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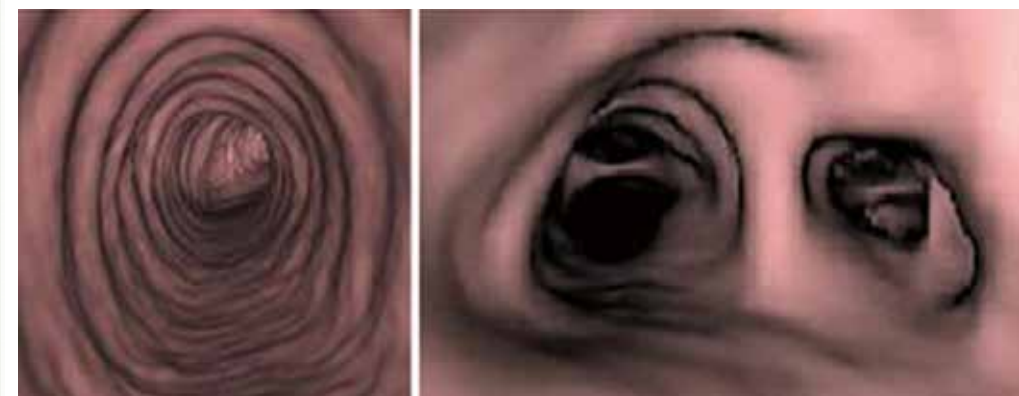


JOURNAL of THORACIC DISEASE



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FOCUSED ISSUE: Crosstalk between the thoracic physician and the surgeon: perspectives on pulmonary infections, malignancy and chest surgery
Guest Editors: Loven Moodley, Keertan Dheda



Published by Pioneer Bioscience Publishing Company

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PubMed, SCI

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Aims and Scope

The *Journal of Thoracic Disease* (JTD, J Thorac Dis, pISSN: 2072-1439; eISSN: 2077-6624) was founded in Dec 2009, indexed in Pubmed/Pubmed Central in Dec 2011, and Science Citation Index (SCI) on Feb 4, 2013. It is published quarterly (Dec 2009- Dec 2011), bimonthly (Jan 2012- Dec 2013), and monthly (Jan 2014-), and openly distributed worldwide. JTD publishes manuscripts that describe new findings in the field provide current, practical information on the diagnosis and treatment of conditions related to thoracic disease (lung disease, cardiology and esophagus disease). Original articles are considered most important and will be processed for rapid review by the members of Editorial Board. Clinical trial notes, Cancer genetics reports, Epidemiology notes and Technical notes are also published. Case reports implying new findings that have significant clinical impact are carefully processed for possible publication. Review articles are published in principle at the Editor's request. There is no fee involved throughout the publication process. The acceptance of the article is based on the merit of quality of the manuscripts. All the submission and reviewing are conducted electronically so that rapid review is assured.

The Official Publication of:

- ❖ Guangzhou Institute of Respiratory Disease (GIRD)
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Cover image:

Virtual bronchoscopy images of the normal proximal (A) and distal (B) trachea. (See P262 in this issue).

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PREFACE

Crosstalk between the thoracic physician and the surgeon: perspectives on pulmonary infections, malignancy and chest surgery

This special edition entitled “Crosstalk between the thoracic physician and the surgeon: perspectives on pulmonary infections, malignancy and chest surgery” is about unifying interaction, collaboration, concepts and ideas at several levels. With the burgeoning increase in pulmonary infections and wider accessibility to cardiothoracic services in developing countries, we thought it appropriate to facilitate greater interaction between the thoracic physician and surgeon in different settings. Furthermore, at a different level given that diseases like tuberculosis (TB) and COPD remain major problems in much of the developing world, further understanding about the surgical aspects of these diseases are warranted.

The first group of papers is dedicated to TB, which remains a public health emergency globally, and is responsible for almost 1.5 million deaths annually. Whilst the disease is treatable with a 6-month course of antibiotics, the extensive lung remodelling and immune-pathology related to the disease results in chronic pulmonary disability, fibrosis, and architectural distortion resulting in broncho-stenosis, bronchiectasis and pleural thickening. Given that globally there are almost nine million prevalent cases of TB annually, it is still a common condition seen in developing countries. It is therefore appropriate that Halezeroğlu and Okur review thoracic surgery for haemoptysis in the context of TB and discuss several management approaches. A new face of the global TB epidemic is that of drug-resistant TB. MDR-TB has now been superseded by XDR-TB and TDR-TB (totally drug-resistant TB, and including XXDR-TB and super XDR-TB). We have now come a full circle, and once again after almost five decades, we are seeing large numbers of therapeutically destitute TB cases due to high grade resistance. In Cape Town, South Africa, we are seeing large numbers of therapeutically destitute cases in clinical practice, many of whom are now being discharged back into the community. In the few patients who are fit and appropriate for surgery, this treatment modality offers the only hope of successful outcome. The papers by Calligaro and colleagues, and Dewan & Moodley, are therefore timely. A condition often seen as a consequence of TB, though it's seen in several other chronic respiratory diseases is that of pulmonary aspergilloma. This remains a major challenge in developing countries and the surgical approach to such patients is discussed in detail by Moodley and colleagues.

By contrast, in much of the developed world, non-tuberculous mycobacterial infections remain an important clinical problem, particularly in elderly patients. The relevant indications, challenges and controversies are discussed in the paper by Johnson and Odell. Thus, non-mycobacterial lower respiratory tract infections remain a problem in both resource rich and poor settings. COPD is a burgeoning epidemic in many resource poor settings driven by smoking, TB, HIV, pollution, and biomass fuel exposure, amongst other factors. COPD remains within the WHO top 10 list of global killers, and COPD incidence is set to increase by 2030. It is therefore appropriate and timely to include a paper on treatment of COPD exacerbations.

Like TB, COPD and pneumonia, malignancy is a burgeoning problem in resource poor settings mirroring the increased incidence of smoking. Terán and Brock discuss N2-specific management aspects of lung cancer, Murrmann and colleagues discuss the approach to a solitary pulmonary nodule in different settings, and Grimm and colleagues discuss surgical aspects of oesophageal malignancies. The paper by Murrmann and colleagues resonates well with this thematic edition, which seeks to bring together thoracic physicians and surgeons, from both resource rich and poor settings, and discuss medical and surgical approaches within specific contexts. Indeed, infections like pulmonary TB have to be taken into account when faced with a patient with a solitary pulmonary nodule in resource poor settings. Finally, Bacon and colleagues and Mueller and coworkers review challenging problems in clinical practice: interventional options for non-resectable tracheal stenosis, and management of air leaks and residual spaces post lung resection, respectively.

We are extremely grateful to all the contributors for their comprehensive and insightful papers, which we hope will foster and facilitate important interaction between thoracic physician and surgeons, and highlight problems faced by both in resource poor and rich settings. We are also extremely grateful to Prof. Nanshan Zhong, Grace S. Li and Melanie C. He from the *Journal of Thoracic Disease* for their kind assistance and support throughout the preparation of this special edition. It was pleasure to work with them. We are also grateful to our families for their support and understanding during the many long hours it took to prepare this special edition.



Cite this article as: Dheda K, Moodley L. Crosstalk between the thoracic physician and the surgeon: perspectives on pulmonary infections, malignancy and chest surgery. *J Thorac Dis* 2014;6(3):181. doi: 10.3978/j.issn.2072-1439.2013.12.41

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doi: 10.3978/j.issn.2072-1439.2013.12.41

Disclosure: The authors declare no conflict of interest.

Thoracic surgery for haemoptysis in the context of tuberculosis: what is the best management approach?

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ABSTRACT

Haemoptysis is not an unusual finding in patients with old or active pulmonary tuberculosis. Because of bronchial artery or a branch of pulmonary artery erosion due to cavitary infiltration, bronchiectasis, fungus ball, broncholithiasis or destroyed lung, the bleeding can sometimes be a life-threatening situation. Assessment of the patient and finding the exact site of bleeding can be difficult especially in a patient with disseminated lung disease. Chest computerized tomography and bronchoscopy remain the methods of choice for lateralization of the disease. Some patients can be treated successfully with endobronchial interventions. Bronchial artery embolization can be rewarding in some patients but the recurrence rate is higher in tuberculosis than other etiologies of haemoptysis. Surgical resection of the lung, mainly lobectomy, remains a life-saving procedure but it should be performed very selectively to avoid higher postoperative morbidity and mortality. Different management options of haemoptysis in patients with pulmonary tuberculosis are discussed in this manuscript.

