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**Long-term oxygen therapy: state of the art****Przewlekłe domowe leczenie tlenem: stan obecny**

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Long-term oxygen therapy is well established as an important part of our therapeutic options for severe COPD. However, for a therapy whose scientific basis was established almost 30 years ago, it is surprising that there is considerable turmoil in the field. Some of this is the result of positive developments, some a result of remaining uncertainty about our use of this therapy and some a result, seemingly, of inadequate attention to assuring that oxygen therapy is delivered to our patients optimally. I am reminded the title of the 1966 movie “The Good, the Bad and the Ugly” (a classic tale of the American West, featuring an excellent cast headed by a young Clint Eastwood) and will use this as the theme of this examination of the state of the art in long-term oxygen therapy.

**The good**

If we wish to see what is good in recent developments in long-term oxygen therapy (LTOT), we can look to technologic developments that have expanded treatment options. If we review the recommendations of the 5<sup>th</sup> Oxygen Consensus Conference, held in Washington, DC almost 10 years ago, we can find the following recommendation concerning ambulatory oxygen therapy: “Ambulatory oxygen equipment must be able to be carried by most patients on their person during activities of daily living. Ambulatory LTOT equipment must weigh less than 10 pounds and provide at least the equivalent of 2 L/min of continuous flow oxygen for 4 hours or more” [1].

At the time, this was an ambitious requirement. Yet, in recent years, we have seen the introduction of options that make lightweight ambulatory supplies widely available.

- Small portable liquid oxygen units, weighing as little as 1.6 kg that the patient can fill from a liquid oxygen reservoir have been developed. Liquid oxygen is the most compact form of oxygen storage, generating roughly 840 liters of gas for every liter of liquid oxygen.
- Lightweight small oxygen cylinders are increasingly an option. Carbon fiber wrapped aluminum cylinders weigh less than standard tanks and have higher filling pressures. Attractive configurations weigh in at about 1.6 kg, including the oxygen regulator.

Another major development concerns how oxygen is delivered to our patients. The cost of transporting oxygen to the patient is a major fraction of the cost of oxygen supply. The stationary concentrator, that separates oxygen from nitrogen in the atmosphere, effectively solves this problem for stationary oxygen supplies. But, until recently, ambulatory oxygen had to be delivered to the patient’s home by a truck. Three “non-delivery” models for oxygen have been developed.

- An oxygen concentrator is configured to fill a lightweight oxygen cylinder that can then be used as an ambulatory source.
- A recently introduced device incorporates a stationary oxygen concentrator capable of generating liquid oxygen. This liquid oxygen can

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then be used to fill a small portable liquid oxygen unit.

- At least five portable oxygen concentrators have been introduced in the past couple of years. These units are battery powered and range in weight from roughly 1.8 to 8 kg. Units range in their time between battery charges and in the flow rate of oxygen they generate. These units have been approved in some countries (and by some airline companies) for use in air flight.

Finally, a related technological development has assisted in enabling patients to more efficiently gauge their oxygen saturation during activities of daily living. Affordable, reasonably accurate pulse oximeters are being used by patients to gauge their oxygen saturations on an ongoing basis. Although the potential exists for patients to overly focus on their oxygen saturation, it seems highly likely that there is a net benefit.

### The bad

Stated succinctly, “The Bad” is that we have unanswered questions that weaken the foundations of clinical practice guidelines for LTOT. To understand why this might be so, consider why we prescribe LTOT. Is it to maintain arterial oxygen partial pressure (or oxygen saturation) above a certain threshold? It is important to realize that our thresholds for treatment are rather arbitrary, established (in essence) by the designers of the trials that demonstrated the value of oxygen therapy (see below). Is it to improve symptoms? Certainly supplemental oxygen improves dyspnea (in particular, dyspnea on exertion) and improves exercise tolerance. But it can be argued that a therapy as expensive as LTOT (it has an estimated cost in the United States of \$3 billion annually) would not be prescribed if symptomatic relief was its only benefit. No, LTOT is prescribed because it improves long-term prognosis. Specifically, in patients with severe resting hypoxemia, it substantially prolongs life. Therapies with mortality benefits have a special place in our therapeutic armamentarium; we are unlikely to deny such therapies irrespective of cost. This was demonstrated in two studies performed in the late 1970s, led by Drs. Thomas Petty and David Flenley [2, 3]. These studies involved a total of only about 300 COPD patients, selected as having severe resting hypoxemia (arterial oxygen partial pressure less than 55 torr) on two occasions. Survival was markedly better at three years in patients averaging 19 hours of supplemental oxygen than those averaging 12 hours of oxygen or no sup-

plemental oxygen at all. Yet it deserves to be stressed that these benefits have been demonstrated to accrue only in patients with severe resting hypoxemia. Why, then, do most guidelines (including Medicare guidelines in the United States) call for oxygen to be prescribed if PaO<sub>2</sub> falls below 55 torr during exercise or sleep, even in patients with higher PaO<sub>2</sub> at rest [4]? It deserves to be stressed there is no clinical trials that demonstrate better survival when patients with isolated exercise or nocturnal hypoxemia receive supplemental oxygen.

