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Obstructive Sleep Apnea: Health Consequences and Who to Treat?

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Introduction

Obstructive sleep apnea (OSA) is a common form of sleep-disordered breathing (SDB) characterized by repetitive episodes of upper airway occlusion resulting from pharyngeal collapse during sleep. It was first described in 1966 and is now recognized to be a common condition encountered frequently in primary practice. Since the report by Sullivan and colleagues that splinting open the upper airway with continuous positive airway pressure (CPAP) via a nasal mask can ameliorate this condition, CPAP has become the treatment of choice for OSA. This article will discuss the health consequences of OSA and which patients will benefit from treatment with CPAP.

Pathophysiology of OSA

During the act of inspiration, air is drawn through the upper airway (UAW) into the lungs. The pressure within the UAW is necessarily negative during this act and the negative pressure will tend collapse this structure (Figure 1). The UAW is in fact an extremely floppy structure, as it is involved in both articulation and deglutition. It is not supported by cartilages as in the lower airways. In the wake state, collapse during inspiration is prevented by the support of pharyngeal muscles. However, during sleep, especially in the deeper stages, the muscles, including pharyngeal muscles undergo relaxation. Therefore, the act of inspiration may collapse the UAW, particularly if it is already narrowed by excessive adipose tissue, cranio-facial abnormalities, or endocrine conditions such as hypothyroidism and acromegaly. This propensity for collapse may be further aggravated by the relaxed tongue falling backwards onto the posterior pharyngeal wall if the subject sleeps in the supine position. When there are repetitive partial (hypopnea) or complete (apnea) occlusions of more than or equal to 5 times per hour, i.e. an apnea-hypopnea index (AHI) $\geq 5/\text{hr}$ on polysomnography, the patient is said to have obstructive sleep apnea (Figure 2).

Health Consequences of OSA

Each episode of collapse is usually terminated by transient arousal from sleep which is necessary to

restore pharyngeal muscles and thus reopen the airway. As airway occlusion and subsequent arousals may occur up to a hundred times per hour, significant sleep fragmentation occurs which may give rise to excessive daytime sleepiness. An important consequence of excessive daytime sleepiness amongst drivers is an increased risk of motor vehicle accidents. A study of 210 patients with untreated sleep apnea found a 3-fold increase in motor vehicle accidents as compared with controls and this increased risk fell to control levels after treatment with nasal CPAP. Chronic sleep deprivation and daytime sleepiness may also give rise to impaired cognitive function, family discord and poor quality of life. There is increasing evidence that patients with OSA have an elevated risk of developing cardiovascular complications such as hypertension, pulmonary hypertension (2), cardiac arrhythmia (3), myocardial infarction (4), and stroke (5). Several epidemiological studies have shown an independent association between SDB and hypertension after controlling for confounding factors such as age, body mass index (BMI), sex, alcohol and smoking. A case control study has also shown that patients with OSA have increased ambulatory diastolic blood pressure (BP) both day and night and increased systolic BP at night. This is hardly surprising as arterial blood pressure monitoring during sleep studies shows that both systolic and diastolic pressures may rise sharply at the termination of an apnea from normal levels to levels of over 200/100 mmHg. This probably arises as a result of sympathetic surge associated with airway occlusion and desaturation. The combination of snoring, excessive daytime sleepiness, hypertension and obesity is said to be highly predictive of sleep apnea.

Cross-sectional associations from the baseline examination of the Sleep Heart Health Study cohort have shown modest to moderate effects of SDB on various manifestations of cardiovascular diseases, and relatively SDB was more strongly associated with reported stroke and heart failure than with coronary artery disease. In addition, a recent longitudinal study over 7 years of otherwise healthy middle-aged men with OSA has shown an increased incidence of cardiovascular diseases.

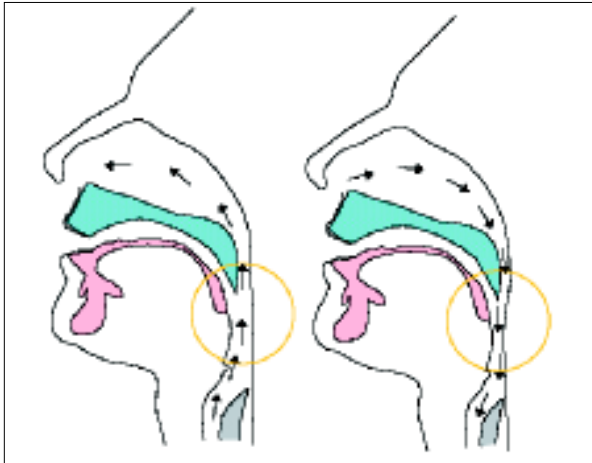


Figure 1. Normal expiration (left) and inspiration (right). The negative pressure generated during inspiration tends to collapse the upper airway.

Hence, in summary, the health consequences of OSA can be divided into those associated with excessive daytime sleepiness resulting from repetitive arousals, and cardiovascular complications (Table 1).