KEYWORDS

Tuberculosis; haemoptysis; treatment; management; surgery

J Thorac Dis 2014;6(3):182-185. doi: 10.3978/j.issn.2072-1439.2013.12.25

Introduction

Haemoptysis in a patient with tuberculosis is not an unusual condition, especially before the antibiotics are administered. This complaint reduces by time with treatment. However, the amount of bleeding can be very high and some patients are lost due to this massive or major haemoptysis.

The definition of major and massive haemoptysis may vary in the literature. Expectoration of 200 to 600 mL of blood in a day is defined as “major” haemoptysis while the amount above this level is generally accepted as “massive” haemoptysis (1,2). Sometimes, lower amount of bleeding in a patient having limited respiratory function may cause life threatening respiratory compromise. Actually, the definition of massive haemoptysis is not only related to the amount of blood expectorated but also

to the risk of aspiration and the degree of respiratory collapse. Clinical deterioration is, most of the time, depends not only to the amount of bleeding but also to the amount of blood aspirated.

Massive haemoptysis constitutes 1-1.5% of all haemoptysis cases and, can be life threatening either as a result of compromised gas exchange or because of circulatory collapse secondary to acute blood loss (3). Without appropriate treatment, life-threatening haemoptysis has a mortality rate of up to 50-100% (4,5).

In etiology of haemoptysis, geographic distribution and socioeconomic level may have importance (6). Pulmonary tuberculosis, with its chronic sequel, is the most common cause of haemoptysis in the third world (6).

Etiologies of haemoptysis in a tuberculosis patient

Bronchial artery is the major cause for bleeding in most patients with haemoptysis. However, in a patient with tuberculosis, the erosion of a ‘Rasmussen aneurysm’, (dilatation of pulmonary artery branches due to chronic inflammation in a tuberculosis cavity) may be responsible for haemoptysis. Chronic inflammation of bronchial walls in tuberculosis bronchitis may cause destruction and, as in the case of bronchiectasis, may lead bronchial artery bleeding. Since bronchial arteries have higher

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Submitted Sep 15, 2013. Accepted for publication Dec 12, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

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pressure than the pulmonary arteries, such bleeding may also be severe and difficult to control.

When a tuberculosis cavity invades parietal pleura and chest wall, erosion of intercostal arteries or subclavian or internal mammary arteries may also be associated with haemoptysis.

Development of fungal infection in old tuberculosis cavity is another important cause of haemoptysis. *Aspergillum* species are most commonly the causative organism but infection with *monosporium* has also been reported (7). Intracavitary mycetomas may be seen with either of these infections.

Broncholithiasis is development of calcium deposits on peribronchial lymph nodes during healing process of chronic granulomatous condition, most commonly tuberculosis. Erosion of bronchial wall and peribronchial arteries by broncholiths may be another cause of severe haemoptysis.

Assessment of the patients

Whatever the etiological factor is, massive haemoptysis in a tuberculosis patient may be a life-threatening situation and immediate medical and surgical management is needed. A brief history may give you valuable information; previous attacks of haemoptysis, amount and duration of bleeding, use of medication (anticoagulants or antithrombotics) should be noted. Patient should be followed in intensive care or high-dependency unit if he or she has a major or massive haemoptysis. Prevention of asphyxiation should be the major goal in such a patient.

Determining the cause and the location of bleeding is an important issue. Radiologic examinations (chest X-ray, thorax computerized tomography) provide valuable information such as presence of an active tuberculosis infiltration or cavity in the lung, mycotic ball in a cavity or broncholiths. Sometimes both lungs may have pathological findings where lateralization and localization of bleeding becomes an important issue. Some patients describe a dull pain at the same side with the pathology but this is not enough to diagnose the side of the bleeding in a patient with bilateral lung infiltration.

The obvious cause of haemoptysis should be treated with specific measures (reversal of anticoagulants, anti-tuberculosis treatment, antibiotics for bronchiectasis).

A bronchoscopic examination is always needed to determine the bleeding site definitely. Rigid bronchoscopy should be preferred over fiberoptic bronchoscopy for its advantages of better ventilation and suctioning. Prompt localization of bleeding site has utmost importance. It should be remembered that the clots could be aspirated to the contralateral lung or to other lobe(s) in the same side and may be misleading to understand the main source of bleeding.

Non-surgical managements

Once the bleeding site is determined, application of iced isotonic saline lavage, adrenalin or thrombin-fibrinogen compounds may be helpful to stop bleeding. Electro-cautery or argon plasma coagulation machine can also be used. Another method for stopping a bronchial bleeding is the insertion of a Fogarty catheter and inflating it in order to create a pressure over the site of bleeding (balloon tamponade). If all these maneuvers fail, intubation by a double-lumen tube may help to stabilize patient until the preparations for definitive surgical treatment done (8).

Bronchial artery embolization

Availability of endobronchial techniques and bronchial artery embolization may control massive bleeding, at least temporarily, and prevents emergency surgical treatment (9). The first report for controlling life-threatening haemoptysis by bronchial artery embolization was done in 1973 by Remi and colleagues (10). By selective bronchial artery angiography, the site of bleeding of a bronchial artery is determined first and then application of embolization material obliterates the site of leak from bronchial artery. Some studies report a 75-94% success rate in immediate termination of bleeding (11,12). Mal and colleagues evaluated 56 patients who had been embolized for haemoptysis and noted that immediate control was achieved in 43 patients.

These series cover patients having haemoptysis due to different kind of etiology, not only due to patients with tuberculosis. A study consisting of only tuberculosis patients having haemoptysis is a few. Since different mechanisms play role in tuberculosis patients (i.e., bleeding also from pulmonary artery) the success rate of embolization may be expected to be lower in this group of patients.

Ramakantan and colleagues performed bronchial artery embolization in 140 patients with haemoptysis due to active or old tuberculosis (13). They report that, 38 (27%) had recurrent haemoptysis that needed other intervention. Hwang and colleagues performed bronchial artery embolization in 72 patients with haemoptysis due to active or old tuberculosis infection (14). They report 40.3% re-bleeding rate after first embolization and argue that the existence of a shunt in angiographic findings; aspergilloma and diabetes mellitus were the risk factors of re-bleeding. Gross and colleagues performed emergency bronchial artery embolization in 61 patients with haemoptysis due to tuberculosis (15). Of these, 11 had died before discharge, while none of the patients who underwent surgical resection died. Lee and colleagues compared their long-term results of embolization in two groups of patients;

patients with chronic tuberculosis and bronchiectasis (16). They found recurrence rate of 56.7% in tuberculosis group and 26% in bronchiectasis group. They argued that presence of fungus ball was an important risk factor for re-bleeding.

White and colleagues suggest that bronchial artery embolization is a palliative procedure and the potential for recurrent haemoptysis exists as long as the disease process is not cured by drug therapy or removed surgically (12). Recurrence after bronchial artery embolization may be related to incomplete embolization, recanalization of embolized vessel, revascularization of collateral vessels associated with the progression of the underlying disease, or bleeding coming from a pulmonary artery branch as in the case of cavitary tuberculosis (17). In patients deemed too ill to undergo elective surgery, embolization may be repeated successfully for repeated haemoptysis (18).

Potential risks of embolization are mediastinal hematoma due to subintimal aortic dissection and neurological damage. The former may occur due to unwanted occlusion of spinal arteries during embolization.

Resectional surgery

Management of massive haemoptysis and timing of surgical intervention pose difficult problems. Gourin and Garzon have recommended prompt surgical resection for patients having more than 600 mL blood in 24 hours (19). For such a patient mortality rate is 18% by surgery as compared to 75% rate in those treated conservatively. Emergency surgery should be reserved only for those patients: (I) having adequate lung function; (II) exact site of bleeding definitely defined; (III) continuing bleeding despite the adequate measures taken (20). Emergency surgery performed for massive haemoptysis has always higher risk than a planned surgery as reported by Jougon and colleagues (21). Most important reasons for increased mortality in emergency situation are the continuing bleeding during the operation and proceeding aspiration to uninvolved lung and hypovolemia. So, deciding to perform an emergency surgical resection in a patient with massive haemoptysis remains a real challenge.

