclear whether this also causes an increased viral load in the lower respiratory tract and whether impaired interferon responses explain susceptibility to viruses. An alternative explanation for the enhanced susceptibility to viral infection is that allergic sensitization or the presence of TH2 cell-driven eosinophilic airway inflammation suppressing antiviral immunity as a secondary effect[85-87]. The interference with antiviral immunity by type 2 immune responses could be an old adaptation response. Alternative activation of macrophages via IL-13 caused upregulation of the chitinase-like protein Ym1, which suppresses antiviral immunity[88]. Chitinases and chitinase-like proteins are strongly upregulated in mouse and human asthma and could be functionally linked to the diminished antiviral state of people with asthma or to cause more neutrophil-rich asthma[89]. Based on this evidence, trials using inhaled interferons to treat viral exacerbations of asthma have been initiated[90]. It is also possible to target the function of chitinase-like proteins in future trials.

Conclusions and future prospects

Asthma is a heterogeneous disease with many endotypes. Various aspects of innate or adaptive immunity to allergens, environmental triggers and viruses are involved in the sensitization to allergens, symptoms of asthma, exacerbations, and response to treatment. There is extensive crosstalk between the airway epithelium and cells of the immune system in the initiation and progression of the disease. No single therapy will be effective for all patients. Still, some medicines might be very effective in selected patients who are carefully identified on the basis of underlying immunological processes or the endotype.

Being a resource-limited setting, most of the advanced treatment options, including monoclonal therapy, are not available in Sri Lanka. However, categorizing patients into different endotypes based on their clinical profile and underlying pathophysiology may still facilitate overall asthma care. Optimization of non-pharmacological interventions would be an effective measure for all patients and offering personalised care plans, at least for difficult asthma patients, would further enhance patient care. In future, if access to biosimilars of monoclonal antibodies used in asthma treatment becomes available in Sri Lanka, need for proper endotyping will be essential. Understanding the basic disease mechanisms is imperative for this approach, and it will facilitate clinical assessment and selection of relevant investigations based on the patient. It needs properly selected cohorts with a multidisciplinary approach addressing all background problems, such as asthma comorbidities. Proper diagnosis, documentation of data and maintenance of registries will form the platform for such interventions. We suggest that streamlining, standardisation and networking of asthma care centers in Sri Lanka is an important aspect that has to be focused upon in future.

Conflicts of interests

The authors declare no conflicts of interests.

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Research paper

A descriptive study on the aetiological factors associated with bronchiectasis in patients receiving treatment from respiratory disease treatment unit of Teaching Hospital, Kandy

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Abstract

Background: Bronchiectasis, has gained much needed attention recently due to increasing number of patients identified, mainly due to increased use of high resolution CT scans. Bronchiectasis is a heterogenous condition with many factors implicated as aetiology. The British Thoracic Society guidelines recommend investigating for the aetiology in all patients. However, despite extensive investigations a cause is not identified in a considerable proportion of patients even in the best of settings. A study on aetiology of bronchiectasis in adults has not been conducted in Sri Lanka previously.

Methodology: The study was carried out as a cross sectional descriptive study in patients who are newly diagnosed with bronchiectasis and in those who have already been diagnosed at the Respiratory Clinic of Unit 2 at Teaching Hospital, Kandy and the Respiratory Disease Treatment Unit at Bogambara. Data collection and evaluation took place over a period of 2 months.

Results and Conclusion: In this study, an aetiological factor was identified in 45/89 patients (50.56%). The commonest aetiological factor was post infective (non tuberculous) which was found in 11 patients (12.36%). Tuberculosis accounted for bronchiectasis in 9 patients (10.11%). When considered together a post infective aetiology was identified in 20/89 patients (22.47%). COPD, cilliary dysfunction and ABPA accounted for the occurrence of bronchiectasis in 7 patients each. Other uncommon aetiological factors identified were rheumatoid arthritis (n=3, 3.37%) and foreign body impaction (n=1, 1.12%). Despite active screening in clinically suspected patients no patients were identified with immunodeficiency, cystic fibrosis or non tuberculous mycobacterial infection. Many patients had evidence of factors that could have contributed to bronchiectasis such as asthma (38.2%), GORD (24.7%), betel chewing and poor oral hygiene (41.6%) and chronic rhinosinusitis (14.6%).

Introduction

Previously known as a rare entity, bronchiectasis has recently received much needed attention. Although previous studies indicated significant prevalence in relatively underprivileged communities with limited access to health care[1], the availability of High Resolution Computed Tomography (HRCT) of the chest has revealed a wealth of information on previously unsuspected, higher prevalence even among communities with good living standards and access to health care[2].

Bronchiectasis, which is a pathological term, describes permanent dilatation of airways[3]. The resultant stagnation of respiratory secretions leads to recurrent infections and a state of chronic infection. Indeed a pathological process known as Cole's vicious cycle hypothesis, best describes this process[3]. The initial insult to the airway maybe exogenous such as an infection or endogenous such as an autoimmune process. Following the initial insult, bronchial inflammation leads to damage to the respiratory tract predisposing to further infection and the cycle would go on, resulting in a progressive lung disease.

Therefore, bronchiectasis is the end result of many pathological processes rather than a disease entity in itself. Cystic fibrosis is one of the main causes of bronchiectasis in the west and due to the complexity of the disease and the different pathological and management aspects involved, it has always been

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discussed as a separate entity. Other causes include past infections such as tuberculosis and severe pneumonia due to a variety of other pathogens, non tuberculous mycobacterial (NTM) infections, allergic bronchopulmonary aspergillosis (ABPA), connective tissue diseases, inflammatory bowel disease, disorders of cilliary function (such as Kartagener's syndrome) and causes of immune dysfunction which may be congenital or acquired. Patients with chronic obstructive pulmonary disease (COPD)[4-6] and asthma[7,8] have been identified to have bronchiectasis on imaging. Therefore the patients are a vastly diverse group.

Identification of causes such as ABPA and NTM infection is also important as these causes are potentially treatable. Globally there is growing interest in bronchiectasis due to the lack of randomized controlled trials which are necessary to formulate guidelines which are evidence based. Currently a European registry is being formulated to bridge some of these gaps[9]. The large studies available to date, which had been done to evaluate the aetiology of bronchiectasis are based in the UK and Europe and in these studies a widely varying percentage (10-53%) of patients were not identified with a possible aetiology despite extensive investigations. A study conducted in 2006 by Shoemark, et al. at Royal Brompton Hospital, which is one of the main respiratory referral canters in the UK, demonstrated that an underlying cause was identifiable in 122/165 patients (74%). These findings influenced the management of 61(37%) patients. The commonest identifiable factor was post-infection (52 patients), but 43 patients had no identifiable cause despite extensive investigation[10]. A study conducted in seven centers in Europe by Lonni, et al. between 2009 and 2013 using data regarding 1258 patients, revealed the following findings[11]. In this study, 60% had an identifiable aetiology while in 40% a cause was not identified despite extensive investigations. The commonest identifiable cause was post-infection, which stood at a level of 20%. The findings influenced the management of 13% of patients. Based on the findings, the authors strongly recommended testing for an aetiology in all patients with bronchiectasis, in line with the BTS recommendations[12]. An older study conducted by Pasteur, et al. between 1995 and 1997 at Cambridge, UK, revealed similar results. Out of the 150 patients, a cause was identified in only 47% of patients and the most frequent identified cause was post-infective (29%)[13].