Who Should be Treated?

Since the 1980s, nasal CPAP has become the treatment of choice for OSA. The delivery of a positive pressure via a nasal mask into the upper airway can effectively prevent repetitive airway occlusion. However, CPAP may not benefit all patients with OSA.

OSA, a form of SDB, merely implies the presence of repetitive apneas or hypopneas (usually taken as an AHI $\geq 5/\text{hr}$) on sleep study. This is in fact a very common phenomenon which occurs in up to 24% of middle-aged Caucasian males and 9% of middle-aged

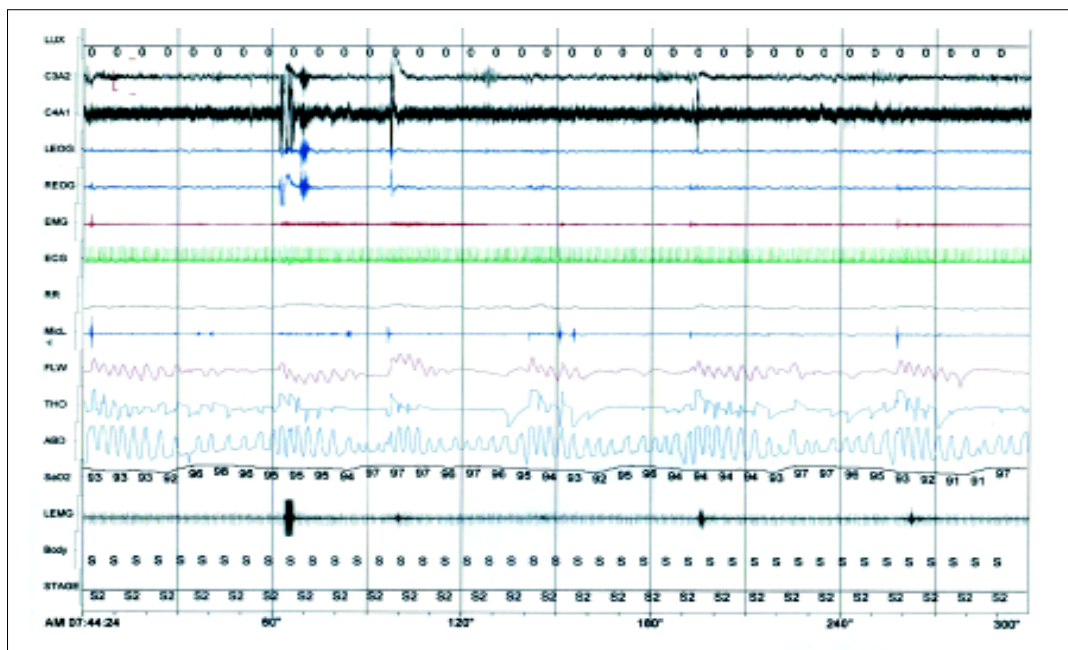


Figure 2. Polysomnogram of patient with obstructive sleep apnea. Note the repeated pauses in the flow signal (FLW) signifying apneas. Each apnea is associated with oxyhemoglobin desaturation and arousal from sleep resulting in sleep fragmentation.

Table 1. Health consequences of OSA

Chronic sleep deprivation	Cardiovascular consequences
Excessive daytime sleepiness	Systemic hypertension
Increased motor vehicle accidents	Pulmonary hypertension
Poor job performance	Cardiac arrhythmias
Increased work-related accidents	Myocardial infarction
Family discord	Congestive cardiac failure
Decreased quality of life	Stroke
Impaired cognitive function	

Caucasian females. Hui and colleagues studied a group of local middle-aged drivers and found that 14.4% have evidence of OSA on sleep study. Ip and colleagues studied middle-aged office workers and found that 8.8% have OSA (14)(Table 2). However, not all patients with OSA have the daytime symptoms of sleep apnea, in particular excessive daytime sleepiness. The term *obstructive sleep apnea syndrome* (OSAS) is used when patients have both OSA on sleep study and the daytime symptoms of sleep apnea. This is a much less common phenomenon, occurring in 2-4% of middle-aged adults. Current opinion is that CPAP is only useful for the treatment of OSAS i.e. only when the patient also suffers from excessive daytime sleepiness.

Clinical Efficacy of CPAP

The past few years have seen a number of randomized controlled trials which confirmed the efficacy of CPAP in improving hypersomnolence, quality of life, mood, alertness, and performance on driving-related tasks in patients with OSAS i.e. CPAP is efficacious in reversing the daytime symptoms of OSAS. Some of these studies were performed on patients with only mild OSA. In other words, even patients with mild OSA will benefit from CPAP provided they have significant daytime symptoms. The efficacy of CPAP in non-sleepy sleep apneics, on the other hand, has been disappointing. Barbe and colleagues performed a randomized placebo-controlled parallel group study on a group of patients with severe OSA on PSG (AHI >30/hr) but with no daytime sleepiness (Epworth sleepiness score of less than 10). After 6 weeks of intervention, they found no significant differences between the study groups in terms of improvement in quality of life, objective sleepiness, cognitive function, or arterial blood pressure. Hence, the value of CPAP in patients with OSA without daytime symptoms appears doubtful.