A double lumen endotracheal intubation for the conduction of anesthesia should be preferred in order to block the bronchus of the bleeding site and prevent aspiration to uninvolved site. A balloon Fogarty catheter occlusion of involved site together with a single lumen tube may also be preferred.

In most emergency cases, the patient had already aspirated some blood to the other lobe(s) and lung functions were already disturbed. Resection of the lung parenchyma may lead respiratory insufficiency. For this reason, the amount of lung

resection should be as small as possible while resecting the main source of bleeding. In most cases, a lobectomy is the standard operation. Because in most cases it is not possible to define the bleeding segment, a segmental resection is rare. In some cases, pneumonectomy is inevitable due to whole lung involvement (destroyed lung) or when the bleeding site is lateralized but not localized. The complication rate is reported to increase by emergency pneumonectomy compared to emergency lobectomy (72% vs. 52%) (2).

Another factor that increases the operative risk is the condition of the lung. Generally accompanying dense pleural adhesions, presence of enlarged sticky lymph nodes, bronchiectasis or broncholithiasis make the surgery very complex and difficult one. Some authors described a method called 'lung exclusion' in patients having dense adhesions making the hilar dissection impossible. In that method, only the bronchus and the artery of affected lobe or lung are obliterated without resection (22).

Erdogan and colleagues reported a series of 59 tuberculosis patients with haemoptysis who underwent surgical resection (20). The pneumonectomy rate was 7% while lobectomy was performed in 65% and the lesser resections in 28% with an overall perioperative mortality about 7%.

An analysis of the nationwide inpatient sample database study was performed recently to define the prevalence and outcomes of anatomic lung resection for haemoptysis in the USA covering a 10-year period (23). Over 457,000 admissions for the diagnosis of haemoptysis were identified. The rate of tuberculosis patients was 0.8% [4,322]. Of all patients with haemoptysis, 2,671 patients (0.58%) underwent surgical resection, 47 (1.8%) for tuberculosis and 157 (5.9%) for fungal infection. This study showed that the increased age and pneumonectomy were the most important risk factors for operative mortality while tuberculosis was not.

Erdogan and colleagues reported three cases of empyema and broncho-pleural fistula in their series containing 59 patients who were operated for tuberculosis related hemoptysis (20). Two of the broncho-pleural fistulas were reported to develop after pneumonectomy (50%) showing the increased risk after pneumonectomy.

In our experience, the rate postoperative surgical bleeding is also increased in this group of patients even if any coagulation abnormality is not detected during preoperative evaluation. Disturbed nutritional balance and low levels of blood proteins may cause increased surgical bleeding in this group of patients.

Conclusions

Haemoptysis in an active or previous tuberculosis patient is a

complex situation. Locating the site of the haemoptysis and defining the etiology may be difficult especially in case of a massive haemoptysis. Bronchial artery embolization may be a good method for controlling haemoptysis and gaining time for a planned surgery in general population. However, in tuberculosis patients the success rate of this method seems to be decreased probably due to the presence of bleeding also from a pulmonary artery branch in this group of patients. In case of massive bleeding, emergency surgery becomes inevitable but carries higher risk than a planned surgery. Surgical resection is still the definitive treatment with acceptable rate of morbidity and mortality.

Haemoptysis can be life threatening in the course of pulmonary tuberculosis. Careful assessment of the condition and quick management remains rewarding.

Deciding the best management option among drugs, bronchoscopic procedures, interventional radiology or resectional surgery is the highlight of the treatment.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Halezeroğlu S, Okur E. Thoracic surgery for haemoptysis in the context of tuberculosis: what is the best management approach? *J Thorac Dis* 2014;6(3):182-185. doi: 10.3978/j.issn.2072-1439.2013.12.25

The medical and surgical treatment of drug-resistant tuberculosis

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ABSTRACT

Multi drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) are burgeoning global problems with high mortality which threaten to destabilise TB control programs in several parts of the world. Of alarming concern is the emergence, in large numbers, of patients with resistance beyond XDR-TB (totally drug-resistant TB; TDR-TB or extremely drug resistant TB; XXDR-TB). Given the burgeoning global phenomenon of MDR-TB, XDR-TB and TDR-TB, and increasing international migration and travel, healthcare workers, researchers, and policy makers in TB endemic and non-endemic countries should familiarise themselves with issues relevant to the management of these patients. Given the lack of novel TB drugs and limited access to existing drugs such as linezolid and bedaquiline in TB endemic countries, significant numbers of therapeutic failures are emerging from the ranks of those with XDR-TB. Given the lack of appropriate facilities in resource-limited settings, such patients are being discharged back into the community where there is likely ongoing disease spread. In the absence of effective drug regimens, in appropriate patients, surgery is a critical part of management. Here we review the diagnosis, medical and surgical management of MDR-TB and XDR-TB.

KEYWORDS

Extensively drug-resistant tuberculosis (XDR-TB); surgery; drug resistance

J Thorac Dis 2014;6(3):186-195. doi: 10.3978/j.issn.2072-1439.2013.11.11

Introduction

The burgeoning drug-resistant tuberculosis (DR-TB) epidemic is a public health problem of global importance. Although TB incidence and mortality has decreased in several parts of the world, the overall prevalence of multidrug-resistant tuberculosis (MDR-TB) is increasing in many high-burden countries, particularly in Africa (1). According to the latest WHO statistics, approximately half a million new cases of MDR-TB are diagnosed every year (2). Of these, it is estimated that approximately 40,000 have extensively drug-resistant tuberculosis (XDR-TB). Despite this, limited

laboratory capacity and lack of widespread drug susceptibility testing in resource-poor settings means that less than 6% of cases are thought to have been correctly diagnosed (2). In 2011, only one in five of the estimated DR-TB cases among patients notified in the world were enrolled on treatment (3). A large reservoir of patients with undiagnosed DR-TB thus exists that continues to drives person-to-person transmission, and threatens to destabilise global TB control (4,5).

The treatment of patients with DR-TB is complex, and characterised by a longer duration of treatment, the use of less potent but more toxic medications, higher relapse rates, and a lower likelihood of treatment success when compared to drug-susceptible TB (6). Treatment for DR-TB treatment is also considerably more expensive: a recent study by Pooran *et al.* estimated that despite only comprising 2.2% of the case burden of TB in South Africa, DR-TB consumed 44% of the total national costs of diagnosing and managing all forms of TB (~\$158 million) in 2011 (7).

In this review, we outline the diagnosis, medical management and treatment outcomes, and indications and outcomes of adjuvant resectional surgery in the management of DR-TB.

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Submitted Sep 17, 2013. Accepted for publication Nov 20, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

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Definitions

MDR-TB is defined as resistance to at least isoniazid and rifampicin, the two most effective first-line antituberculous drugs, while XDR-TB is defined as MDR-TB plus resistance to any fluoroquinolone and any second-line injectable (either kanamycin, amikacin or capreomycin) (3). Pre-XDR-TB refers to MDR-TB resistant to either a second-line injectable drug or a fluoroquinolone.

Other terms such as extremely drug-resistant TB (XXDR-TB) (8) or totally drug-resistant TB (TDR-TB) (9,10) have been used by various authors to describe strains with more extensive patterns of resistance (to all first-line and second-line drugs). These reports have given rise to the spectre of so-called “untreatable” TB, which has been sensationalized in the media. However, due to problems with the reliability and reproducibility of in vitro drug susceptibility testing for second-line drugs, no international consensus has been reached about the definition of more extensive resistance patterns, and the term “resistance beyond XDR” is preferred. The relevance of these resistance patterns on outcomes is also an active area of study.

