UNIT NO. 6

A REVOLUTION IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Over the past decade, there has been a revolution in the treatment of COPD. Until recently, the focus has been on the relief of symptoms with bronchodilators. This emphasis has now shifted to reducing mortality, preventing exacerbations, minimising hospitalisations, and preserving quality of life in advancing disease. Management of acute exacerbations with non-invasive ventilation, use of ICS, ICS + LABA, or inhaled tiotropium bromide to reduce number of exacerbations, and early intervention of exacerbations at the outpatient setting to reduce admissions to hospitals are effective. Pulmonary rehabilitation and exercise programmes, universal interventions of smoking cessation, influenza vaccination, and maintaining a normal diet and weight will add to a better quality of life. The primary physician also has to detect signs of advancing disease early and engage the family in planning the end of life decisions.

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BACKGROUND

As a result of aging populations, the developed world is facing a pandemic of chronic obstructive pulmonary disease (COPD). In Singapore COPD is one of the 3-4 most common major chronic diseases resulting in death and hospital admissions. For many years, COPD was considered an untreatable, intractable disease and we doctors could only watch helplessly at the bedside as our patients pant on to their deaths. The only effective interventions were smoking cessation, a universal recommendation anyway, and long term home oxygen supplementation for the minority of persistently hypoxic patients. However, over the past decade there has truly been a revolution in the treatment of COPD and this has coincided with a remarkable increase in the research and understanding of this chronic debilitating disease.

This article reviews the major advances in the management of COPD over the past decade, directed at meaningful improvement clinical outcomes, and with relevance to primary care practice.

A SHIFT IN THE GOALS OF TREATMENT

Until recently, the treatment of COPD was to focus on the relief of symptoms mainly by utilising bronchodilators. This treatment alone was not very effective in patients with little reversibility in airways obstruction, which is a hallmark of COPD. And as the disease progresses, the frequent exacerbations were usually managed in hospital with more bronchodilators plus corticosteroids and antibiotics. However, in the past few years, we have shifted the emphasis towards treatments aimed at achieving additional benefits in key clinical outcomes, such as reducing mortality, preventing exacerbations, minimizing hospitalizations and preserving the quality of life in advancing disease[1,2,3]. (Table 1)

Table 1. Treatment for COPD related to specific goals

Intervention	Goal/s
Cessation of cigarette smoking	Stops COPD progression and lowers mortality
Long term home oxygen	Lower mortality in severely and persistently hypoxic patients
Inhaled long acting bronchodilators (LABA or Tiotropium bromide)	Less symptoms, better QOL Fewer exacerbations
Inhaled corticosteroids	Better QOL, fewer exacerbations Lower mortality?
Inhaled ICS+LABA	Better QOL, fewer exacerbations Lower mortality?
Non-invasive ventilation	Lower mortality, fewer intubations, ICU admissions and hospital pneumonias
Home nursing service	Fewer and shorter hospitalisations

LABA: long action beta agonist
ICS: inhaled corticosteroid
QOL: quality of life

REDUCING MORTALITY

There is robust evidence that the mortality rate from COPD can be reduced by appropriate management of severe acute exacerbations of (AE) COPD with non-invasive ventilation (NIV)[3]. This was proven in a series of randomised controlled trials in the 1990s and is currently the standard treatment of AE COPD with acute respiratory acidosis which fails to respond promptly to emergency treatment with oxygen and inhaled bronchodilators[3]. In National University Hospital (NUH) the mortality rate of patients with AE COPD has fallen from 6% to 3% after we implemented a systematic NIV program (Figure 1). The additional benefits include fewer tracheal intubations, less ICU admissions and lower rates of hospital infections (Figure 1). This is entirely consistent with the clinical evidence which suggests that we need to treat only 5-6 patients with NIV to prevent one death[3].

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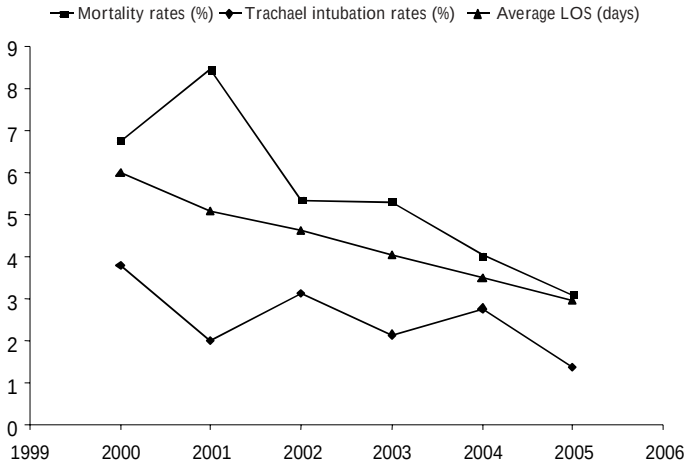
There is growing evidence that treatment with inhalational cortico-steroids (ICS) and perhaps a combination of inhaled cortico-steroid and a long acting beta agonist (ICS + LABA) may also reduce mortality from COPD[4-7]. The evidence for treatment with ICS is based upon post hoc analysis of pooled data from clinical trails, which were not designed primarily to examine the effect on mortality, and from several high quality observational studies (about 25% reduction in all cause mortality)[4-6]. The evidence for treatment with ICS+LABA is based upon a single trail with borderline results on the primary analysis of effect on mortality (17.5% mortality reduction, p = 0.052)[7].