Although CPAP cannot improve clinical outcomes in OSA patients with no significant daytime symptoms, it is nevertheless desirable to treat this condition to reduce the cardiovascular consequences associated with this disorder. What is missing, however, is clinical evidence that long-term treatment with CPAP can indeed substantially reduce this risk. Several randomized

controlled studies have examined the usefulness of CPAP in improving hypertension in patients with OSA. Results have been controversial with both negative and positive outcomes. Both the negative studies were performed on non-sleepy subjects whilst both the positive trials were performed in sleepy subjects. Hence, it would appear that for sleepy patients, CPAP has the additional benefit of modest blood pressure lowering whereas it is probably not useful in lowering blood pressure in non-sleepy subjects. There is currently no data to support that CPAP can reduce the risk of heart failure, stroke or myocardial infarction in patients with OSA.

CPAP is a potentially intrusive device and patients who derive symptomatic benefit will often demonstrate good compliance whereas those who are asymptomatic or whose symptoms do not improve with treatment will often cease using CPAP in the long run. Hence, its prescription to a largely asymptomatic population to reduce the cardiovascular complications associated with OSA is neither viable nor practical.

Summary

OSA a common condition characterized by repetitive airway occlusion during sleep. Sympathetic overdrive from repetitive arousals and oxyhemoglobin desaturation gives rise to various cardiovascular consequences including systemic hypertension. Chronic sleep fragmentation results in daytime sleepiness, impaired cognitive function, and poor quality of life in certain but not all individuals. For patients who suffer from daytime symptoms, treatment of choice is CPAP which can effectively improve symptoms and perhaps lower blood pressure in such individuals. However, for patients who are asymptomatic, there is neither clinical evidence that the use of nasal CPAP can reduce cardiovascular risk, nor evidence that patient will adhere to therapy. Hence, decisions about treatment must be based not simply on consideration of the laboratory abnormality alone, but rather the total clinical picture. What remains uncertain is whether nasal CPAP can improve cardiovascular consequences other than hypertension, or whether other modes of treatment such as the mandibular advancement splint, which is generally less intrusive to the asymptomatic individual, can improve cardiovascular consequences in such patients.

Table 2. Prevalence of sleep disordered breathing and obstructive sleep apnea syndrome amongst middle-aged males

	Age (years)	SDB/OSA	OSAS
Young et al	30-60 (employees of state agency)	24%	4%
Hui et al	Mean age 42.4 (bus drivers)	14.4%	4.6%
Ip et al	Mean age 41 (office workers)	8.8%	4.1%

Changing Approaches to Lung Cancer

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Lung Cancer: Still Prevalent & Most Lethal in Hong Kong

Lung cancer is the most common cancer in males and the second most common cancer in females in Hong Kong. The age-standardised incidence rates of lung cancer for both male & female showed an overall decline over the past two decades, possibly due to anti-smoking campaign. However, there should not be any complacency as smoking prevalence in the young & females are increasing in recent years. Lung cancer is the leading cause of death among cancers for both males & females in Hong Kong, as most patients present with advanced disease. Nearly 90% of lung cancer nowadays is non-small cell lung cancer (NSCLC) and the remaining 10%, small cell lung cancer (SCLC). Among NSCLC, adenocarcinoma is the commonest.

New Staging System for Lung Cancer

Staging classification for non-small cell lung cancer was revised recently (www.nccn.org) in an attempt to refine the placement of patients into strategies with similar survival rates & therapeutic options. For example, some tumors previously staged as IIIA are now re-categorised as IIB and become resectable.

New Techniques for Sampling Mediastinal Lymph Nodes

Mediastinoscopy or mediastinotomy may, in the future, be replaced or combined with less invasive techniques such as fine needle aspiration of mediastinal lymph nodes through bronchoscope or esophagoscope with endoscopic ultrasound or CT guidance. Preliminary results are encouraging with good yield, sensitivity & specificity.

New Imaging Techniques for Staging Cancer

The introduction of positron emission tomography (PET) has facilitated the staging of lung cancer. PET scan measures the metabolic activity of the lesion. Malignant cells tend to take up & retain more of the injected 18fluorodeoxyglucose (FDG). As 18fluorine decays, it emits positron and is then scanned. PET scan has been shown to be much more sensitive & specific in detecting malignant mediastinal lymph node involvement than CT scan. When PET is done simultaneously with CT (fusion scan), the anatomical area of high metabolic activity is better defined.

However, PET scan may be false positive in tuberculosis and false negative in lesions <1 cm, alveolar cell carcinoma & carcinoid. Whole body PET scan can identify non-cerebral, extra-thoracic metastasis not detected by CT in up to 20% of cases. For cerebral metastasis, a MRI brain scan is preferred.