Diagnosis of drug-resistant tuberculosis

Culture-based tests for DR-TB

For many years, the laboratory diagnosis of DR-TB has depended on the demonstration of the presence of *M.tb* growth in the presence of specific antituberculous drugs—so-called conventional drug-susceptibility testing (DST). Solid agar methods are the diagnostic gold standard (11), while liquid culture methods such as the Bactec MGIT 960 system (Becton-Dickinson, Sparks, MD, USA) have equivalent performance, and are WHO-endorsed (12). However, a lack of laboratory infrastructure in developing countries means that very few countries have access to any DST at all: the WHO reports that globally less than 4% of bacteriologically-positive cases and only 6% of retreatment cases were tested for DR-TB in 2011 (13). Another major disadvantage of these culture-based methods is the long delay (usually several weeks) in obtaining DST results. During these delays, regimens may be used which are not only ineffective, but which encourage the development of further drug resistance, and crucially, allow for resistant disease to be spread. A strategy that aims to control DR-TB must therefore aim not only to increase access to DST, but also to reduce the lead-time for accurate diagnosis (14). New advances in rapid growth- and microscopy-based DST, such as the microscopy observed drug susceptibility (MODS) method and thin layer

agar (TLA) technique have shortened the delay to less than two weeks, but are limited by the need for labour-intensive laboratory infrastructure (15). More recently, the direct nitrate reductase assay (NRA), a rapid, low-cost, phenotypic method based on the metabolic activity of *M.tb* which is usually performed on solid media, has been shown to accurately diagnose DR-TB after ~21 days when performed directly on smear-positive specimens (16).

Molecular DST

New nucleic acid amplification tests (NAATs) promise to reduce the interval between sample acquisition and susceptibility result from weeks to hours, and are also becoming increasingly automated and easy to perform. They have the potential to transform the drug-sensitive and drug resistant TB epidemic in high burden countries by providing rapid DST results at the time of TB diagnosis, increasing the number of cases that are diagnosed with DR-TB and started immediately on the correct treatment, and impacting on transmission rates (17).

Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) is a semi-nested quantitative real-time polymerase chain reaction (PCR) assay that can deliver simultaneous diagnosis of TB and rifampicin resistance in less than two hours. It is an automated, cartridge-based system that can be performed in decentralized locations, outside of reference laboratories and potentially at point-of-care, by staff with minimal laboratory training. It has been widely validated on sputum samples, although reports are also emerging on its accuracy in other respiratory specimens and extrapulmonary samples (18-21). A recent meta-analysis has reported the sensitivity and specificity of the assay for the detection of rifampicin resistance in sputum to be 94.1% and 97.0%, respectively (22). Based on this evidence, the WHO has strongly recommended that Xpert® MTB/RIF, where available, should be the first investigation in all patients suspected of having DR-TB or HIV-associated TB (23). A disadvantage is that Xpert® MTB/RIF does not assay for isoniazid resistance and therefore isoniazid mono-resistance, which has a frequency of about 10-15% in high burden settings, will be missed (24,25). Another concern with Xpert® MTB/RIF is suboptimal positive predictive value in settings where the prevalence of drug-resistant TB is less than 20%. In relatively high-burden settings, even in South Africa where MDR-TB prevalence rates are ~5% to 6% (14), the positive predictive value is only likely to be approximately 70% to 80%, though the precise figure remains unclear. This means that approximately one in three or four rifampicin-resistant results will possibly be falsely positive, creating uncertainty around the decision to start MDR-TB treatment. In South Africa, the policy is to initiate MDR-TB treatment on an Xpert® MTB/

Table 1. First- and second-line drugs based on the World Health Organization classification (32).

Group 1: first-line oral TB drugs

Isoniazid (H)
 Pyrazinamide (Z) or PZA
 Ethambutol (E) or (EMB)
 Rifampicin/rifampin (R) or (RIF)
 Rifabutin (RFB)

Group 2: second-line injectable TB drugs

Kanamycin (KAN)
 Amikacin (AMK)
 Capreomycin (CAP)
 Streptomycin (STR)

Group 3: fluoroquinolones

Levofloxacin (LFX)
 Moxifloxacin (MFX)
 Ofloxacin (OFX)
 Gatifloxacin (GFX)

Group 4: oral bacteriostatic second-line TB drugs

Para-aminosalicylic acid (PAS)
 Cycloserine (DCS)
 Terizidone (TRD)
 Ethionamide (ETH)
 Prothionamide (PTO)

Group 5: TB drugs with unclear efficacy or unclear role in treating drug resistant-TB

Clofazimine (CFZ)
 Linezolid (LZD)
 Amoxicillin/clavulanate (AMX/CLV)
 Thiacetazone (THZ)
 Clarithromycin (CLR)
 Imipenem/cilastatin (IPM/CLN)
 High-dose isoniazid (high-dose H)

RIF showing rifampicin resistance, particularly if the patient is unwell, until further confirmatory test results on two samples (either phenotypic DST or alternative PCR-based test like Hain MTBDR_{plus}) become available.

A line probe assay is laboratory-based type of nucleic acid amplification assay in which products are hybridized onto a nitro-cellulose strip. An example is the MTBDR_{plus} assay (Hain Lifesciences), which offers similar performance to Xpert MTB/RIF for TB detection, and has excellent performance for the detection of MDR-TB (26,27). It has the advantage of interrogating for both rifampicin and isoniazid resistance. More recently, the MTBDR_{sl} assay (second line) assay has

been introduced which tests for drug-resistance to second line injectable drugs (mutations on the *rrs* gene), fluoroquinolones and ethambutol (28). However, this assay has diminished accuracy in smear-negative specimens (29), meaning that culture isolates still need to be awaited to rule-in resistance.

The diagnosis of extrapulmonary DR-TB is even more challenging as obtaining samples for diagnosis often requires specialized skills (e.g., lumbar puncture or biopsy), and the traditional methods of smear microscopy and culture perform poorly on paucibacillary non-sputum samples. Performing an Xpert MTB/RIF on concentrated urine can identify 40% of HIV-TB cases who are sputum-scarce (30), and sensitivity is approximately 23%, 53%, and 78% in the pleural, pericardial and CSF compartments, respectively [R. Meldau and K. Dheda, submitted; S. Pandie and K. Dheda, submitted; (31)]. In the CSF and urine compartments, centrifuging the fluid significantly improved accuracy. In BAL fluid obtained by bronchoscopy, Xpert yield was ~75% and was unaffected by HIV status (18).

Medical management of DR-TB

MDR-TB treatment

The treatment regimen for MDR-TB consists of a backbone of a later generation fluoroquinolone (moxifloxacin, gatifloxacin or levofloxacin) and an injectable aminoglycoside (either amikacin or kanamycin), any first line drug to which the isolate is susceptible, and the addition of group 4 drugs such as cycloserine/terizidone, and ethionamide, such that at least four drugs to which the isolate is likely to be susceptible are being used (see Tables 1,2). The intensive phase (with injectable) is eight months, followed by a continuation phase of 12 to 18 months. The recommended duration of treatment is guided by culture conversion and is usually determined by adding 18 months to the date of the first of consecutive negative cultures; the WHO recommends a total treatment duration of at least 20 months (33). Non-adherence, incorrect drug dosage, hetero-resistance, and malabsorption should be considered in patients who do not show a clinical response and remain persistently culture-positive despite exhibiting consistent susceptibility to second-line drugs. These patients may be considered for the addition of alternative second line agents to their regimens, and/or referred for surgery after appropriate investigations are undertaken.

XDR-TB treatment

With the loss of two of the most potent groups of second-line drugs (namely fluoroquinolones and aminoglycosides), the

Table 2. Principles of management of drug-resistant TB.