A study conducted on a large cohort of patients in Taiwan revealed that 24% developed bronchiectasis post-pneumonia and 12% developed post-tuberculosis[14]. COPD was an important aetiological factor, similar to European studies. A systematic literature review on aetiology of bronchiectasis which was conducted in 2016 revealed that significant geographic variability exists[15].

In keeping with the global interest in broadening knowledge and obtaining evidence based management guidelines for bronchiectasis, it is vital to obtain information on Sri Lankan patients to ensure generalizability of these guidelines.

Methodology

The study was carried out as a cross sectional descriptive study in patients who are newly diagnosed with bronchiectasis and in those who have already been diagnosed at the respiratory clinic of Unit 2 at Teaching Hospital, Kandy and the Respiratory Disease Treatment Unit at Bogambara. Data collection and evaluation took place over a period of 2 months. The patients were selected through non probability convenience sampling according to the inclusion and exclusion criteria. Patients with radiologically confirmed bronchiectasis were included in the study. Patients with traction bronchial dilatation secondary to interstitial lung disease and those who did not give consent were excluded from the study.

Data collection

Information necessary to establish the aetiology of bronchiectasis was collected through a data collection form which included details of the patients' symptoms, past medical history, a thorough examination, and details of investigations done including blood investigations, chest xray, HRCT of chest and bronchoscopy. Identification of post infectious aetiology was done through the patients history and evaluation of available medical records. However it is acknowledged that this is a difficult task due to recall bias and also due to the fact that recurrent infections, which are sometimes severe may be the presenting feature of bronchiectasis. Identification of aetiologies such as connective tissue disease and inflammatory bowel disease was done through history and blood tests such as rheumatoid factor and ANA where clinically indicated. Testing for ABPA with serum IgE levels and skin prick testing was offered to those with a suggestive history and HRCT findings. Where indicated, the patients underwent bronchoscopy to identify proximal mechanical obstruction and also to obtain samples for microbiological evaluation, particularly non tuberculous mycobacterial infection. All patients were screened for HIV. Expensive tests for identification of other immune deficiencies and genetic testing for cystic fibrosis was only offered to those who have a

history suggestive of these disorders. This is in contrast to the BTS recommendation to routinely offer testing for immunoglobulin levels for all patients[12]. This decision was taken owing to the lack of resources in this setting.

Patients with a history suggestive of cilliary dysfunction and patients with disease onset at a very young age underwent saccharine test. More advanced and sensitive tests for cilliary dysfunction were not offered due to the unavailability of these investigations.

The evaluation was performed by a qualified respiratory team. The findings were tabulated using Microsoft Excel and subsequently analysed using SPSS.

Ethical considerations

All patients were informed regarding the study and consent was obtained prior to collecting information. All information gathered was kept under the care of the investigator. Patient confidentiality was maintained at all times. Ethical clearance was obtained from the Ethical Committee of Teaching Hospital, Kandy.

Results

A total of 89 patients were recruited for the study, out of which 62 (69.66%) were females and 27 were males (Figure 1). The age range was 11- 84 and the mean age was 53 years.

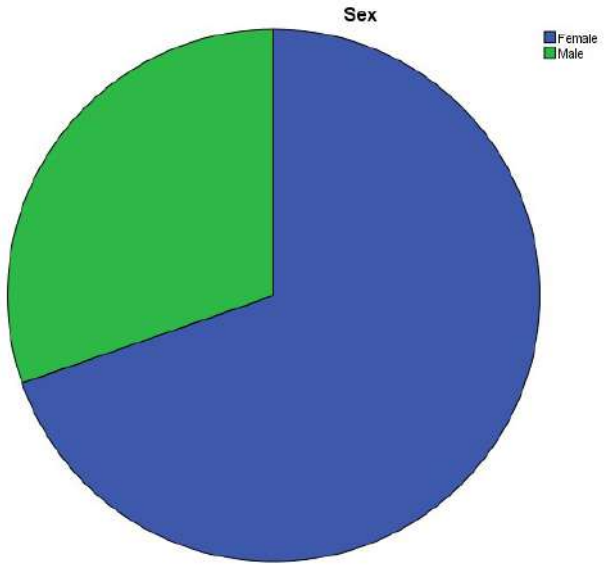

Figure 1. *Pie chart indicating the sex distribution of the cohort of patients with bronchiectasis.*

Malnutrition is a known feature in bronchiectasis and monitoring of weight is a mandatory component of management. BMI was assessed in all the patients of this cohort and it was found that 41(46%) had a BMI less than 18.5 which is the cut off value to define underweight individuals in Sri Lanka[16]. 41 (46%) had a BMI between 18.5 and 24.9, which is considered normal. Only 7 (7.86%) patients were overweight with a BMI between 25 and 29.9, and none of the patients were obese. These findings are displayed in Figure 2.

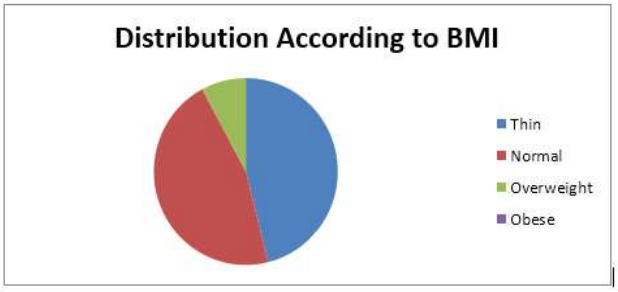

Figure 2. *Distribution of the cohort of patients according to BMI.*

In terms of specific tests leading up to an aetiological diagnosis, all patients underwent a thorough evaluation to exclude active tuberculosis with sputum studies for acid fast bacilli, sputum for tuberculosis culture, and Mantoux test. The entire group was negative for active tuberculosis but on history some had evidence of past tuberculosis which had likely contributed to the diagnosis.

Targeted testing for allergic bronchopulmonary aspergillosis (ABPA) in the form of testing for serum IgE and skin prick test for *Aspergillus* was only offered to those who had suggestive features on HRCT. Due to limitations in resources testing for immunoglobulin and complement levels was done only for those with extensive disease and those with disease onset in their childhood. On this basis 11 patients were offered serum immunoglobulin levels, complement levels and neutrophil function tests, and all indicated normal results. All patients underwent screening for HIV which was negative in all.

Based on the history, patients were screened on the possibility of defects in cilliary function. Kartagener's syndrome was diagnosed on the presence of the classic triad of bronchiectasis, chronic sinusitis and dextrocardia. Other patients with bronchiectasis, who had bilateral involvement with a family history, history of neonatal respiratory distress, chronic sinusitis or a history of subfertility were screened with sachcharine

tests. Out of the 6 patients who were screened with sachcharine test, all were negative. However, if the history was strongly suggestive of cilliary dysfunction, the aetiological diagnosis was taken as possible cilliary dysfunction despite the negative sachcharine test due to the poor sensitivity of the test and the lack of other facilities to perform confirmatory tests.

Patients with extensive disease and disease onset in childhood also underwent testing for CFTR gene mutation to screen for cystic fibrosis. Affordability also had to be taken into consideration as this test was not available in the government sector. All 5 patients who were tested were negative. None of the patients in the cohort gave a clinical history suggestive of cystic fibrosis with malabsorption or pancreatic dysfunction.