New Surgical Techniques for Lung Resection

Lobectomy, or even pneumonectomy, has been done with less invasive video-assisted thoracoscopic surgery (VATS). There are reports of VATS for lung cancer with less post-operative wound pain & less hospital stay.

New Radiotherapy Techniques

Better targeting of radiation to the tumour with CT planning (3D conformal RT) may enhance efficacy & reduce side effects. Intensity modulated radiotherapy (IMRT) may allow safer escalation of radiation dose.

Modern Chemotherapy More Effective & More Tolerable

Platinum-based combination chemotherapy is proven, by many randomised control trials, to be better than best supportive care alone in patients with advanced non-small cell lung cancer, provided patients have good performance status. One year survival is 10% more with chemotherapy and there is also improvement in symptoms & quality of life.

The newer agents such as paclitaxel, doxorubicin, gemcitabine & vinorelbine are a little more active with extension of median survival to 10 months & 1 year survival to 40%.

Side effects such as nausea, vomiting, leukopenia & anaemia can be effectively prevented with medications. Nowadays, chemotherapy can be given easily on an outpatient basis.

The nihilism for chemotherapy is not justified.

The problem with chemotherapy is the cost.

Promising New Molecular Targeted Therapy

Drugs for cancer chemotherapy are broad spectrum in action. There are now new, narrow-spectrum, agents which target tumour cells at specific molecular sites, so

as to inhibit tumour growth, block new blood vessel formation into tumour, or abolish "immortality" of abnormal cells. The first to be marketed will be an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor called gefinitib (Iressa). Gefinitib, used alone as second or third line salvage therapy for patients with NSCLC refractory to platins or taxols, will give median survival of 6-7 months. More importantly it relieves symptoms quickly within 7-10 days in 40% of patients.

If gefinitab is combined with concurrent chemotherapy, there is no additional benefit. The reasons are not clear. Chemotherapy may have altered EGFR.

Trials are conducted to determine whether EGFR inhibitor may act synergistically with radiotherapy.

Justified Treatment for the Fit Elderly

Majority of lung cancer patients are elderly (≥ 70 years). Age alone has no prognostic significance in lung cancer.

No active treatment was offered to them in the past. Current data suggest that they tolerate surgery, radiotherapy & chemotherapy equally well as the young, provided that they have good performance status. Post-treatment survival & symptoms control is satisfactory. The fit elderly should not be denied active treatment.

New Methods for the Early Detection of Lung Cancer

As most patients present late with advanced disease, it may be possible to improve cure rate of lung cancer if tumour can be detected early enough for surgery.

In 1970's, many trials have used annual chest X-ray & sputum examination for cytology for early detection of lung cancer. The result was disappointing as it was ineffective.

In 1990's, low-dose spiral CT thorax was introduced for lung cancer screening in middle-aged smokers. As expected, CT detects more lung cancer compared with chest X-ray & most of lesions found are small & early enough for surgery. However, CT is so sensitive that it also picks up other non-malignant, non-calcified lung nodules such as tuberculomas, so that the false positive rate is high. Whether CT screening would improve survival or not is too early to be certain.

Another new technique to detect early lung cancer is laser-induced fluorescent endoscopy (LIFE). Blue light instead of white light is used during bronchoscopy & pre-invasive bronchial lesions will be identified as they emit less green fluorescence. These early lesions may then be removed with photodynamic therapy. However the false positive rate of LIFE is high. The natural history of such pre-invasive lesions is also uncertain; not all of them will develop cancer later; some may regress spontaneously.

New Methods for Relieving Endobronchial Obstruction

Palliative measures to un-block tumour obstruction of bronchi may be achieved with laser, electrical cauterisation or brachytherapy (radiation implant).

Conclusion

The problem of lung cancer is huge worldwide. Regrettably this can largely be prevented if anti-smoking measures could become more rigorous.

Some progress has been made in the early detection & management of patients with both early & advanced lung cancer. Practitioners should adopt a more positive attitude in disease control, especially in the elderly.

Useful Websites for New Information

National Comprehensive Cancer Network, USA - www.nccn.org

National Institute for Clinical Excellence - www.nice.org.uk

British Thoracic Society - www.brit-thoracic.org.uk

Cancer Care Ontario Practice Guidelines Initiative, Canada - www.ccopebc.ca

US National Cancer Institute - www.cancer.gov

European Society for Medical Oncology - www.esmo.org

American Society of Clinical Oncology - www.asco.org

Management of Chronic Obstructive Pulmonary Disease (COPD)

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The Disease Burden of COPD

COPD is a leading cause of morbidity and mortality in many parts of the world. Worldwide, COPD accounts for 4% of all death, and the number of deaths has increased 185% over the last 2 decades. In 1990, COPD was ranked 12th in terms of overall burden of disease; the World Health Organization projects that by the year 2020, it will be fifth. In Hong Kong, COPD has been ranked as the 4th to 5th cause of mortality in the past decade and accounted for 3% of all public hospital admissions and 9% of all medical bed days in 2001. In United States, the mortality of heart disease, cancer and cerebrovascular disease all show a falling trend in the past decades except COPD. Moreover, recent study revealed a quarter of COPD patients suffer from depression.