Principles of medical management of MDR-TB

- A regimen is based, when possible, on proven or likely susceptibility to at least four drugs
- A regimen is generally based on a backbone of a later generation fluoroquinolone (moxifloxacin or levofloxacin), and injectable agent (usually an aminoglycoside, i.e., either amikacin or kanamycin), any first line drug to which the isolate is susceptible (see Table 1), and addition of group 4 drugs such as cycloserine/terizidone and ethionamide, and others, such that at least four drugs to which the isolate is likely to be susceptible are being used
- The injectable drugs are used for 6-8 months, and longer in certain cases, and the total duration of treatment is suggested to be 24 months
- If the patient has previously been on treatment with a specific drug for three or more months, then this drug is generally avoided
- Addressing psychological factors to ensure compliance is critical
- Patients should be monitored for adverse drug reactions, which are common
- A single drug should not be added to a failing regimen

Principles of medical management of XDR-TB

- Regimens should be constructed based on prevailing DST patterns
- Given the high background rates of TB and MDR-TB in several countries, and lack of availability of newer agents like linezolid and bedaquiline, regimens are often constructed around a backbone of capreomycin and PAS
- Any drug that the isolate is susceptible to from category 1, and any remaining available drugs from category 3 or 4, are added to the regimen
- Patients should be carefully monitored for adverse drug reactions, particularly capreomycin (renal failure, hypokalemia and hypomagnesaemia), which are common
- Patients on capreomycin should have weekly urea and electrolytes monitored for the first eight weeks and then monthly thereafter. Attention should be paid to correcting risk factors for renal failure (dehydration, nausea, vomiting and diarrhea, avoidance of other nephrotoxic drugs (cotrimoxazole and nevirapine), and early identification of underlying renal disease (diabetes and HIV-associated nephropathy)

design of a treatment regimen for XDR-TB is more complex (see Table 2). Extended regimens in TB-endemic countries, given the lack of availability of linezolid, often consist of a backbone of capreomycin and para-aminosalicylic acid (PAS), with other first-line, second-line or third-line anti-TB drugs added to which susceptibility has been demonstrated, or at the discretion of the attending clinician. The intensive phase with capreomycin should be at least eight months (15). The exact number of drugs used to treat XDR-TB is not known, but most patients will receive five to six drugs. Unfortunately, high rates of capreomycin resistance (~80%) in XDR patients have been observed (E. Pietersen and K. Dheda, unpublished work), presumably due to cross-resistance with the other aminoglycosides (34); similarly, as the majority of patients with XDR-TB have been previously treated for MDR-TB (35,36), prior exposure to drugs like ethionamide and terizidone usually excludes their use. Despite documented fluoroquinolone resistance, moxifloxacin is usually added to the regimen because it has increased antituberculous activity compared with ofloxacin, and because there is differential strain-specific susceptibility to the fluoroquinolones (37).

Moxifloxacin has been shown to be effective against isolates phenotypically resistant to ofloxacin or ciprofloxacin (38), and may be associated with improved outcomes for patients with XDR-TB (39). In isolates where lack of isoniazid susceptibility results from mutations in the promoter region of the *inhA* gene (40-42), low-level resistance can likely be overcome by increased doses of the isoniazid ("high-dose INH") (43). This pattern of resistance is often accompanied with cross-resistance to other second line anti-tuberculosis agents, specifically ethionamide, as it has a structural similarity to isoniazid (44). Other drugs like clofazamine (45) and beta-lactam antibiotics like meropenem and co-amoxiclav (46) from group 5 are also used, although good quality efficacy data is lacking. Bedaquiline, the first novel antituberculous drug to emerge in almost half a century (47), has been cautiously approved in an interim recommendation by the WHO for patients in whom a regimen containing four effective second-line drugs cannot be constructed, or in patients where there is MDR-TB plus documented resistance to a fluoroquinolone (pre-XDR-TB), provided that bedaquiline can be protected by at least three effective drugs (48). The latter

Table 3. Criteria for selection for candidates for surgery in DR-TB.

- Persistently positive smear or culture despite optimal antituberculous therapy
- Extensive isolate drug resistance pattern with high probability of failure or relapse
- Radiographically localized disease with high probability of near-total resection
- Expectation of adequate cardiopulmonary reserve post-surgery
- Presence of sufficient drug activity to facilitate healing of the bronchial stump

is often not possible in TB-endemic countries with currently available drugs. Safety concerns have been raised about the interaction between bedaquiline and clofazamine and the fluoroquinolones, as all cause QT prolongation. The addition of linezolid to the regimen of patients failing standard XDR-TB treatment has been shown to improve culture-conversion, but longer-term outcomes are unknown, and cost and toxicity are major concerns (49). Neither bedaquiline nor linezolid are currently available to National Treatment Programs in countries where XDR-TB is prevalent and endemic.

Monitoring during treatment

Treatment for DR-TB involves the use of toxic medications: drug-associated adverse effects are common, and can frequently interrupt treatment (50). In addition to monitoring sputum cultures, it is essential to monitor renal function and potassium at least monthly during the intensive phase of treatment involving an injectable. Ototoxic hearing loss is common in patients with DR-TB treated with aminoglycosides: a recent study from South Africa found that 57% of patients had developed high-frequency hearing loss after three months of aminoglycoside treatment (51). All patients should therefore be screened monthly with audiometry during the intensive phase of treatment. Thyroid function should be monitored between six and nine months of treatment with ethionamide, prothionamide or PAS, and a full blood count should be checked monthly in patients taking linezolid.

Treatment outcomes in DR-TB

Globally, survival and treatment outcomes of drug-resistant TB vary widely depending on geographical location, regimen choice, duration of treatment, and background prevalence of TB and HIV (6), but in general, correlate with the degree of drug resistance. The overall treatment outcomes are far from satisfactory: the WHO reports that of the estimated half a million MDR-TB patients started globally on treatment in 2009, only 48% were treated successfully (2). Treatment outcomes

in XDR-TB are even worse; while the overall success rate for XDR-TB in a recent meta-analysis was reported to be 44% (39), additional resistance to second- and third-line TB medications beyond the minimum definition of XDR-TB was associated with further reductions in the likelihood of success. The cure rate in high-burden countries may be even lower: in South Africa, less than 20% of patients with XDR-TB culture-converted within six months of initiation of treatment, and this poor outcome was independent of HIV status (35). There is thus a desperate need for new drugs and additional interventions to improve these outcomes, particularly in XDR-TB. A number of novel drugs are undergoing clinical testing, but are unlikely to be available for several years yet (52).

Adjuvant surgical management of drug-resistant TB

Rationale and indications for surgery

Thick walled cavitary lesions and areas of destroyed lung contain up to 10^7 to 10^9 *M.tb* organisms (53), harbouring actively replicating bacilli even in patients who are sputum culture-negative (54,55). These tuberculous lesions have reduced exposure to host defenses, and are penetrated poorly by antituberculous drugs (56). Cavities act not only as huge reservoirs of *M.tb* infection (with the potential for intrapulmonary or contralateral spread), but also as the likely site of the development of drug resistance (57). The rationale behind surgery for DR-TB is that excision of these cavities (along with “debulking” of any necrotic or non-viable lung tissue) will dramatically reduce the overall organism burden in the lung while simultaneously removing the sites of high concentrations of drug resistant bacilli. The surgical removal of cavities is hoped to enhance the sterilizing properties of post-surgical chemotherapy and increasing the likelihood of treatment success (58,59). Complications of TB including massive haemoptysis, aspergilloma, bronchiectasis, pneumothorax, bronchopleural fistula, tracheal or bronchial stenosis and empyema remain valid indications for surgery in both drug-sensitive and drug-resistant

Table 4. Pre-operative workup of patients for surgery for DR-TB.

- HRCT to assess for bilateral disease and to plan surgical approach (PET/CT may be a useful adjunct to confirm contralateral metabolically active nodal or parenchymal disease in borderline cases or those with radiological changes secondary to previous TB)
- Spirometry
- ECG (\pm echocardiogram) to exclude pulmonary hypertension
- Six-minute walking test (6MWT), quantitative ventilation: perfusion scanning and arterial blood gas measurement in borderline cases
- CD4 count in patients with HIV co-infection
- Nutritional assessment by dietician with supplementation if required

TB (60), but these topics are beyond the scope of this review.

The indications for surgery for DR-TB have remained largely unchanged since they were first described by Iseman *et al.* in 1990 (61), (an adaptation of which is shown in Table 3). Potential surgical candidates include those patients with localized disease and adequate pulmonary reserve who have either: persistently positive sputum smears and/or cultures despite an adequate trial of appropriate chemotherapy; or those who have relapsed, or are thought to be at high risk of relapse based on results of drug resistance profiling or radiological findings. The lack of effective sterilizing chemotherapy for XDR-TB means even “cured” patients remain at high risk for relapse, and may be considered candidates for resection regardless of sputum culture status. The prerequisite of the presence of sufficient susceptible drug activity to facilitate healing of the bronchial stump is also less relevant in the setting of XDR-TB, where extended resistance patterns mean that surgery often remains the only option for cure.