Taking all the information gathered into consideration a possible aetiological diagnosis was assigned in all possible cases. After detailed consideration, an aetiological factor was found in 45 (50.56%) patients. An aetiology was not found in 44 (49.44%) patients. Out of these 44 patients, 4 patients had isolated middle lobe and lingular involvement. However, bronchoalveolar lavage for non tuberculous mycobacterial cultures were negative in all 4 patients. Therefore Lady Windermere Syndrome[18] could not be diagnosed and the aetiology was taken as idiopathic. 9 patients had post tuberculous bronchiectasis while 11 others had post infective bronchiectasis due to infections other than tuberculosis. Of these 11 individuals, 9 had evidence of severe pneumonia preceding symptoms of bronchiectasis, 1 had a history of pertussis and 1 had history of invasive aspergillosis. 7 patients had COPD, 1 had a foreign body and 3 had rheumatoid arthritis. 7 patients were diagnosed with allergic bronchopulmonary aspergillosis (ABPA). 4 patients met the criteria to diagnose Kartagenner syndrome. 3 others had evidence of cilliary dysfunction such as subfertility, family history, early symptom onset, but could not be confirmed as cilliary dysfunction owing to lack of facilities to do so. However due to the volume of clinical evidence they were still considered as patients with bronchiectasis due to cilliary dysfunction. These findings are tabulated in Table 1.

It should be noted that there were no patients with immunedeficiencies and no patients with cystic fibrosis.

Some patients had evidence of asthma, gastro oesophageal reflux disease, betel chewing with poor oral hygiene and chronic rhinosinusitis which are factors known to contribute to, cause or worsen bronchiectasis. However, none of the patients had severe asthma and therefore it was difficult to attribute the occurrence of bronchiectasis to asthma. Similarly, the severity of GORD and its significance was difficult to assess due to the unavailability of pH monitoring. Owing to the difficulty of demonstrating a causal relationship between these factors and bronchiectasis they were taken as possible contributory factors. The occurrence of these factors are tabulated in Table 2.

Table 1. Aetiology of bronchiectasis

Diagnosis	*Number*	*Remarks*
Idiopathic	44 (49.44%)	4 - middle lobe and lingular involvement
Post-tuberculous	9 (10.11%)	
Post-infection (other than TB)	11 (12.36%)	9 - Severe pneumonia
		1 - Pertussis
		1 - invasive aspergillosis
COPD	7 (7.86%)	
Cilliary dysfunction	7 (7.86%)	4 - Kartagenner syndrome
		3 - Clinical evidence of cilliary dysfunction
ABPA	7 (7.86%)	
Foreign body	1 (1.12%)	
Rheumatoid arthritis	3 (3.37%)	

Table 2. Presence of factors which may contribute to occurrence or worsening of bronchiectasis

Contributory Factor	*Number*
Asthma	34 (38.2%)
GORD	22 (24.7%)
Betel chewing	37 (41.6%)
Chronic rhinosinusitis	13 (14.6%)

Some patients with an identified aetiological factor had concurrent factors which are known to cause bronchiectasis. However, these factors were not given as the aetiological factor due to either the inability to demonstrate causal relationship or inconsistency with the disease onset. However they would have contributed to progression of the disease. These factors are demonstrated in Table 3 and for the purpose of this study will be named as possible second aetiological factor.

Table 3. Possible second aetiological factor

Possible second aetiological factor	*Number*
Past infection	9
COPD	2
Tuberculosis	4
ABPA	1
Radiation	2

Discussion

Bronchiectasis is a condition that is still being managed without robust evidence. However, many efforts are currently underway to bridge these gaps. The European Bronchiectasis Registry (EMBARC)[9] is one of the many efforts taken in this regard. Bronchiectasis is the end result of many insults to the lung, hence bronchiectasis is a heterogeneous condition. However, whether knowledge regarding the aetiology of the condition alters the management is a topic that has gained much attention. There had been many studies conducted to find common aetiological factors with regard to bronchiectasis in different settings. Most of these studies have been conducted in the west, in resource rich settings[10,11,13]. In these studies, as discussed previously, there were some similarities as well as some disparities. The identification of aetiology influenced the management in 37% of patients in the study done by Shoemark whereas it only influenced the management in 13% of patients in the study done by Lonni. These findings are difficult to generalize to the Sri Lankan population owing to the different characteristics, different genetic background and differences in prevalence of infections such as tuberculosis which are known causes of bronchiectasis. A study conducted in Taiwan, which is expected to have more similarities with the Sri Lankan population than European populations revealed that 24% of patients with bronchiectasis, developed so following pneumonia and 12% developed post tuberculosis[14].

In this study, 50.56% of patients were identified to have an aetiological diagnosis, leaving 49.44% to be labeled as idiopathic bronchiectasis. This is a much higher value than the two most recent European studies and also the Taiwanese study. However, as with all the studies reviewed, the commonest identified aetiology was post infective (including TB) with 22.47% of patients.

Remarkably, this study did not reveal a single patient with immunodeficiencies, inflammatory bowel disease, cystic fibrosis or non tuberculous mycobacterial infections. Cystic fibrosis is a rarely reported condition in Sri Lanka with only a few case reports noted[19]. This factor is further confirmed in this study, where none of the patients revealed any specific symptoms of cystic fibrosis, but those who had fairly extensive bronchiectasis from a very young age were screened, but all were negative.

Similarly, all patients in the study underwent sputum cultures for mycobacterial infection and all the patients with middle lobe and lingular involvement, and all the patients with CT evidence of progressive disease underwent bronchoscopy and BAL for mycobacterial culture, and all were negative for active tuberculosis or non tuberculous mycobacterial infection.

In contrast to the BTS guidelines[12], all patients were not screened with investigations for ABPA, and a complete panel of immunoglobulin levels. However, all patients with young onset extensive disease were offered testing for immunological function such as immunoglobulin levels, complement levels and neutrophil function tests. But the tests results were negative in all those who were tested. ABPA was tested for in those who had suggestive features on CT and for those who gave classic clinical features. 7 patients in this study were identified with ABPA.

This study also revealed an unexpectedly high number of patients with cilliary dysfunction (7 patients). This maybe due to the fact that the study was conducted in a referral center for a fairly large region, and patients are more likely to be followed up in a tertiary care center with this particular diagnosis.

Many patients had factors such as asthma (38.2%), GORD (24.7%), betel chewing with poor oral hygiene (41.6%) and chronic rhinosinusitis (14.6%) which were not given as the aetiological diagnosis due to the paucity of confirmatory evidence. In patients who had asthma, other than the patients with ABPA, none had features of severe asthma and had not been on long term oral corticosteroids which made the attribution of bronchiectasis to asthma, a difficult task. Betel chewing and chronic aspiration with poor oral hygiene maybe a leading cause of bronchiectasis in the Sri Lankan population but more robust evidence in needed to prove this fact.

Conclusion

In this study, an aetiological factor was identified in 45/89 patients, which amounts to 50.56%. The commonest aetiological factor was post infective (non tuberculous) which was found in 11 patients (12.36%). Tuberculosis accounted for bronchiectasis in 9 patients (10.11%). When considered together a post infective aetiology was identified in 20/89 patients (22.47%). COPD, cilliary dysfunction and ABPA accounted for the occurrence of bronchiectasis in 7 patients each. Other uncommon aetiological factors identified were rheumatoid arthritis (n=3, 3.37%) and foreign body impaction (n=1, 1.12%). Despite active screening in clinically suspected patients no patients were identified with immunodeficiency, cystic fibrosis or non tuberculous mycobacterial infection. Despite the high percentage of patients for whom an aetiological diagnosis could not be found, many patients had evidence of factors that could have contributed to bronchiectasis such as asthma (38.2%), GORD (24.7%), betel chewing and poor oral hygiene (41.6%) and chronic rhinosinusitis (14.6%). Betel chewing with poor oral hygiene and chronic aspiration maybe a leading cause of bronchiectasis in Sri Lanka which needs further confirmatory investigations.