Global Initiative for Chronic Obstructive Lung Disease (GOLD)

Despite the heavy health burden of this disease, COPD had seldom attracted adequate attention among the medical field until the recent decade. The European Respiratory Society, American Thoracic Society, British Thoracic Society and the Hong Kong Lung Foundation had published several important consensus-based treatment recommendations in the past decade.

Recently, a committed group of international scientists encouraged the US National Heart Lung, and Blood Institute and the World Health Organisation to form the Global Initiative for Chronic Obstructive Lung Diseases (GOLD). GOLD is the first global concerted effort to address the prevention, diagnosis and treatment of COPD. The working group had reviewed extensively the most recent scientific evidences, and finally formulated the workshop report. The whole report and related information on COPD can be accessed via the designated COPD local website www.copdhk.com <<http://www.copdhk.com>>.

Prevention and Early Diagnosis of COPD

COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious

particles or gases. Being a progressive disease, prevention and early detection is of paramount important. The key modifiable risk factors are avoidance of the "total inhaled particles", which include tobacco smoke, occupational dusts and chemicals (vapours, irritants and fumes), environmental tobacco smoke and outdoor air pollution like automobile emissions.

Early symptoms of COPD like coughing and increased sputum can be non-specific and easily ignored. When a patient presented with dyspnoea, infection or acute exacerbation, the disease may already reach moderate severity. The recently conducted National Health and Nutrition Evaluation Survey III (NHANESIII) of USA reported the screening of more than 16,000 individuals. In the group of moderate severe COPD ($FEV_1 < 50\%$ of predicted), 50% had never been diagnosed with lung disease. Therefore early detection by a sensitive, specific and simple screening test is crucial for preventing disease progression. Neither chest radiograph nor peak flow rate can serve as a sensitive and specific screening for COPD. A well-performed office-based spirometry with FEV_1 and FVC values is a simple and useful screening test for the diagnosis of COPD. The presence of a postbronchodilator $FEV_1 < 80\%$ predicated together with an $FEV_1/FVC < 70\%$ confirms the presence of airflow limitation. A postbronchodilator improvement of $> 12\%$ and an absolute value of > 200 ml in FEV_1 is taken as indicating reversibility. Despite spirometer was invented by Hutchison in 1846, it has not yet reached a wide popularity like sphygmomanometer and electrocardiograph. Base on these observations, the "National Lung Health Education Program" (NLHEP) was launched in United States for the early detection of COPD by using spirometry among primary care. The current recommendation is that spirometry test should be considered in any individual who has chronic cough, sputum or dyspnoea, and/or a history of exposure to risk factors like smoking.

Towards an Evidence-based Stepwise Treatment Approach

A stepwise management approach that based on disease severity is advocated by GOLD as illustrated in Table 1.

Table 1. Therapy at each stage of COPD

Patients must be taught how and when to use their treatments and treatments being prescribed for other conditions should be reviewed. Beta-blocking agents (including eye drop formulations) should be avoided.

Stage	Characteristics	Recommended treatment	
ALL		<ul style="list-style-type: none"> Avoidance of risk factor(s), especially smoking Influenza vaccination 	
0: At Risk	<ul style="list-style-type: none"> Chronic symptoms (cough, sputum) Exposure to risk factor(s) Normal spirometry 		
I: Mild COPD	<ul style="list-style-type: none"> FEV₁/FVC <70% FEV₁ ≥80% predicted With or without symptoms 	<ul style="list-style-type: none"> Short-acting bronchodilator when needed 	
II: Moderate COPD	IIA: <ul style="list-style-type: none"> FEV₁/FVC <70% 50% ≤ FEV₁ <80% predicted With or without symptoms 	<ul style="list-style-type: none"> Regular treatment with one or more bronchodilators Rehabilitation 	<ul style="list-style-type: none"> Inhaled glucocorticosteroids if significant symptoms and lung function response
	IIB: <ul style="list-style-type: none"> FEV₁/FVC <70% 30% ≤ FEV₁ <50% predicted With or without symptoms 	<ul style="list-style-type: none"> Regular treatment with one or more bronchodilators Rehabilitation 	<ul style="list-style-type: none"> Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations
III: Severe COPD	<ul style="list-style-type: none"> FEV₁/FVC <70% FEV₁ <30% predicted or presence of respiratory failure or right heart failure 	<ul style="list-style-type: none"> Regular treatment with one or more bronchodilators Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations Treatment of complications Rehabilitation Long-term oxygen therapy if respiratory failure Consider surgical treatments 	

The management of stable COPD involve several steps:

1. Reduction of risk factor exposure and particularly smoking;
2. Optimizing expiratory flow by the use of bronchodilator drugs;
3. Reducing pulmonary inflammation most commonly attempted using corticosteroid; and
4. Prevention and managing acute exacerbations of COPD.