Figure 1: Annual avergae mortality rates, trachael intubation rates and length of stay (LOS) in patients hospitalised with COPD exacerbations in the National University Hospital.



Enhanced management programs for COPD were implemented in 2002. The falls in mortality and LOS were statistically significant.

PREVENTING SEVERE EXACERBATIONS

Acute exacerbations of COPD are a constant feature of advanced COPD and thus, an indicator of disease severity[2]. They are associated with fall in quality of life, loss of pulmonary function and increased mortality. Severe AEs result in hospital admissions, complications and escalating economic costs. Thus, the effective prevention of AE COPD has become a primary goal of management plans.

There is good evidence that treatment with either ICS, ICS+LABA or inhaled tiotropium bromide will reduce AE COPD effectively[2, 8]. These drugs may be used in sequence or in combination, and an additive effect is likely. Thus, patients with one or more severe AE COPD requiring emergency treatment are at risk for more severe relapses and therefore, should be treated with these drugs.

Although clinical trials are underway, at this time, there is no conclusive evidence to recommend the use of empiric and prophylactic antibiotics in preventing AE COPD.

REDUCING HOSPITALISATIONS

Patients with advanced COPD suffer from a larger number of acute exacerbations (AEs). As the disease progresses, these occur more frequently and become more severe. While some milder AEs can be effectively managed by patients with escalation of rescue inhaled bronchodilators, a large proportion of AEs will bring patients to doctors for urgent management.

The treatment of AE COPD in the clinic or emergency department (ED) is with inhaled bronchodilators by wet nebulization. Most patients will also be hypoxic and supplementary oxygen also should be administered. A short course of oral prednisolone (0.5mg per kg for 7-10 days) will speed up recovery and avoid treatment failures. This should be prescribed for most patients after initial relief of acute symptoms.

Antibiotic treatment do not benefit all patients with AE COPD. Treatment with antibiotics is only indicated in patients with severe AE COPD, who also expectorate frankly purulent sputum. There is yet no conclusive evidence that any antibiotic type or class is superior to others in the treatment of AE COPD. Thus, empiric treatment with either a beta lactam or macrolide antibiotic is appropriate. In Singapore, because of the prevalence of pulmonary tuberculosis (PTB) in elderly men, we do not recommend the empiric use of quinolone antibiotics in this setting, unless PTB can be excluded with confidence with a least a chest radiograph. Empiric treatment with quinolones has been associated with delayed diagnosis of PTB and worse prognosis.

We anticipate that the general practitioner will assume a bigger role in the effective out-patient management of COPD exacerbations in the future. The key to effective treatment of AE COPD and avoiding hospitalisation is early intervention. It is recommended that effective treatment should be initiated not later than 2-3 days after escalation of symptoms.

HOME SUPPORT SERVICES FOR COPD

There is good evidence from several clinical trials, that patients with AE COPD who respond to emergency treatment, are not persistently hypoxic, and do not have serious co-morbidities can be promptly discharged from either the clinic, ED or hospital wards and be safely managed at home with further support from home visits nurses[9]. We have implemented these services in Singapore with positive outcomes and achieved significant and sustained reductions length of hospitalization, in relapse and readmissions rates in several hospitals (Figure 2). This reduction in hospitalisation also associated with less expense and more convenience for patients and their families. The hospitals also benefit from freeing up of bed capacities for other acute conditions.

ALLEVIATING SYMPTOMS AND PRESERVING THE QUALITY OF LIFE

Long acting bronchodilators are recommended as the first line drugs for symptomatic relief and preserving the quality of life in COPD[8]. These are best taken by inhalation and are either LABAs, like formoterol or salmeterol, or anti-cholinergics like Tiotropium bromide. Tiotropium bromide, a new, once per

day anti-cholinergic is more convenient and may be more effective, but is also more costly than the LABA drugs. Also, different patients may have individual preferences for the drugs and delivery devices and thus, a trial and error approach guided by symptomatic response would be most appropriate. As the disease progresses and symptoms become more severe, added treatment with ICS+LABA or Tiotropium bromide or both might be indicated. In cost conscious patients, oral long acting bronchodilators, like slow release theophyllines, may be useful initially, but these are not as effective and have a lower margin of safety than inhaled drugs.