Limitations

Currently there is no registry of patients with bronchiectasis in Sri Lanka. If such a registry was available, many more patients from different centers could have been recruited for the study, and a more diverse group of patients could have been included. A population based prevalence study has also not been conducted in Sri Lanka and would reveal very valuable information for this study.

The outcome of this study could have been improved if all patients were offered testing for immune function, and if facilities were available for pH monitoring to assess the severity of GORD and for confirmatory testing of cilliary dysfunction.

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Case report

Successful treatment of complex parapneumonic effusions with low dose intrapleural alteplase; experience in Sri Lanka

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Asian Journal of Lung Health, 2024, **1**, 28-31

Key words: empyema, alteplase, intrapleural fibrinolytics

Abstract

Introduction: Complicated pleural infections caused by bacterial infections or *Mycobacterium tuberculosis* contributes to a significant morbidity and mortality. Intercostal tube drainage of loculated pleural effusions is challenging and requires thoracoscopic debridement or decortication. Patients who are not surgical candidacy, intrapleural fibrinolytics (IPFT) in combination with DNase is recommended in guidelines. Here, we report a case series of administration of intrapleural alteplase alone with a successful outcome.

Case presentation: Case 1: A 29-year-old man with left sided tuberculous pleural effusion due to disseminated tuberculosis developed shock and became unsuitable for surgery. Intrapleural alteplase resulted in successful drainage of loculated pleural effusion with a good clinical recovery.

Case 2: A 66-year-old man with left sided complex parapneumonic effusion (PPE) had minimal drainage through the plural catheter. There was rapid drainage of effusion with lung expansion following intrapleural alteplase therapy.

Case 3: A 37-year-old man with left sided PPE had inadequate drainage following wide bore intercostal tube. He had remarkable drainage after administration of alteplase through the IC tube.

Conclusions: For critically ill patients with PPE, instillation of IPE is a lifesaving and an alternative treatment modality for surgical treatment. Intrapleural alteplase monotherapy is promising to achieve successful outcomes with minimal adverse events.

Introduction

Pleural infections affects more than 65,000 of patients per year with mortality rate are up to 20% and the proportion of surgical referrals is 50%[1]. Complicated parapneumonic effusions (PPE), require timely drainage either with needle aspiration or intercostal tube drainage along with appropriate antibiotic treatment. Decortication or thoracoscopic debridement is considered for patients in whom the drainage is not satisfactory or the lung expansion is inadequate. Patients who are not fit for surgical interventions, intrapleural enzyme therapy (IPE) is a lifesaving procedure.

In this case series we encapsulate three cases of parapneumonic effusions that were successfully managed with intrapleural alteplase, in two different tertiary care centres in Sri Lanka.

Case presentation

Case 1

A 29-year-old man admitted with left sided pleuritic chest pain and breathlessness for 2 days. He had loss of appetite, weight loss and fever for 2 months duration. Saturation was 96% with 3 L oxygen.

Initial chest radiograph (Figure 1a) showed left side large pleural effusion and ultrasound chest showed organized multi-septated encysted pleural effusion.

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Enhanced computed tomography (CT) chest and abdomen revealed complicated encysted pleural effusion with nodular septal thickening (Figure 1b), hepatosplenomegaly, mediastinal, axillary and para-aortic lymphadenopathy. His total white cell count (WCC) and C-reactive protein were 34,000 and 236 mg/L respectively. Needle thoracentesis yielded only 70 ml of pleural fluid which had low pH of 7.12, exudative and lymphocytic. The adenosine deaminase value gave 55 U/L and the lactate dehydrogenase (LDH) was 335 U/L. Pleural fluids and lymph node gene X pert for *Mycobacterium tuberculosis* was positive.

Alternative anti-tuberculous treatment consists of meropenem 1g 8 hourly, levofloxacin 750mg daily and linezolid 600mg 12 hourly were administered because of deranged liver function tests. Intercostal costal tube drainage (ICD) (24 Fr) had minimal output and the patient continued to have high fever and later developed septic shock. Patient was deemed unfit for surgical decortication. Intrapleural alteplase was commenced on the fourth day of admission. Alteplase 5mg dissolved in 20ml of sterile saline was injected under sterile conditions into the ICD with adequate pain relief. The drain kept clamped for 60 min before allowing free drainage. Six consecutive doses were injected 12 hours apart.

Over 3000 ml of fibrinopurulent fluid was drained without immediate complications. Marked clinical, radiological and biochemical improvement was observed and patient was discharged with standard anti TB treatment. On follow-up 8 weeks later, patient exhibited enormous clinical and radiological improvement (Figure 1d).

Case 2

A 66-year-old man admitted with fever and left sided pleuritic chest pain for 5 days duration. His chest radiograph was suggestive of encysted pleural fluid collection (Figure 2a) and CT chest confirmed loculated pleural effusion (Figure 2b). His WCC was 36000 and C-reactive protein was 384 mg/dL.

He was treated with intravenous ceftriaxone 2g daily in combination with clindamycin 600mg 8 hourly. Small-bore chest drain was inserted under ultrasound guidance. The pleural fluid analysis showed exudative neutrophilic effusion. The drainage was minimal and therefore intrapleural alteplase 5mg twice daily administered 2 days after insertion of pleural catheter. There was more than 1000 ml output without bleeding on first day. Therefore, another 2 consecutive days intrapleural alteplase was continued 10mg twice daily. The chest radiograph (Figure 2c) taken after completion of alteplase showed marked improvement and the Figure 2d is the chest X-ray after 3 weeks.

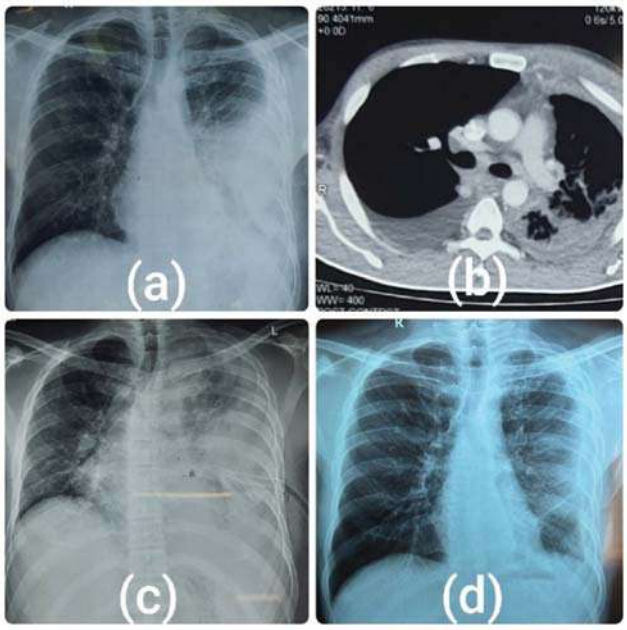

Figure 1. *On admission chest X ray left side encysted effusion (a), enhance CT shows effusion with septations and lung consolidation (b), following ICD chest X ray (c), after IPFT on follow up 8 weeks chest X ray (d).*