Smoking cessation and long-term oxygen therapy

for hypoxaemic COPD are the two key proven strategies to improve the long-term survival in COPD. The accelerated decline from continual smoking and the delay in lung function deterioration after smoking cessation was documented by Fletcher in 1977 and Scanlon in 2000. All COPD smokers should be advised on smoking cessation irrespective stage of the disease. A brief tobacco dependence counseling result in cessation rates of around 12%. With more complex intervention that involve behavioral approaches and psychosocial support, quit rate can reach 20-30%. Recently there are important pharmacotherapies for tobacco dependence when counseling fail. This includes nicotine replacement products, antidepressants

bupropion and nortriptyline. A randomised controlled-trial showed quit rates at one year of 30% with bupropion alone and 35% with bupropion plus nicotine patch.

Bronchodilator Therapy

Bronchodilator drugs include the inhaled short and long acting beta 2-agonist, inhaled short and the novel long acting anticholinergics, and phosphodiesterase like theophylline. Physiologically, bronchodilators alter smooth muscle tone causing increase in FEV1 and FVC, reduce resting and dynamic hyperinflation of the chest, and increase maximal oxygen uptake. Clinically, they reduce dyspnoea at rest and during exercise, increase exercise capacity and improve health status. The functional benefits of inhaled bronchodilators may occur even in the absence of spirometric bronchodilator response. Evidence shows that the improvement in breathlessness is due to a reduced dynamic hyperinflation during exercise. Inhaled short acting beta 2-agonist and anticholinergics are generally equipotent, with some studies suggesting the latter are more likely to be effective in a given setting. Empirical treatments trials, rather than a laboratory assessment of bronchodilator should be used to determine the choice of bronchodilators. The choice between beta 2-agonist,

anticholinergic, or theophylline depends on the availability and individual response. The bronchodilator effects of short-acting beta 2-agonist like salbutamol and terbutaline usually wear off within 4 to 6 hours, and anticholinergic like ipratropium usually up to 8 hours. Failure of one bronchodilator class to control symptoms should prompt a trial of the other class, and if symptoms are still troublesome, a combination of drugs. Because of the potential toxicity, theophylline is usually prescribed after combined inhaled bronchodilators are used. Long acting beta 2-agonist like salmeterol and formoterol have 12 hours of action, and the long acting anticholinergic tiotropium has 24 hours of action and is recently available on market. They are much more expensive but convenient, and have shown to reduce nighttime symptoms, improve health status and reduce the frequency of exacerbations.

Inhaled Glucocorticosteroids

Oral corticosteroids are currently not recommended as maintenance therapy for stable COPD, based on the lack of evidence of benefits, and the large body of evidence on side effects. There are four large studies on the long-term effects of inhaled glucocorticoids in COPD (Copenhagen City, EUROSCOP, ISOLDE, Lung Health Study). They reported interesting and somewhat conflicting conclusions. The common conclusions are inhaled glucocorticosteroid do not retard the decline in FEV_1 . In two studies there was a small but statistically significant improvement in postbronchodilator FEV_1 evident by three months and persistent throughout the study and this varied between 60 and 100 mL. Moreover, cases complaining new onset of breathlessness and the number of exacerbations were significantly reduced in the Lung Health study and ISOLDE respectively. The current recommendation is that regular inhaled glucocorticosteroid in moderate dose should be prescribed for symptomatic COPD with a documented spirometric response to glucocorticosteroids or in those with an $FEV_1 < 50\%$ predicted and repeated exacerbations.

Other Pharmacological Treatments

Based on the current evidence that Influenza vaccines can reduce serious illness and death in COPD patients by 50%, Influenza vaccines should be given once a year before the peak season. A pneumococcal vaccine containing 23 virulent serotypes has been used, but sufficient data to support its general use in COPD patients are lacking. The overall benefits of mucolytic agent are small and the widespread use of these agents cannot be recommended. Anti-oxidants, in particular N-acetyl-cysteine, have been shown to reduce the frequency of exacerbation and could have a role in the

treatment of patients with recurrent exacerbation. Its definite role awaits the result of ongoing trial.

Non-pharmacological Treatment

Besides smoking cessation, oxygen therapy is the only other intervention shown to improve long-term outcome, reduce mortality, and improve quality of life. The indication for long term oxygen therapy are: 1) PaO_2 at or below 7.3 kPa (55 mm Hg) or SaO_2 at or below 88% with or without hypercapnea; or 2) PaO_2 between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg) or SaO_2 at or below 89% if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive heart failure or polycythemia (hematocrit $> 55\%$).

A multi-disciplinary pulmonary rehabilitation program with exercise training, training in activities of daily living and education; has shown to reduce dyspnoea, improves exercise capacity, improves health-related quality of life, reduces anxiety and depression and reduces the number of hospitalizations. Moderate to severe COPD patients with dyspnoea and functional disability, who has no contraindication to exercise can be a candidate of pulmonary rehabilitation program.