Timing of surgery

Ideally, surgery should be performed once culture-conversion has been achieved to minimize the risk of post-surgical complications. Performing surgery later in the course of treatment may also allow for time for nutritional supplementation and control of coexisting medical conditions. However, particularly in the case of XDR-TB (as outlined above), this is unlikely to ever be achieved. Delaying surgery and persisting with ineffective chemotherapy may only facilitate progression of disease, and further promote the development of drug resistance (62). The timing of adjuvant surgery must consider the likelihood of potential culture-conversion based on the resistance profile of the *M.tb* isolate; however, a minimum of three to six months of pre-operative chemotherapy is usually given (62-66).

An additional consideration in the setting of HIV/DR-TB co-infection is that surgery may need to be postponed until immunity has been restored with antiretroviral therapy (ART)

to the point at which it is expected that major surgery can be withstood.

Preoperative workup, surgical approach and complications of surgery

The preoperative workup is directed at assessing disease extent and estimating cardiopulmonary reserve (see Table 4). A high-resolution CT chest is a prerequisite to assess the presence of contralateral disease, and to plan the surgical approach. Spirometry is required to estimate pulmonary reserve, while a 6-minute walk test (6MWT) is a good test of functional capacity. In borderline cases, quantitative perfusion lung scanning can assist in estimating the degree of functional loss following surgery. Cut-off values for predicted postoperative lung function are not defined in this group of patients, but can be adapted from studies of resectional surgery for lung cancer: predicted post-operative forced expiratory volume in one second (FEV_1) should likely be greater than ~800 mL for pneumonectomy candidates (67). An ECG followed by an echocardiogram, where indicated, may be useful in excluding pulmonary hypertension, which would otherwise contraindicate surgery. Positron emission tomography-computed tomography (PET/CT) has been proposed as a noninvasive imaging method that may give additional information about tuberculous disease status, particularly about the presence of contralateral parenchymal as well as nodal metabolic activity (68,69). Its role in guiding surgery remains unclear. The preoperative improvement of nutritional status has been advocated by many authors (64,65,70,71) to improve wound healing and post-operative recovery.

The extent of anatomical resection (wedge resection versus segmentectomy, lobectomy or pneumonectomy) is determined by the distribution of radiological disease, and is balanced by the desire to remove as much pathological lung as possible while preserving post-operative pulmonary reserve. While the procedures performed in case series and cohort studies were predominantly lobectomies or pneumonectomies for unilateral

disease, sequential resection of bilateral cavities in patients with adequate pulmonary reserve has also been described (70,72,73).

The surgical approach is almost always via a muscle-sparing posterolateral thoracotomy; the median approach has also been studied, but offers limited exposure for left-sided resections (74). Video-assisted thoracoscopic surgery (VATS) is associated with less wound pain, fewer pulmonary complications, and a shorter hospital stay than with a thoracotomy. This technique has recently been shown to be a feasible option for smaller wedge resections and isolated lobectomies in carefully selected patients with less extensive disease (75). The obliteration of the pleural space, the presence of infected lymph nodes in the peribronchial area, and extensive adhesions (between the lung, vasculature and the chest wall) occurring as a result of chronic tuberculous sepsis, typically limit thoracoscopic intervention and are a contraindication to VATS (63).

Bronchial stump closure is usually by stapling, although interrupted sutures with absorbable or non-absorbable sutures (either on their own or as additional reinforcement), are also used (59,65). Muscle-flap buttressing of the bronchial stump has been advocated to prevent the post-operative complication of bronchopleural fistula especially in patients with positive sputum at the time of operation (65); however, this practice has not been universally adopted, and a series of 106 patients from South Africa in which bronchial stump reinforcement was only performed in two cases reported no cases of bronchopleural fistula formation (64).

With careful patient selection, the operative mortality in lung resection is less than 5% (62-66,76). Common complications range in frequency between 12% and 30%, and include bleeding, empyema, wound complications and bronchopleural fistula.

Outcomes of surgical treatment

There is a dearth of good quality of data supporting the use of adjuvant surgical treatment for DR-TB, and current recommendations are based on expert opinion. No randomized controlled trials have been performed, and it is likely that the available data from case series and cohort studies is biased towards surgery in patients with less extensive disease. Nevertheless, a recent systematic review and meta-analysis of 24 comparison studies of MDR- and XDR-TB (involving more than 5,000 patients) found a significant association between surgical intervention and successful outcome when compared to non-surgical treatment alone (OR 2.24, 95% CI: 1.68-2.97) (77). Sub-group analyses of studies involving XDR-TB patients revealed an even more pronounced treatment effect (OR 4.55, 95% CI: 1.32-15.7), which would support the widely held

view that surgery as a therapeutic option becomes even more attractive as effective chemotherapeutic options dwindle.

Conclusions

MDR-TB, XDR-TB, and now resistance beyond XDR-TB (TDR or XXDR-TB) are growing epidemics fuelled by failing national TB programs, HIV co-infection, and poverty, and not only have a high mortality but threaten to destabilise many national TB programs. For example, in South Africa, despite drug-resistant TB forming less than 3% of the total case load, it consumes over 40% of the ~US\$160 million national TB program budget. There is also the growing problem of therapeutic failures who, because of lack of appropriate alternative facilities, are now being discharged back into the community (78). Although surgery remains a critical part of management, only a small number of patients are amenable to surgery. In TB endemic countries, where it is needed most, qualified thoracic surgeons and surgical facilities are lacking. Even where thoracic facilities are available, there may be hesitation and reluctance amongst some thoracic surgeons to operate on patients with a deadly disease. Even with surgery, outcomes in TB endemic countries are poor. New TB drugs are urgently needed, however, policy makers face an ethical dilemma of making these available as part of drug-sensitive regimens, thus preserving their medium to long term efficacy, or risking shortening the effective lifespan of these drugs by using them first in those with DR-TB. Newer and less costly point-of-care diagnostics for drug-resistant TB are also needed, as is an effective TB vaccine. Above all, however, existing national TB programs need to be strengthened so that drug-resistant TB is prevented. In parallel, the existing case burden needs to be tackled and ongoing transmission minimised.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Calligaro GL, Moodley L, Symons G, Dheda K. The medical and surgical treatment of drug-resistant tuberculosis. *J Thorac Dis* 2014;6(3):186-195. doi: 10.3978/j.issn.2072-1439.2013.11.11

Resurgence of therapeutically destitute tuberculosis: amalgamation of old and newer techniques

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ABSTRACT

Most of thoracic surgery developed as a result of efforts to treat tuberculosis (TB). The role of surgical therapy has declined but the role of surgery in TB still remains in situations like diagnostic difficulties, persistent sputum positive state despite therapy and complications and sequel like haemoptysis, destroyed or bronchiectatic lungs or empyema with or without broncho-pleural fistula (BPF). Various procedures have a role according to the indication. Some of the procedures have become obsolete but lobectomy, pneumonectomy, thoracoplasty, decortication and open window thoracostomy continue to be relevant. Recent published series have demonstrated mortality ranging from 0% to 3.1%. Surgery for complications and sequel of pulmonary TB still remain an important intervention for alleviation of human misery.

KEYWORDS

Thoracic surgery; tuberculosis (TB); surgery; pneumonectomy; thoracoplasty; decortication; window thoracostomy

J Thorac Dis 2014;6(3):196-201. doi: 10.3978/j.issn.2072-1439.2013.12.19

Introduction

Most of thoracic surgery developed in late 19th century and early 20th century specifically to deal with the management of tuberculosis (TB) patients (1,2). The same challenges were also encountered while dealing with various infective lung conditions. The management strategy progressed from the isolation, fresh-air sanatoria to various surgical collapse techniques to surgical resection. Surgical therapy was perfected in the mid-1950s, but subsequently declined with the emergence of effective anti-tubercular chemotherapy. Thereafter, reports of surgical intervention for TB have been extremely rare especially from the Western countries. In fact, most of the literature in thoracic surgery after 1960s deals with neoplasm of the lung, with occasional reports focussing on TB and other infective lung conditions. However, the problem of TB continued to exist

in developing countries in sizable numbers. For the last five decades, caseloads of thoracic surgeons working in developing countries and recently, emerging economies, have been much higher than those working in Europe, USA and advanced countries. After globalization in 1990s, many case reports from former Soviet states, African countries, Italy, Japan, India and Pakistan are being published with regular frequency (3).