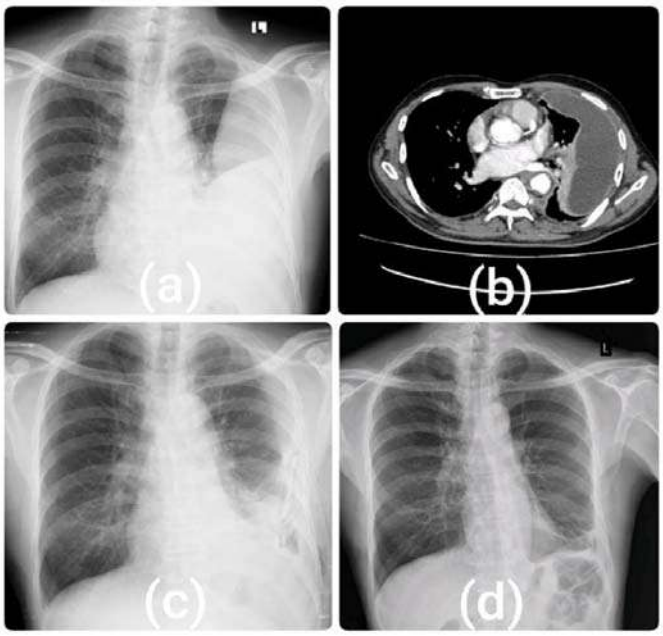

Figure 2. *On admission chest X ray left side encysted effusion (a), enhance CT shows effusion with septations and lung consolidation (b), following ICD chest X ray (c), after IPFT on follow up 3 weeks chest X ray (d).*

Case 3

A 37-year-old man had fever, left side chest pain and breathlessness for 1 week. He had WCC of 29450 and C-reactive protein of 284 mg/dL. The chest X-ray (Figure 3a) was suspicious left sided large effusion which was confirmed by ultrasound chest and computed tomography (Figure 3b). Intercostal tube was inserted immediately and he was commenced on intravenous ceftriaxone 2g daily and clindamycin 600mg 8 hourly. The tube drained approximately 100 ml of effusion, which was neutrophilic with lactate dehydrogenase of 3500 U/L. Three days later, intra-pleural alteplase therapy was commenced with a dose of 5mg twice daily in day 1 followed by 10mg twice daily for additional 2 days. The chest X-ray 2 weeks later noted marked improvement (Figure 3d).

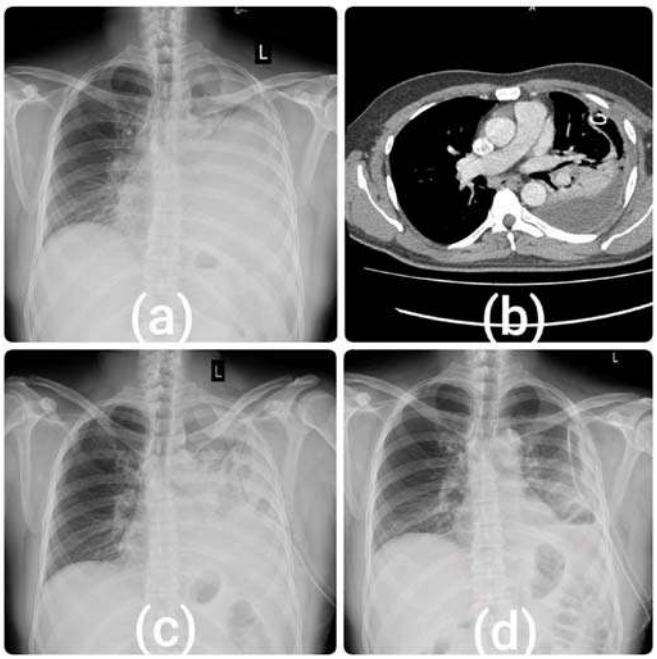

Figure 3. *On admission chest X ray left side large encysted effusion (a), enhance CT shows septations (b), following ICD chest X ray (c), after IPFT on follow up 2 weeks chest X ray (d).*

Discussion

Parapneumonic effusions (PPE) are pleural effusions that form in the pleural space adjacent to a bacterial pneumonia and around 40% of bacterial pneumonias will result in complex parapneumonic effusions[2]. Imbalance between fibrinolytic activity and PAI result in a profibrotic stage which will form loculations inside the pleural space[1,3]. Standard therapy consists of appropriate antibiotics and drainage of the infected pleural fluid by either needle aspiration or IC tube drainage. Those who failed to drain the effusion with satisfactory lung expansion need thoracic surgical interventions. Patients who have poor surgical candidacy, instillation of intrapleural enzymes such as urokinase, streptokinase, rhecombinant tissue plasminogen activator (alteplase) are widely used[4]. British Thoracic Society Guidelines recommendation based on MIST 2 trial is to combined use of alteplase with DNase. This combination therapy improve the fluid drainage in patients with pleural infection and reduce the frequency of surgical referral and the duration of the hospital stay[5]. However, in resource poor settings as in current Sri Lanka, high cost of DNase make it unavailable and single use of alteplase has been widely used[6].

Our patients didn't have any adverse reactions related to IPFT such as intra pleural bleeding or gastro intestinal bleeding. All of them had marked clinical and radiological response at the end of treatment. On follow up they had minimal pleural thickening and didn't further needed any surgical interventions.

Conclusions

For critically ill patients with PPE, instillation of IPE is a lifesaving and an alternative treatment modality for surgical intervention. Intrapleural alteplase is promising to achieve successful outcomes with minimal adverse events.

Abbreviations

CT – computed tomography
ICD – intercostal costal tube drainage
IPE – intrapleural enzyme therapy
IPFT – intrapleural fibrinolytics
LDH – lactate dehydrogenase
PPE – parapneumonic effusions
WCC – white cell count

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Case report

A case of pleural endometrisosis

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Asian Journal of Lung Health, 2024, **2**, 32-34

Abstract

Introduction: Endometriosis is presence of endometrium-like tissue outside the uterine cavity. The commonest extra abdominal site is thoracic cavity and endometrial deposits may present in lung parenchyma, pleura, or diaphragmatic surface. Right predominance is seen in pleural endometriosis. Catamenial pneumothorax and hemothorax seen in pleural disease and former is the commonest.

Case presentation: A 35-year-old woman presented with right sided chest pain and dyspnea recurring during menstruation. She found to have a hemothorax and thoracoscopy and biopsy confirmed endometriosis of the pleura. She started and responded well to progestogen therapy. Few years later, she presented with similar symptoms and found to have a secondary spontaneous pneumothorax. VATS reveled presence of endometrial deposits on diaphragm and pleura. Due to recurrence, she was treated with pleurodesis and post operative hormonal therapy.

Conclusion: Thoracic endometrial syndrome is a debilitating illness and high clinical suspicion needed for diagnosis. The management is multidisciplinary. In situations where recurrence and hormonal therapy failure occurs, definitive surgical elimination is mandatory.

Introduction

Endometriosis is a condition where the endometrium-like epithelium and/or stroma, which normally lines the uterine cavity, grow outside the uterus. It is a chronic inflammatory disease. Endometriosis is about 2%-10% prevalent in the female population and usually present in women of reproductive age. The exact pathophysiology of endometriosis is still not confirmed, but there are several theories to describe this clinical sequalae.

Though, the abdominopelvic cavity is the comment site for presentation of endometriosis, thoracic cavity is the second highest site. It can usually develop in the lung parenchyma, pleural surfaces, or thoracic surface of the diaphragm and clinical manifestation depends on the site of presentation. The most frequent presentation of thoracic endometriosis is pneumothorax which is 92% on the right side. Also, hemothorax, hemoptysis, pulmonary nodules and diaphragmatic deposits are some other presentations. This is termed as thoracic endometriosis syndrome (TES).

The purpose of this article is to discuss about a less common case of pleural endometriosis initially presented as a catamenial hemothorax and later complicated with a secondary spontaneous pneumothorax despite medical therapy.