Management of Exacerbations

Fourteen randomized trials have shown that inhaled short-acting beta 2-agonist and anticholinergic bronchodilator are equally efficacious in the care of patients with acute COPD exacerbation. In general the short-acting beta 2-agonist is preferred. If a prompt response does not occur, the addition of an anticholinergic is recommended. Six randomized controlled trials have shown that systemic corticosteroid administration for up to two weeks are helpful for hospitalized COPD patients in exacerbation. Eleven randomized controlled trials have shown that antibiotic treatment is beneficial in selected COPD patients with exacerbation. The choice of antibiotics should cover Penicillin resistant *S. pneumoniae*, beta-lactamase producing *Haemophilus influenzae*, and *M. catarrhalis*. The first line choice of antibiotics include amoxicillin-clavulanate, ampicillin-sulbactam or new fluoroquinolones like levofloxacin. The local resistant rate of *S. Pneumoniae* to first and second-generation macrolides reaches 70%.

There are five randomized controlled trials and five observational studies confirmed the beneficial effect of Non-invasive positive pressure ventilation (NIPPV) in COPD patients with acute exacerbation and respiratory acidosis. It serves to improve ventilation and as a means of avoiding intubations. However, close monitoring

should be provided and contraindications should be followed strictly. NIPPV should only be prescribed under the close supervision of experienced staff.

Surgical Treatment

Bullelectomy can be considered in carefully selected patients. Lung volume reduction surgery (LVRS) is a surgical procedure in which parts of the lung are resected to reduce hyperinflation. Positive early results have been reported in many studies. Its long-term effect awaits the result of a randomized controlled study currently conducted in USA.

Novel Therapy

Second generation phosphodiesterase type 4 inhibitors are currently under evaluation because of their favorable profile in patients with COPD. Many novel agents

targeted at the pathophysiological abnormalities are under experimental investigations. These include mediator antagonists, new anti-inflammatory agents, protease inhibitors, mucoregulators, and agents that stimulate the regrowth of damaged alveoli.

With all the above treatment strategies and the potential novel therapy, we are looking forward for an era of improved outcome in COPD patients.

Abbreviations

FEV₁: forced expiratory volume in 1 second

FVC: forced vital capacity

FEV₁/FVC: ratio of forced expiratory volume in 1 second to forced vital capacity

FEV₁ predicted: predicted forced expiratory volume in 1 second

ABC of Respiratory Infections in Hong Kong

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Respiratory infections are common causes of admission to HA and private hospitals. The common types of respiratory infections include:

A) Viral respiratory infections (VRI) – *Rhinoviruses* cause a majority of the VRI. Adults have an average of 2-4 colds and children have an average of 3-8 colds per year. VRI causes a significant economic burden for the society. In contrast to *influenza* which causes airborne transmission and widespread outbreaks, close contact is required for *rhinovirus* infection and households and schools are common sites for transmission. The common symptoms of VRI include coryza, sorethroat, headache, cough, activity restriction and fever. The features are similar for disease caused by *rhinoviruses*, *respiratory syncytial virus*, *parainfluenza virus*, *influenza A & B* and *haemolytic streptococci*. Similar to children and younger adults, rhinoviruses are more common causes of upper respiratory infections than influenza. The clinical symptoms are similar to younger subjects, but the elderly patients are more likely to have longer duration of illness (median 1 day), more likely to be confined to bed (19%), have restriction of daily activities (26%) and more likely to have lower respiratory tract symptoms (63%). Besides causing upper respiratory symptoms, respiratory viruses are also common pathogens in causing acute bronchitis. 40% of non-asthmatic patients with acute bronchitis had FEV1 \leq 80% of predicted. Bronchial reactivity may remain increased up to 5 weeks after an episode of acute bronchitis. Therefore, lung function tests should be delayed for 6-8 weeks if underlying asthma is suspected as a cause of recurrent cough. Antibiotics are commonly prescribed for VRI in Hong Kong. In one study, it was found that up to 7.5% of patients with the diagnostic label of upper respiratory infections were given antibiotics. Patient satisfaction is more closely related to the quality of communication than receipt of antibiotics. Judicious use of antibiotics may reduce treatment cost and lead to a lower incidence of antibiotics resistance in the community.

