

# Pre-operative evaluation of lung function test results

To the Editors:

The European Respiratory Society/European Society of Thoracic Surgeons joint clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy) were published in the July 2009 issue of the *European Respiratory Journal* [1]. This comprehensive and very important document provides guidelines for the risk evaluation of candidates for lung cancer surgery. We fully agree that the lung function variables forced expiratory volume in 1 s (FEV<sub>1</sub>) and diffusing capacity of the lung for carbon monoxide (DL<sub>CO</sub>), together with exercise capacity, are essential components in the risk stratification. We do not, however, agree on the recommended interpretation and evaluation of the test results. In the guidelines, lung function results are evaluated as customary in terms of percent of predicted normal values, *i.e.* corrected for sex, age, height and, for some variables, also weight (exercise test) [1]. In our opinion, the correction for age is inappropriate when estimating peri-operative risk. This is because expressing lung function results in percent of predicted normal values results in ignorance of the normal age-related decline in lung function and exercise capacity. The guidelines recommend a post-operative predicted FEV<sub>1</sub> value of 30% predicted to be a high-risk threshold. 30% pred normal FEV<sub>1</sub> for a 70-yr-old male with a height of 178 cm is 0.9 L compared with 1.3 L for a male of the same height aged 25 yrs [2]. Thus, according to the recommendations, the high-risk threshold regarding FEV<sub>1</sub> is 0.9 L for a 70-yr-old patient but 1.3 L for the 25 yr old! There are of course similar consequences regarding DL<sub>CO</sub> and exercise capacity.

One of several possible ways to deal with this problem is to express results of lung function tests and exercise tests of adults as percent of predicted normal at age 25 yrs (% pred<sub>25yrs</sub>) irrespective of the actual age. In the example above regarding the 70-yr-old patient, the guideline recommended high-risk threshold of post-operative predicted 30% pred corresponds to 0.9 L, which is equivalent to a post-operative predicted value of ~20% pred<sub>25yrs</sub>. Thus, we suggest the high-risk threshold to be 20% pred<sub>25yrs</sub> for FEV<sub>1</sub>, DL<sub>CO</sub> and exercise capacity.

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**Statement of Interest:** None declared.

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From the authors:

We read with interest the correspondence by B. Houltz and co-workers in which they comment on the recently suggested update of an algorithm for the functional assessment before lung resection, which forms part of the European Respiratory Society (ERS)/European Society of Thoracic Surgeons (ESTS) clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy) [1]. This algorithm, originally proposed in 1998 [2], is based on four key parameters: 1) a cardiac evaluation according to time-honoured principles well-known in the cardiology literature (ECG, stress ECG, *etc.*); 2) a pulmonary evaluation with assessment of pulmonary mechanics using spirometry (forced expiratory volume in 1 s; FEV<sub>1</sub>); 3) a pulmonary evaluation with assessment of gas exchange using the diffusing capacity of the lung for carbon monoxide (DL<sub>CO</sub>); and 4) for patients who do not qualify/disqualify for a given amount of resection after these initial tests, a combined cardio-pulmonary exercise test with the determination of peak oxygen uptake ( $V'O_{2,peak}$ ) is proposed. While B. Houltz and co-workers agree with all parameters used in the algorithm, they query the use of percent of predicted values for the variable age, while not contesting them for sex, height and weight. They argue that correction for age is inappropriate as the normal age-related decline in lung function and exercise capacity is ignored. Interestingly, we do not ignore this decline; on the contrary, this decline is used in order not to rule out older people from resections simply because their absolute values for a given parameter have declined. To use the example given by B. Houltz and co-workers: the new lowest cut-off for safe resection of pulmonary tissue proposed by the ERS/ESTS Task Force is 30% post-operative predicted (ppo) for FEV<sub>1</sub> and DL<sub>CO</sub>, which for the 70-yr-old male would amount to 0.9 L for FEV<sub>1</sub> [3]. If this male was aged 25 yrs 0.9 L would only be 20% of predicted, therefore, B. Houltz and co-workers argue that 20% ppo adjusted for 25 yrs be used for all ages for FEV<sub>1</sub>, and also for DL<sub>CO</sub> and  $V'O_{2,peak}$ .