Case presentation

The patient was a 35-year-old female, mother of one child, initially presented with a cyclical right sided dull, pleuritic type chest pain associated with shortness of breath for three months. The pain was characteristically occurring around the time of menstruation. The examination findings were suggestive of right sided pleural effusion. No other abnormal symptoms and signs were identified. The effusion was hemorrhagic and thoracoscopic findings included multiple adhesions with numerous discrete nodular lesions in pleural surfaces. The histology of pleural biopsy revealed stromal cells with glandular lining epithelial cells in favor of pleural endometriosis. She was initiated on medical therapy with intramuscular medroxyprogesterone acetate (DMPA) for which the disease responded satisfactorily for almost seven years.

Later, she presented again with similar symptoms and clinical evaluation revealed an apical pneumothorax with mild hemothorax. She has undergone video assisted thoracoscopic surgery (VATS) and found to have multiple perforations in the right hemidiaphragm with multiple pleural cysts and a small pleural effusion

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which is suggestive of recurrence. There she had undergone diaphragmatic plication and pleurodesis with diathermy. Post operative hormonal therapy was prescribed.

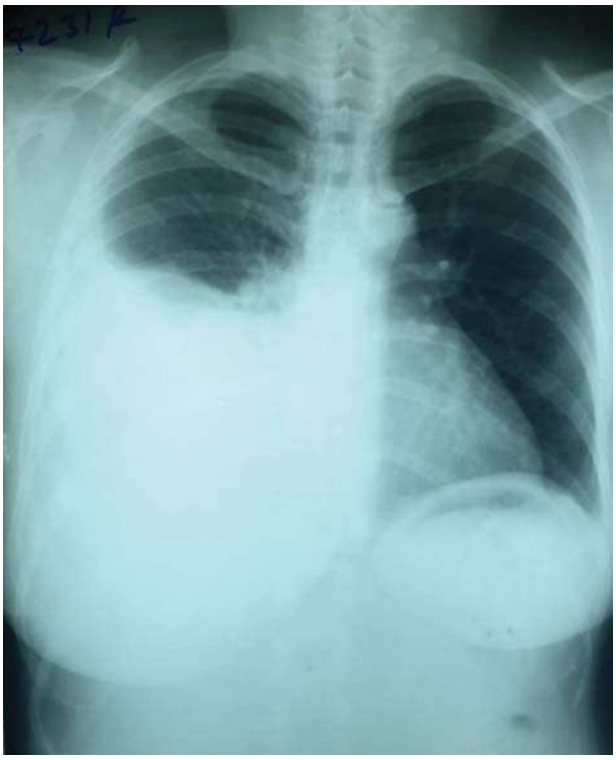

Figure 1. *Chest radiograph demonstrating initial presentation of right pleural effusion.*

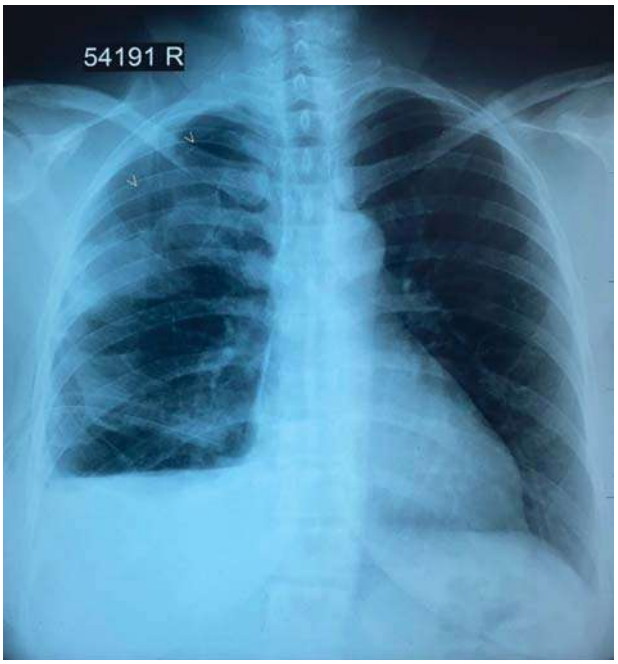

Figure 2. *Chest radiograph showing apical pneumothorax with recurrence of pleural effusion.*

Discussion

Though most women with endometriosis are asymptomatic and underdiagnosed, it can be debilitating in some. Rarely, extra-genital endometriosis occurs isolated, but majority has simultaneous lesions in the genital organs. Thoracic endometriosis is usually seen in 32-35-year age group and the commonest presentation is catamenial pneumothorax. Catamenial hemothorax is a less frequent. Both has right predominance. The recurring symptoms such as chest pain, dyspnea, cough, and hemoptysis occurring within 72 hours before or after menstruation in a woman of reproductive age, prompt the suspicion of catamenial origin.

Our patient presented with a typical history suggestive of thoracic endometriosis. But she had no symptoms of pelvic endometriosis which is a rare as most cases has concomitant pelvic endometriosis.

The process of diagnosing thoracic endometriosis is mostly clinical but can be supported by investigations. Chest radiograph and computed tomography of chest aid in identifying pleural effusions, pneumothoraxes, pneumomediastinum, pleural cysts, bullae or deposits of lung parenchyma and airways. Magnetic resonance imaging is preferable in identifying diaphragmatic deposits. Bronchoscopy is helpful to identify bronchial deposits in airways. Thoracoscopy is performed to visualize both pleural surfaces and the diaphragmatic surface of the thorax. Also, biopsies can be obtained for cellular diagnosis. The video assisted thoracoscopic surgery (VATS) is gold standard which is both diagnostic and therapeutic. But it is not mandatory to perform VATS in all patients. The inspection may reveal diaphragmatic deposits and fenestrations, pleural deposits, pleural cysts bullae and scarring.

This patient has undergone imaging initially. Bronchoscopy was normal. The thoracoscopic findings and pleural biopsy confirmed the initial diagnosis of catamenial hemothorax. However, VATS was performed as she developed secondary pneumothorax during hormonal therapy suggesting recurrence. The diaphragmatic perforation and pleural cysts found during VATS may explain the development of pneumothorax in this patient with leak of air from abdominal cavity through diaphragmatic perforations and/or from perforated visceral pleural cysts.

Endometriosis is a steroid dependent state. Therefore, the aim of treatment is to suppress ovarian steroid hormone production by medical or surgical means. Medical therapy includes progestogens, combined oral contraceptives GnRH agonists, levonorgestrel intrauterine systems, danazol and aro-