B) Acute exacerbation of COPD (AECB) – The pathology of COPD includes hypertrophy and hyperplasia of mucous glands, airway inflammation, delayed mucociliary clearance and bacterial colonization by *H. influenzae*, *S. pneumoniae* and *M. catarrhalis* in 25% of cases. AECB is defined as increased dyspnoea, sputum volume or purulence in addition to at least one

feature of: (i) infection of the upper respiratory tract within the previous 5 days, (ii) fever without other cause, (iii) increased wheezing, (iv) increased cough, (v) increased in either respiratory rate or heart rate, by 20% of baseline. In patients with acute tracheal bronchitis and near normal lung function, respiratory viruses and *Mycoplasma pneumoniae* are common pathogen. With deteriorating lung function, the causative organisms of AECB become *Pneumococcus*, *H. influenzae*, *M. catarrhalis*, and in end stage lung disease with bronchiectasis, *P. aeruginosa*. Hospital admission for acute exacerbation is required for (1) poor response to outpatient therapy (2) significant reduction in exercise tolerance (3) inability to eat or sleep due to dyspnoea (3) inability to manage at home and alternative home support not immediately available (4) significant co-morbid conditions whether respiratory or not (5) type I or II respiratory failure (6) mental disturbances such as confusion or disorientation. The high risks patients are those with frequent exacerbations, significant comorbidity, prolonged history, advanced age and continued smoking. The high risks patients are more likely to fail beta-lactam therapy, develop respiratory failure and require ICU admission or die. Identification of high risks patients would indicate aggressive antibiotics therapy and consideration of hospital admission. Besides treatment with oxygen, hydration and chest physiotherapy, aggressive antibiotic would improve outcome particularly in the high risks group. The antibiotic of choice for AECB includes a macrolide for suspected *Mycoplasma* infection (For patients in whom coverage of both *Mycoplasma* and *H. influenzae* is needed, a newer generation macrolide has to be considered). A betalactam-betalactamase inhibitor (such as augmentin or unasyn) would be indicated for infections suspected to be due to *H. influenzae* or *B. catarrhalis*. A quinolone may be considered for mild to moderate infections in patients with poor lung function and suspected *Pseudomonas* infection. In hospitalized patients with poor premorbid condition and poor lung function, intravenous antibiotics such as 3rd generation cephalosporins may be required to cover *Pseudomonas* infection.

C) Community-acquired pneumonia (CAP) – The diagnostic approach to CAP includes: (i) Is this pneumonia? (ii) Does the patient require admission to hospital? (iii) What is the likely microbiological agent? (iv) What is the treatment?

Clinical features of pneumonia are not uncommonly nonspecific, particularly for the elderly. Although there are a number of differential diagnoses of consolidative changes, chest radiograph is frequently required for a firm diagnosis of pneumonia. On the other hand, it is difficult to differentiate typical from atypical pneumonia from the chest X-ray changes alone. The diagnostic clues to the likely pathogenic organisms include host factors (e.g. older age, COPD, chronic alcoholic, diabetes mellitus, bronchiectasis and preceding influenza), season, habitation, travel history and exposure to animals. Risk stratification would help to identify patients who can be managed at home and those who require hospital admission. Younger patients (<50 years of age), without underlying diseases (eg neoplasm, heart failure, CVA, renal or liver disease) and without adverse clinical signs (such as confusion, tachycardia, tachypnoea, hypotension) are at low risk of death from CAP and can be considered for outpatient treatment or abbreviated inpatient treatment. Overseas studies and previous study in HK showed that *S. pneumoniae* was the commonest cause of CAP. In addition, *M. tuberculosis* had to be considered for cases of CAP in HK. More recent study in a regional general hospital in HK showed that the common causes of CAP were *H. influenzae* (13.7%), *Mycoplasma pneumoniae* (11.8%) and *S. pneumoniae* (5.9%). The cause of the lower incidence of CAP due to *S. pneumoniae* was not known, but it was possible that the widespread use of antibiotics makes it difficult for the pneumococcus to be isolated in

culture. In the past few years, there was an increasing incidence of penicillin resistant *S. pneumoniae* (PRSP) in HK. Latest data showed that almost 80% of the *S. pneumoniae* in HK were PRSP. The high incidence of PRSP in HK is almost certainly related to the common prescription of antibiotics but the clinical significance of the high prevalence of PRSP was not known. A study of penicillin resistance of *S. pneumoniae* in a district regional hospital in HK showed that 34% of the *S. pneumoniae* were penicillin sensitive, 63% were intermediate resistant to penicillin (i.e. can still be treated with high dose penicillin) and only 3% were highly resistant to penicillin. The presence of PRSP was related to previous antibiotic therapy and recent hospital admission. Most of patients had only minor chest X-ray changes and there was no difference in mortality between those patients with penicillin sensitive and those with penicillin resistant strains. A number of antibiotic guidelines for the treatment of CAP had been developed by international professional organizations such as the American Thoracic Society and Infectious Disease Society of America. The IMPACT guidelines of HK recommends the follows regimes for the treatment of CAP: (i) CAP (not hospitalized) – PO augmentin/unasyn ± macrolide or PO amoxicillin + a newer macrolide; (ii) CAP (hospitalized in general ward) – IV/PO augmentin or unasyn ± a macrolide, alternative – cefotaxime or ceftriaxone±macrolide; (iii) CAP (hospitalized in ICU or serious CAP) – (IV tazocin or cefotaxime or ceftriaxone) + macrolide, alternative – cefepime + a macrolide.