This suggestion implies that irrespective of age one needs a certain absolute value and, therefore, younger people could have a lower functional reserve when expressed in predicted values. Although this suggestion sounds interesting, we would definitely like to caution against its use. First, we are not aware of any published data supporting this view and secondly lowering the ppo values for FEV<sub>1</sub> and DL<sub>CO</sub> from the original 40% suggested in 1998 [2] to 30% [1] is a major step and needs prospective validation in larger studies. The suggested lowering of this cut-off value to 20% adjusted for 25 yrs of age may

well put young people at an unacceptable risk. A young person most likely needs higher absolute values to qualify for safe resection; in other words, a 25-yr-old patient with 20% ppo function for FEV<sub>1</sub> has much more unhealthy lungs than a 70-yr-old patient with a ppo value of 30%, although in absolute values they both have 0.9 L.

The current use of percent of predicted values has been shown to work well and, generally speaking, guidelines should suggest cut-off values which err on the side of safety. The trend to include more patients with marginal cardio-pulmonary functional reserves for resection will continue [4], but must be based on evidence.

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# Assessment of linezolid efficacy and safety in MDR- and XDR-TB: an Indian perspective

To the Editors:

We read with interest the analysis of the efficacy, tolerability and safety profile of linezolid in multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) in the retrospective TBNET (Tuberculosis Network European Trials group) study by MIGLIORI *et al.* [1]. Before this publication, scattered case reports and small case series have been the only source of data on the efficacy and safety of this drug in the treatment of MDR- and XDR-TB cases.

Linezolid is the first oxazolidinone to be developed and introduced in clinical use. *In vitro* studies have shown good activity against different species of mycobacteria, including resistant strains. The linezolid minimum inhibitory concentration to inhibit the growth of 90% of organisms for *Mycobacterium tuberculosis* is in the range of 1–2 mg·L<sup>-1</sup> [2]. However, clinical experience with the use of linezolid in the management of mycobacterial infection is still sparse.

The use of linezolid is especially relevant in a country like India, which bears the burden of a third of the world's MDR-TB patients. The most recent, *i.e.* fourth, World Health Organization global resistance report, released in February 2008, estimated there were 110,132 cases of MDR-TB from India in 2006. This accounted for 20% of the world's MDR-TB burden. Between them, India and China accounted for 50% of the global MDR-TB burden [3].

Acquired drug resistance, not just to isoniazid and rifampicin, but also to other second-line drugs is also common in India

and XDR-TB strains have been increasingly reported since the first report from India was published in 2007 [4]. Physicians increasingly need to fall back on newer (Group V) and experimental drugs in order to make up the minimum recommended number of active drugs (ideally four or five) to ensure a successful regime. Linezolid has been increasingly used in this role. It is relatively cheap, available off-patent and there are currently 10 generic preparations available in the Indian market. Little is known about its efficacy or toxicity in the Indian context.

We report our clinical experience with the use of linezolid in a cohort of 78 Indian MDR- and XDR-TB patients (36 males and 42 females) being treated at the chest outpatient department of a large private tertiary referral hospital in Mumbai (India). In this prospective, non-randomised study from 2000 to 2007, 18 out of the 78 patients received linezolid. Of these 18 patients, seven harboured XDR-TB and 11 were MDR-TB patients. The mean duration of therapy with the drug was as long as 20.6 months. All 18 patients received the drug only in a dose of 600 mg, once a day. Of these 18 cases, 11 patients were cured, four failed treatment and three were lost to follow-up. In our cohort, the use of linezolid was not associated with any difference in treatment outcome.

In comparison with the TBNET cohort (table 1), we noticed a higher incidence of major adverse reactions (61%) in our patients. Chief among these was a severe peripheral neuropathy. 16 patients were affected by sensory-motor neuropathy.