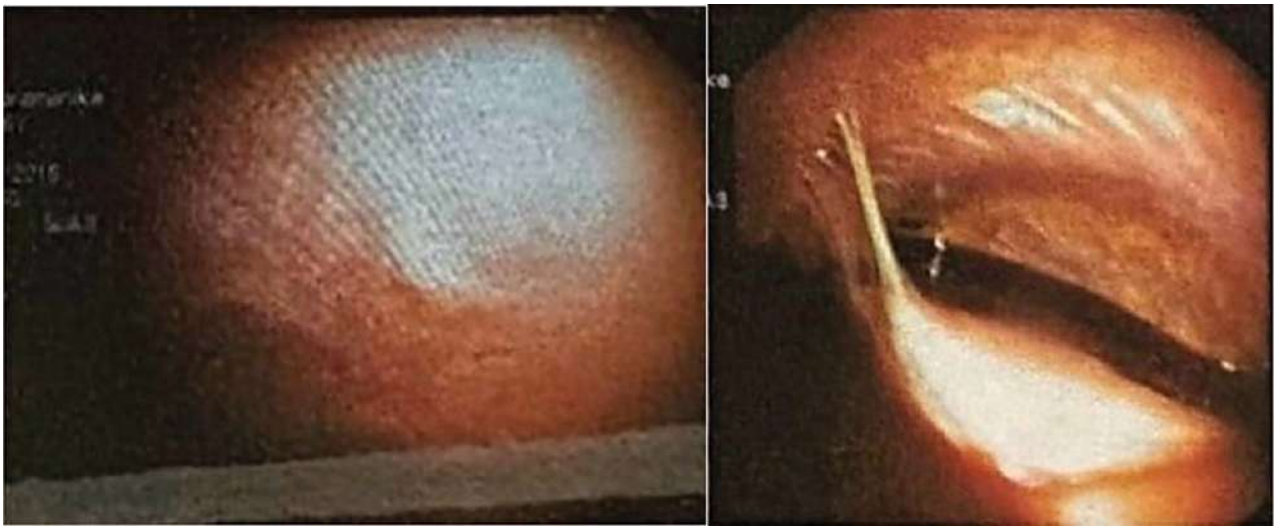

Figure 3. *Thoracoscopic view of nodular lesions in the pleura and pleural adhesions.*

matase inhibitors. The hormonal therapy in extra-pelvic endometriosis found to have high recurrence. This patient was started on a progestogen. GnRH-analogues were not prescribed due high incidence of side effects.

Surgical treatment aims to elimination of endometrial tissue by excision, ablation, or diathermy. In pleural endometriosis, pleurodesis, pleurectomy or pleural abrasion can be done. The diaphragmatic lesions/perforation can be excised and sutured. In this case diaphragmatic plication and pleurodesis performed considering likelihood of further recurrence. Post operative hormonal therapy was also offered to further reduce the recurrence. The women with no fertility wishes can be offered with bilateral salpingo-ophorectomy.

Conclusion

Thoracic endometriosis is less frequent manifestation of endometriosis. High clinical suspicion is necessary to arrive at an early diagnosis to manage appropriately and to prevent disease progression. Though there is a risk of recurrence with medical treatment, hormonal therapy is the first line approach to suppress ovarian steroids. In recurrent disease, surgical elimination of the endometrial tissue followed by post procedural hormonal therapy is indicated.

Abbreviations

TES – thoracic endometriosis syndrome

DMPA – depot medroxyprogesterone acetate

VATS – video assisted thoracoscopic surgery

GnRH – gonadotropin releasing hormone

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Case report

Indwelling pleural catheter for the management of empyema in a patient with learning disability – a case of medical complexity

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Asian Journal of Lung Health, 2024, **1**, 35-36

Key words: indwelling pleural catheter, empyema, schizophrenia, learning disability, challenging behaviour

Abstract

Introduction: Routine use of IPC in the management of infection of the pleural space is contraindicated although there are challenging situations in which chest drains cannot be used due to number of reasons.

Case presentation: A 63-year-old patient with a background of paranoid schizophrenia and severe learning disability with challenging behaviour presented with deterioration of mental health status for 2 days and chest discomfort and was managed as aspiration pneumonia. Her clinical condition deteriorated despite treatment and repeat CXR showed right sided effusion. Effusion was suspected to be pleural empyema and it was treated with chest drains. The patient pulled out three chest drains and it was challenging to retain the drain in situ to manage the empyema. There was concern of a trapped lung and pus was building up as the chest drains could not be maintained. A multi-disciplinary meeting was held, and it was decided to proceed with an indwelling pleural catheter (IPC) with intermittent drainage, as keeping the IPC connected to water seal was not possible.

Conclusions: IPC can be used in specific situations to treat empyema when chest drain insertion is challenging. Best interest meeting attended by multi-disciplinary teams is of immense help in challenging situations where patients lack capacity.

Introduction

There are ample studies to highlight the place of indwelling pleural catheters (IPC) in the management of malignant pleural effusions. Empyema of the lung is managed with draining of the pus combined with antibiotics. Routine use of IPC in the management of infection of the pleural space is contraindicated although there are challenging situations in which chest drains cannot be used due to number of reasons. Here we describe a case of an empyema managed with IPC due to poor tolerance of chest drains.

Case presentatation

A 63-year-old patient with a background of paranoid schizophrenia, oesophagitis, hiatus hernia, severe learning disability with challenging behaviour presented with deterioration of mental health status for 2 days. This was associated with decrease in oral intake, vomiting for 24 hours and chest discomfort. She was clutching her chest on admission. There was no fever or breathlessness noted on arrival. On examination she was slightly aggressive and afebrile. Examination was limited due to uncooperative behaviour. However, there was reduced breath sounds on right side of the thorax.

Initial chest X ray showed right sided haziness and with the given history it was decided to manage her as aspiration pneumonia. She was started on intravenous antibiotics and fluids. Her clinical condition deteriorated despite treatment and repeat CXR showed right sided effusion and she was transferred to ICU due to the development of hypoxia. Initially effusion was suspected to be empyema and it was treated with chest drains. The patient pulled out three chest drains and it was challenging to retain the drain in situ to manage the empyema. There was concern of a trapped lung and empyema was building up as the chest drains could not be maintained. A multi-

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disciplinary meeting was held, and it was decided to proceed with an indwelling pleural catheter (IPC) with intermittent drainage, as keeping the IPC connected to water seal was not possible. The IPC was inserted under sedation and was used to drain the empyema and there was successful clinical recovery and it was removed after 2 months.

She had a very prolonged hospital stay of 4 months complicated with seizures, feeding issues and the complexity of placement issues due to multiple social problems.

Discussion

Empyema is characterised by the presence of pus in the pleural space and the cornerstone of treatment is prompt removal of the collection of infection from the pleural space and antibiotic therapy. Antibiotics should ideally be pathogen specific and guided by the sensitivity pattern. We would like to highlight the fact that bacteriology involved in pleural infection is distinct from that of pneumonia and has different transmitting mechanisms predominantly originating from haematogenous and oropharyngeal sources[2,3].

With the advent of small-bore pleural tube, drainage of the empyema became the treatment of choice at the initial stage combined with appropriate antibiotics. Our patient was initially managed with intercostal tube drainage for the management of empyema and the chest drain had to be inserted several times as she was pulling out the tubes. It was noted that maintenance of chest drains was not possible in her case due to the poor cooperation and expected improvement could not be achieved due to lack of continuous drainage.

Severe inflammatory reaction secondary to empyema results in residual pleural thickening. Previous studies have demonstrated use of antibiotic treatment with pleural drainage in early stages to relieve dyspnoea and reduce residual pleural thickening. There were a few obstacles that we faced in our case. As she was diagnosed with learning disability and paranoid schizophrenia, she lacked the capacity to make decisions. In addition, empyema was building up as she could not keep the chest drains in-situ which could make her more symptomatic and septic. Her case was further complicated as there was limited family involvement intially and discussions were between the health staff.

A best interest meeting was arranged and after a detailed discussion with other specialties including critical care it was decided to treat her with indwelling pleural catheter to drain her empyema intermittently. There were no previous case reports to highlight the use of IPC in the management of bacterial empyema. There was one case report from India in which the authors used an IPC in the management of a tuberculous empyema as an outpatient[1]. Use of IPC in pleural infection is usually considered as a contraindication. However, our case was exceptional as we did not have a choice to drain her infected pleural collection due to the number of reasons outlined above. She was not a candidate for surgery based on her co-existing conditions and showed fluctuating emotional changes throughout the disease course.