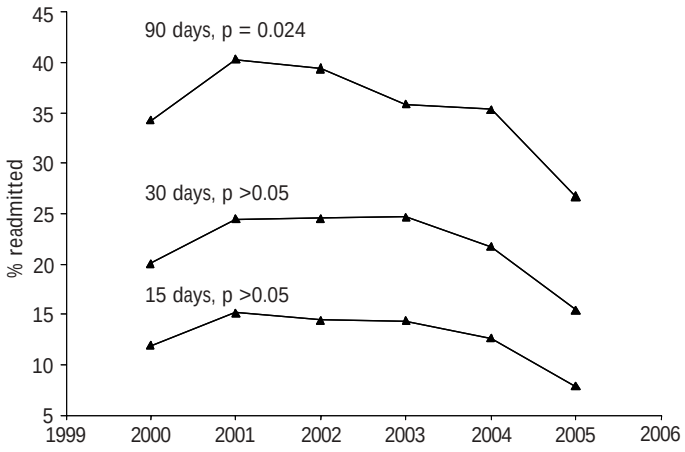
PULMONARY REHABILITATION AND EXERCISE PROGRAMS

Pulmonary rehabilitation with exercise is a fundamental component of all COPD management programs because it improves effort tolerance, quality of life, feeling of wellness and may reduce the duration of hospitalisation. Yet, in Singapore, we have been particularly unsuccessful in enabling a high proportion of our patients with COPD to participate in these programs. This failure is the result of complex cultural and socio-economic factors which deserve a lot more attention. Nevertheless, all patients with COPD should be encouraged to and be assisted in keep physically active as much as possible.

EXPERIMENTAL SURGICAL AND ENDOSCOPIC OPTIONS

There are several surgical and endoscopic options for patients with severe refractory COPD which have gained some publicity. For example, lung volume reduction surgery (LVRS), lung transplantation and endoscopic lung volume reduction. Only LVRS has been subjected to a controlled study in the US[10]. This study reported no overall benefits in mortality. But, a minority of very carefully selected patients may benefit from LVRS with improved symptoms and survival. These are experimental methods and not recommended as routine treatments.

Figure 2: Decline in re-admission rtaes at 15, 30 and 90 days after hospital discharge for COPD exacerbations from the National University Hospital.



UNIVERSAL INTERVENTIONS

Universal recommendations for all older patients and especially those with COPD include smoking cessation, influenza vaccination and maintaining a normal diet and weight. Quitting smoking will preserve lung function and improve survival while flu vaccination will also reduce exacerbations[11]. Weight loss is a poor prognostic feature in COPD and should be avoided with appropriate diet and nutritional supplements.

PALLIATION AND END OF LIFE ISSUES

Despite major advances in the treatment of COPD in recent years, it is still a progressive disease which will eventually result in refractoriness to therapy, severe breathlessness, disability and death. The primary physician must detect the signs of advancing disease early and engage patients and their families in planning their end of life decisions. Persistent breathlessness and frequent re-admissions for NIV, despite adequate medical therapy with poor lung function, are signs of advanced disease. Futile efforts to escalate treatment and add ventilator support are inappropriate, prolong suffering needlessly and should be avoided. In this setting, there is a role for palliative treatment with opiates administered in graduated doses.

CONCLUSIONS

Recent therapeutic advances have transformed COPD from being an almost untreatable condition to an eminently treatable disease. It is a multi facet and systemic disease which responds to a variety of interventions. This may be result from using old drugs, new drugs, drugs in combinations, innovative hospital support modalities, physical therapies, nursing support procedures coupled with patient education and/or changes in life style and disease coping behavior. Thus, the physician who manages patients with COPD needs to decide, in conjunction with patients and their families, the primary goal(s) of therapy and select the appropriate treatment modality or class of drug. Furthermore, a large number of important studies in COPD treatment are currently underway. Thus, we can anticipate more progress in this area in the near future. The GOLD website is a good source of up to date information for both physicians and patients[12].

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LEARNING POINTS

- **COPD is now no longer considered a condition which is untreatable and intractable.**
- **The focus of treatment has changed from relief of symptoms mainly by using bronchodilators to treatment of exacerbations, reducing their frequency, and avoiding admissions to hospitals.**
- **The use of ICS, ICS+LABA, or inhaled tiotropium bromide will be effective in reducing acute exacerbations.**
- **Early treatment of exacerbations within 2-3 days of escalation of symptoms will prevent the need for admission to hospitals.**
- **Pulmonary rehabilitation and exercise programmes improves tolerance, quality of life, feeling of wellness, and duration of hospitalisation.**
- **Universal interventions of smoking cessation, influenza vaccination, normal diet and weight help to achieve a better quality of life.**
- **The primary physician must be able to detect the signs of advancing disease early and engage patients and families in planning their end of life decisions**.