The spectre of human immune deficiency virus (HIV)-AIDS has added new dimensions, challenges and complexities in the last two decades. However, TB with or without HIV remains the single most important challenge. Since there are no randomized prospective studies, surgical recommendations for surgery are based primarily on case reports, retrospective studies, experience and consensus (1). The management of TB as well as other infective lung conditions is primarily medical, with surgery being indicated only occasionally.

Main indications for surgical intervention (2,3)

- (I) Diagnostic procedures to confirm TB and to rule out other causes including cancer.
- (II) Excision surgery to remove worrisome disease in drug resistant cases.
- (III) Symptom control for conditions like haemoptysis, empyema or recurrent chest infections.

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Submitted Nov 20, 2013. Accepted for publication Dec 11, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

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History of surgery for TB

There is a fascinating history of development of surgery for these conditions. This helps us to better understand their rationale and changing role in the present scenario. A Roman physician, Gorgio, in 1696, reported that a TB patient had improved dramatically after he suffered a sword wound in his chest, which produced a pneumothorax. This started the concept of collapse therapy. Carson, in 1822, suggested that something must be done in order to force artificially, by external means, the diseased lung to rest. Forlanini, an Italian physician, observed in 1890 that lung collapse tended to have a favourable impact on the outcome of the disease. This ended the depressing era of helplessness in the face of advanced TB and active therapy had begun. Later many other surgical procedures, e.g., artificial pneumo-peritoneum, phrenic crush, plombage, thoracoplasty and resection followed. In the postsurgical era, introduction of successful anti-tubercular chemotherapy decreased the need of surgical intervention. Most TB surgeons took to developing cardiac surgery. The need for surgery in India, on the other hand, always remained considerable because of sheer number of cases. With multi drug resistant tuberculosis (MDR-TB) and HIV, the west rediscovered interest in the subject. In the post-globalization phase, publications of interest are coming from former Soviet republics, Japan, Italy, Hungary, Turkey, Argentina, Peru, Pakistan and elsewhere (3-8).

Types of surgical procedures performed for TB (I)

There have been many surgical procedures which have been or are being currently used for diagnosis and management of TB. They can be classified as under:

- (I) Procedures of historical interest
 - (i) Sandbag/diseased side down;
 - (ii) Pneumothorax, artificial;
 - (iii) Intra-pleural pneumonolysis; apicolysis (injection of air, or paraffin-oleo thorax), utilizing open or Thoracoscopic approach of Jacobaeus;
 - (iv) Pneumo-peritoneum;
 - (v) Multiple intercostal neurectomies to decrease costal excursions;
 - (vi) Scalenectomy to decrease upper costal excursions and to depress the lung apex;
 - (vii) Phrenic nerve crush or paralysis;
 - (viii) Transection of accessory muscles of respiration (scalenotomy);
 - (ix) Extra pleural plombage of pneumothorax (space between parietal pleura and endo-thoracic fascia);

- (x) (injection of air, nitrogen, paraffin wax);
- (x) Sub costal and extra periosteal plombage ("bird cage") (periosteal stripped from upper five ribs) Lucite balls used most commonly;
- (xi) Caverostomy (monaldi procedure);
- (xii) Thoracoplasty (staged).

Although many of these procedures are for historical significance in the western world, some of these procedures are still being used, at least in developing countries. These procedures are tailored to address the clinical condition and scenario and form a very important part of the surgeon's armamentarium.

- (II) Diagnostic procedures
 - (i) Thoracocentesis;
 - (ii) Trans thoracic needle aspiration;
 - (iii) Closed/open pleural biopsy;
 - (iv) Bronchoscopy (flexible/rigid), trans-bronchial needle aspiration;
 - (v) Mediastinoscopy/ anterior mediastinoscopy (Chamberlain procedure);
 - (vi) Thoracoscopy (video-assisted thoracic surgery);
 - (vii) Exploratory/diagnostic thoracostomy-wedge biopsy.
- (III) Therapeutic procedures
 - (i) Decortication—with or without lung resection;
 - (ii) Drainage (closed/open) (temporary/permanent); pleuro-cutaneous window;
 - (iii) Thoracotomy with resection;
 - Segment/wedge
 - Lobectomy
 - Pneumonectomy (trans-pleural; extra pleural; completion)
 - (iv) Chest wall/vertebral body-disc resection/stabilization;
 - (v) Muscle flaps (myoplasty);
 - (vi) Thoracoplasty (modified/tailored);
 - (vii) Omental transfer.

Summary of surgical options in different clinical conditions of TB

Persistently active disease

The decision about proper case selection is the most important one in this situation. There is a justified indication for surgery in only some of the selected cases in this category. These situations are:

- (I) The disease is sufficiently localized;
- (II) Adequate trial of anti-tubercular treatment (ATT) has been given;
- (III) There has been drug failure (drug resistance);

- (IV) Patient is a chronic secretor;
- (V) Life-threatening complications.

These are broad indications for surgery in patients having persistently sputum positive status in spite of supervised therapy. Some of these patients may be drug-resistant TB cases.

However, there are specific situations listed below where surgery is a good adjuvant in the management (3):

- (I) When sputum smear or culture is positive for AFB, despite four to six months of appropriate and supervised ATT;
- (II) When there have been two or more relapses;
- (III) One or more relapse while on therapy;
- (IV) The organism has been shown to be resistant on culture and sensitivity;
- (V) When the patient is likely to relapse in the judgment of the physician;
- (VI) Anticipated non-compliance in an admitted patient after discharge.

Surgery plays an important role in the overall management of MDR-TB with acceptable mortality and morbidity (9-15). Surgical interventions, in carefully selected cases, along with 2nd line ATT appears as the most favourable option since even the best available medical therapy alone only provides bacteriological cure in the order of 44-77% vis-à-vis more than 90% success rate with adjuvant surgery (12). Operative mortality is no longer a prohibitive issue, with most series reporting fewer than 3% early mortality (4,9). Though operative mortality has decreased, significant morbidity continues to be a nagging problem, broncho-pleural fistula (BPF) with empyema formation being the most distressing manifestation. In thoracic surgery, poor nutritional status and positive sputum are associated with higher rate of complications. Unequivocal consensus is lacking in the literature regarding the application of peri-operative ATT. The rationale behind selecting the exact timing of intervention needs to be logical and scientific, and whereas it appears logical to use surgery after a defined induction phase of chemotherapy, a scientifically defined induction phase has yet to be worked out. Generally accepted timing of surgery is after three months of carefully prescribed 2nd line ATT, achieving optimal bacterial suppression at the time of surgery yet avoiding delaying the surgery to a point where the bacillary load is at a perilous high. Continuation of drugs for 18-24 months postoperatively seems reasonable by most authors, though given the economics involved, completion of this task is frankly daunting, if not utopian. Indications of surgery in MDR-TB remain a contentious issue, however broad consensus is now apparent. Bacteriological cure in many series has been fairly impressive, with well over 90% success achieved with adjuvant surgery. Occasionally,

thoracoplasty rather than lung resection surgery is justified in some patients having bilateral disease in such a setting (Figure 1).

Hemoptysis

Surgery is not immediately required in cases of hemoptysis caused by pulmonary TB. Massive recurrent hemoptysis is the only justified indication in this setting. Conservative measures like positioning the good lung up after localizing the site, antibiotics, rest and sedation are almost always successful in controlling lung bleeding and surgery can be planned on an elective basis. Very often, post tubercular cavities are colonized by aspergillus fungus (aspergilloma) resulting in recurrent haemoptysis (Figure 2). There are interventional measures other than surgery, which have their selected role in appropriate situations (3):

- Endo-tracheal intubation to secure airway, suctioning;
- Endo-bronchial tamponade with Fogarty catheter;
- Laser photocoagulation (Nd-yag or argon);
- Endo-bronchial haemostatic agents;
- Selective bronchial artery embolization.