Our patient with empyema was successfully managed with IPC with intermittent drainage for 2 months as an in-patient. Interval between drainages was increased or reduced based on fluid drained. IPC is typically used for the outpatient management of preferably malignant effusion; however, the purpose of its use is totally different in our case as she had ongoing pleural infection and complex placement issues. She was an inpatient for a further 4-month period after removal of the IPC as it was very difficult to find a placement for her, highlighting the complexity of the management of this patient.

Conclusions

IPC can be used in specific situations to treat empyema when chest drain insertion is challenging. Best interest meeting attended by multi-disciplinary teams is of immense help in challenging situations where patients lack capacity.

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Guidelines

Key changes from the Old to the New GOLD Reports, Global COPD Guidelines

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Chronic obstructive pulmonary disease (COPD) is one of the major diseases with high morbidity and mortality worldwide[1]. The report from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) for the diagnosis, management, and prevention of COPD has been revised recently[2]. Thus, key changes in this report should be reviewed. The GOLD report may not be a kind of guideline, but for convenience I will call it a guideline in this editorial.

Key changes in the GOLD 2024

1) The section on **PRISm** (preserved ratio but impaired spirometry) has been expanded.
PRISm is defined as FEV1/FVC≥70% and FEV1<80% of reference after bronchodilation. PRISm is associated with increased risk of cardiovascular disease, hospitalization, all-cause and cardiovascular death, and developing airway obstruction.

2) A new section on **Hyperinflation** has been added.
Hyperinflation contributes to dyspnea, impaired exercise tolerance, increased hospitalization, and increased mortality in patients with COPD. This condition arises due to the loss of elastic recoil and expiratory flow obstruction. Hyperinflation can be measured by body plethysmography or gas dilution techniques.

3) A new section on **Pre-bronchodilator Spirometry** has been added.
Pre-bronchodilator spirometry can be used as an initial test to investigate whether a patient has airflow obstruction. If the pre-bronchodilator spirometry result does not show airflow obstruction, post-bronchodilator spirometry is not necessary. On the contrary, if pre-bronchodilator spirometry shows airflow obstruction, the diagnosis of COPD should be confirmed by post-bronchodilator spirometry.

4) A new section on **Screening for COPD in Targeted Populations** has been added.
Leveraging Lung Cancer Imaging for COPD screening: Thorough assessment of symptoms and performance of spirometry in individuals undergoing low-dose chest CT for lung cancer screening represents a unique opportunity to screen individuals for symptoms of COPD and airflow obstruction.

Leveraging Incidental Lung Imaging Abnormalities for COPD Screening: Lung imaging abnormalities of emphysema, air trapping, airway wall thickening, and mucus plugging may not only indicate the presence of airflow obstruction but also imply a more rapid decline in lung function and worse quality of life.

5) Entries on **Blood Eosinophil Count** have been updated in the **Initial Assessment** section.
Blood eosinophil counts predict the effect of inhaled corticosteroid (ICS) administered on top of bronchodilator maintenance therapy to prevent future exacerbations in patients with COPD. Thus, blood eosinophil counts are recommended by GOLD to guide the use of ICS.

6) A section of **Interstitial Lung Abnormalities (ILAs)** has been added.
ILAs are radiologic abnormalities found incidentally during chest CT that are potentially related to interstitial lung diseases. ILAs are associated with increased mortality, and some of them can progress. The prevalence of ILA is 4%-9% among adults with age over 60 years.

7) Other changes
The section on **Smoking Cessation and Vaccination Recommendations** has been revised. **Managing Inhaled Therapy** has been expanded and includes information on a patient's **Ability to Use the Delivery System Correctly** and **Choice of Inhaler Device**. A new section on **Pharmacotherapies for Smoking Cessation** has been added.

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Key changes in the GOLD 2023

Several changes in the GOLD 2023 are so essential such that the key changes should be discussed in this editorial, although they have already been implemented in the year of 2023.

1) Grouping of patients with COPD

Patient groups had changed from GOLD A, B, C, and D to GOLD A, B, and E. The new group E is the combination of groups C and D from the older version of the GOLD guideline. Patients with COPD are grouped primarily to guide physicians in planning the initial pharmacological treatment. Patients in the new group E are frequent exacerbators. Thus, they should be given more attention and treated more aggressively with the initial treatment of a long-acting muscarinic antagonist (LAMA) and a long-acting beta-agonist (LABA).

2) Initial treatment for group B patients

Combined inhalation of LAMA and LABA is recommended for the initial treatment of group B patients with COPD. This change is supported by the updated evidence that such combination is superior to a monotherapy in the treatment for this group B patients.

3) New definition of COPD

A new definition of COPD was proposed with the removal of the first component among the four components of the past COPD definition (i.e., first: long-term exposure to gases and dust; second: chronic respiratory symptoms of dyspnea, cough, and phlegm; third: persistent airflow limitation; and fourth: structural abnormalities of chronic bronchitis, chronic bronchiolitis, and emphysema). The new definition may expand the extent of the disease. Thus, the concept of COPD may include various conditions, such as reduced lung development and childhood respiratory infection, in which patients may have no exposure to gases or dust.

4) New definition of COPD exacerbation

A new definition of COPD exacerbation was also proposed. In addition to symptoms, objective measurements of respiratory rate, heart rate, serum C-reactive protein, pulse oximetry, and arterial blood gases are required in the new definition. These changes may be important not only in clinical practice and disease statistics but also in the communication among healthcare practitioners, patients, and the general public. Thus, the new definitions should achieve a consensus from various experts and be validated by supporting evidence.

Table 1. Key changes in the GOLD guidelines from old to new

A. Key changes in the GOLD 2024

Topics	Key changes
PRISm	PRISm is associated with increased risk of cardiovascular disease, hospitalization, all-cause and cardiovascular death, and developing airway obstruction.
Hyperinflation	Hyperinflation contributes to dyspnea, impaired exercise tolerance, increased hospitalization, and increased mortality in patients with COPD.
Pre-bronchodilator spirometry	Pre-bronchodilator spirometry can be used as an initial test to investigate whether a patient has airflow obstruction.
Screening for COPD in targeted populations	Leveraging lung cancer imaging and incidental lung imaging abnormalities for COPD screening.
Blood eosinophil count	Blood eosinophil counts predict the effect of inhaled corticosteroid administered on top of bronchodilator maintenance therapy to prevent future exacerbations in patients with COPD.
Interstitial Lung Abnormalities (ILAs)	ILAs are radiologic abnormalities found incidentally on chest CT that are potentially related to interstitial lung diseases. ILAs are associated with increased mortality, and some of them can progress.
Other changes	Sections on Smoking Cessation, Vaccination Recommendations, and Managing Inhaled Therapy have been revised. A new section on Pharmacotherapies for Smoking Cessation has been added.

B. Key changes in the GOLD 2023	
Topics	**Key changes**
Grouping of patients with COPD	Grouping of patients with COPD has been changed from GOLD A, B, C, D to GOLD A, B, E.
Initial treatment for group B	Combined inhalation of LAMA and LABA is recommended for the initial treatment for group B.
New definition of COPD	A new definition of COPD was proposed with the removal of a component among four components of the past COPD definition. The removed component is "long-term exposure to gases and dust."
New definition of COPD exacerbation	In addition to symptoms, objective measurements of respiratory rate, heart rate, serum CRP, pulse oximetry, and arterial blood gases are required in the new definition of COPD exacerbation.

COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; LAMA: long-acting muscarinic antagonist; LABA: long-acting beta-agonist; CRP: C-reactive protein.

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