It can be argued that at least four large-scale long-term clinical trials with a survival outcome need to be performed:

- stationary oxygen plus ambulatory oxygen vs. stationary oxygen alone for patients who are hypoxemic both at rest and during exercise;
- ambulatory oxygen vs. no oxygen for patients who are normoxic at rest and desaturate with exercise;
- nocturnal oxygen vs. no oxygen for patients who are normoxic at rest and desaturate with sleep;
- stationary oxygen plus ambulatory oxygen vs. no oxygen for patients with mild hypoxemia at rest.

The need for such clinical trials was emphasized by a recently-published National Heart Lung and Blood Institute workshop report [5]. In fact, one of these trials (the last in the list above) is in the planning stage. This despite this question having previously been addressed by an excellent Polish study [6]. (It can be argued that the Polish study had too small a sample size to definitely exclude a clinically significant benefit.) This study, dubbed the long-term oxygen therapy trial (LOTT) proposes to recruit approximately 3200 COPD patients whose resting oxygen saturation is in the range of 89–93% (i.e., milder hypoxemia than incorporated in current guidelines) and randomize them to either full-time oxygen (stationary plus ambulatory) or no oxygen therapy. The duration of the trial is designed so that the average observation period is approximately 3.5 years; it is powered to determine survival differences between the two groups and is scheduled to be completed by 2013. Special challenges of this study include assuring that participants assigned to the LTOT arm actually utilize supplemental oxygen for a large fraction of their day; special procedures to assess and promote oxygen adherence are incorporated.

### The ugly

The challenges we face in efficiently delivering LTOT differ from country to country and re-

gion to region. I will emphasize the United States perspective and invite the reader to consider the situation in his/her own country.

### Recertification issues

Perhaps the most common situation in which LTOT is first prescribed is when the patient experiences a disease exacerbation and is hospitalized. A level of hypoxemia consistent with LTOT prescribing guidelines is detected and the patient is sent home with oxygen supplies. Many of these patients will, however, experience an improvement in oxygenation as their exacerbation resolves and, after a time, will no longer meet oxygen prescribing guidelines. A recent Canadian study found that re-evaluation two months after exacerbation resulted in roughly 20% of patients being able to discontinue oxygen [7]. My personal estimate is that, in the United States, this is likely a low-end estimate. An organized system of recertification would doubtless result in substantial cost savings.

### Oxygen conserver effectiveness

Oxygen conservers are devices that endeavor to maintain desired levels of oxygenation while using less oxygen than continuous flow oxygen. This is enabled by delivering oxygen early in the inhalation (when the oxygen bolus is most likely to reach the gas exchange area) and turning it off in periods when it would be wasted (late in inhalation and during the whole of expiration). There are several dozen oxygen conservers being marketed, with a range of pulse-dosing strategies. These oxygen conservers have made possible the revolutionary availability of light-weight yet long-lasting oxygen supplies. Few have received extensive clinical testing in the patients for whom they are intended. Anecdotal evidence exists that, particularly during exercise, oxygen conservers sometimes do not provide adequate oxygen saturation. Specifically, the assumption that the conserver setting delivers an equivalent saturation to that obtained with continuous flow oxygen with the same liter/minute flow is hazardous.

### Oxygen titration practices

Oxygen flow rates often need to be adjusted from the resting prescription when the patients either exercises or sleeps. Rules of thumb that flow rates should be increased, say, by a liter/minute in either situation are to be discouraged. Patients should be tested and titrated during both exercise and sleep *employing the device the patient will be using*. Only in this way can adequate treatment be reasonably assured.

### Benefits of lightweight supplies

Until fairly recently, the standard provision of ambulatory oxygen was by means of an E-cylinder mounted on a cart and towed by the patient. This configuration weighs about 10 kg and has been perceived as being an impediment to ambulation. Recently, as detailed above, lightweight oxygen supplies have been introduced. Intuitively, lightweight ambulatory supplies should engender a range of benefits, including:

- promoting an increase in activities of daily living;
- increasing the number of hours the patient uses supplemental oxygen;
- improving long-term outcomes.

However, we lack clinical studies convincingly demonstrating any of these benefits.

### Adherence to oxygen therapy

LTOT is expensive therapy. For patients with severe hypoxemia, the long-term clinical trial evidence we have, tells us that the more hours per day that oxygen is used, the better the survival outcome. However, the few studies that have estimated adherence have, shown that adherence is not generally good [8, 9]. It seems reasonable to propose that adherence monitoring and promotion should have high priority. I make the specific suggestion that pulmonary rehabilitation is a good setting for LTOT adherence promotion and that, whenever possible, all LTOT patients should be considered for pulmonary rehabilitation.

### Governmental attempts to reduce oxygen therapy costs

Budgetary constraints coupled with rising numbers of patients receiving LTOT have spurred regulators to devise strategies to reduce LTOT costs. In the United States, one proposal has been to, after an initial period, mandate that patients own and maintain their oxygen equipment. Another proposal requires that oxygen suppliers be selected regionally by a bidding process awarding the lowest bidder exclusive distribution rights. These specific proposals have recently been tabled, but these and similar proposals are likely to be pursued as cost cutting measures.

In conclusion, long-term oxygen therapy is a valuable therapeutic option in a subset of late stage COPD patients. However, a substantial amount of work remains before we can claim to be capable of its optimal delivery.

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