However, surgical resection of involved portions of the lung is the most definitive and curative modality for treating massive and recurrent haemoptysis (16). These are challenging surgeries involving careful dissection because of dense and unpredictable adhesions. A properly placed double lumen endo-tracheal tube, by which the anaesthesiologist can collapse or inflate the lung depending upon the needs of the surgeon, is crucial. Position of this tube is confirmed with paediatric fibre-optic bronchoscope and the time spent here is time well spent. This also protects the other healthy lung and ensures safety during surgery. The dissection of vascular structures at hilum or in the fissure requires precise combination of sharp and blunt dissection. Adhesions are always a major challenge in this surgery. Use of a trans-fixation suture or double ligature on the proximal side while dividing arteries and veins is crucial to prevent catastrophic post operative haemorrhage. Bronchus is closed with a bronchial stump stapler or interrupted sutures. Equally good results have been shown by either of these techniques.

Empyema

Empyema is a challenge, and requires a common sense approach, for its management (3). The management depends upon the stage of presentation. Most of the cases can be effectively managed with prolonged and expert inter-costal tube management. In the sub acute stage, drainage can be assisted by either video-assisted thoracic debridement or instillation of intra-pleural anti-fibrinolytic agents like streptokinase or urokinase. Decortication



Figure 1. Post-operative X-ray of a patient who has undergone thoracoplasty for persistent sputum positive status.



Figure 2. X-ray chest of a patient of aspergilloma in right upper lobe.



Figure 3. A case of tubercular empyema. Even after appropriate decortication, the lung fails to fully re-expand to fill the pleural space. This case is hence suited for an attending thoracoplasty.

is indicated in persistent pleural spaces with late fibrino-purulent stage. Thoracoplasty is partial decostalization of the thoracic cage to obliterate persistent pleural space. Whenever lung is unlikely to expand because of extensive disease or multiple BPF, thoracoplasty is an appropriate intervention (Figure 3) and is required quite often in our setting. Post operative empyema or persisting space problems almost always require thoracoplasty for ultimate resolution.

Other procedures

Open window thoracostomy

Eloesser described a procedure to establish long term open drainage of chronic empyema cavities in 1935. The procedure basically involves creating an open window thoracostomy in the chest wall for facilitating long term open drainage without the need for an indwelling catheter. Various modifications of the procedure have been developed and described in the literature. It is an excellent procedure, the efficacy of the procedure in the management being matched by the beauty of its simplicity. Two to three ribs overlying the empyema cavity in the axillary region are partially resected and the underlying pleura is sutured with the skin using interrupted sutures. With good drainage being established, the empyema cavity slowly heals and many a times closes over a period of months. Kohli and colleagues described complete expansion of lung in 56% of 50 patients treated with open window thoracostomy over a period of 3 to 24 months after creating the flap (17) (Figure 4). Any patient of chronic empyema in whom the lung has not



Figure 4. Fully healed pleuro-cutaneous window, eight months after the procedure.

expanded after an adequate period of closed chest tube drainage and who is judged to be not suitable for decortication because of diseased underlying lung can be managed with this procedure with excellent results.

Bronchoscopy

Both rigid and fibre-optic bronchoscopy are excellent procedures and every thoracic surgeon should be able to perform them well. It is required in pre-operative evaluation prior to all these surgical operations. Sometimes, bronchoscopy is needed in post-operative period to remove thick secretions or blood clots from the tracheo-bronchial tree.

Mediastinoscopy

It is required less often nowadays. However, a mediastinal lymphadenopathy, which can be TB, sarcoidosis or lymphoma, is a perplexing clinical situation and if other measures fail to show a conclusive diagnosis, mediastinoscopy is a justified.

Adjuncts to surgery

Pre-operative work up of a thoracic surgical patient

There are some well-established pre-requisites before a patient is taken up for surgery. It is of utmost importance that a detailed discussion is held with the patient and his relatives. This should include an open talk about the natural course of the disease in the absence of any surgical intervention and the exact aim

and objective of the proposed surgery in a given case. Risks of surgery and anaesthesia are carefully explained and also the short term and long term results, if surgery is successful. It is of vital importance that a patient of pulmonary TB has taken an adequate course of ATT before the surgical decision is taken. Even an episode of massive hemoptysis as a presenting feature of pulmonary TB in a non-treated case is rarely an indication of surgical intervention. Patient's cardio-respiratory reserve to withstand surgery of this magnitude or proposed lung resection is carefully assessed. Various criteria have been laid down for different surgeries and decision should be made jointly by the thoracic surgeons and the chest physician about the fitness of a given case after taking into account all the factors. Patients are urged to stop smoking at least three weeks before surgery in order to ensure better post-operative results. Post-operative physiotherapy exercises like deep breathing, coughing and shoulder exercises are taught to the patient in the pre-operative period while forewarning him or her about a certain amount of expected post-operative pain. The patient should be as 'dry' as possible before surgery, meaning thereby that sputum or pus production (in cases of empyema) should be minimized by appropriate measures like antibiotics, postural drainage, respiratory exercises, steam inhalation and nebulizers etc. Some of these patients are quite weak and depleted nutritionally. Their nutritional status is built up before surgery by rest and adequate diet ensured by hospitalization.

Post-operative management

Results in surgery for TB and inflammatory lung disease improve if attention to detail is given in post-operative period. Initial management is ideally done in an Intensive Care Unit (ICU). Antibiotics and painkillers are routinely given. Blood is transfused as per requirements. Respiratory exercises should be encouraged and all measures to relieve pain should be taken. Incentive spirometry is a useful tool to achieve these aims. Care of the chest tubes is an essential ingredient of this care and they should be removed only when their output has minimised sufficiently. Persistent air leaks, development of BPF, residual pleural space are the most important issues to be watched for in the post-operative period and onwards. These complications may require various kinds of intervention, including open window thoracostomy and thoracoplasty.

Results after surgery for pulmonary tuberculosis

Recent published series have demonstrated mortality ranging from 0% to 3.1% (3,4,18-22). Morbidity reported in most series

ranges from 3% to 53.7%. Postoperative empyema and BPF are best managed by prolonged tube drainage followed by open-window thoracostomy and thoracoplasty, if required.

Conclusions

Surgery for complications and sequel of pulmonary TB still remain an important intervention for alleviation of human misery. It is a high cost and sophisticated intervention, which demands high levels of surgical skill and judgment. There is a continued need to further develop skills and techniques in this area. All these issues require continued commitment from all the stakeholders to improve the results of this highly complicated and complex set of surgical patients (3).

Use of newer technologies like surgical staplers, refined blood transfusion technologies, argon beam coagulation, monitoring devices and safer anaesthesia have improved the results of surgery substantially. The number of surgeons engaged in this specific field of pathology has declined tremendously with the advent of ATT. The ravages of TB are on the rise again especially since drug resistant TB has come to the fore. This calls for a dire need to re-invent the wheel of TB-surgery to adequately address this health hazard. The amalgamation of the older TB surgical techniques with the current developments of surgery in general, is needed.

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Cite this article as: Dewan RK, Moodley L. Resurgence of therapeutically destitute tuberculosis: amalgamation of old and newer techniques. *J Thorac Dis* 2014;6(3):196-201. doi: 10.3978/j.issn.2072-1439.2013.12.19

Aspergilloma and the surgeon

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ABSTRACT

Aspergillus fungus is a ubiquitous saprophyte that is the causative organism for the development of an aspergilloma. The most common species causing an aspergilloma is the *Aspergillus fumigatus*. An aspergilloma is a conglomeration of mucus, inflammatory cells and altered blood elements. Aspergillomas typically form in pre-existing lung pathology, most notably and commonly in old healed tuberculosis cavities. They are classified into simple and complex types that have clinical relevance. Symptoms are very variable and it is not uncommon to incidentally find a lung aspergilloma. In most case series, the most common presenting symptom is haemoptysis which varies from mild to catastrophic bleeds. Given the limited information about the natural history of the disease, there is unfortunately no recognised factor or variable which can predict how an aspergilloma will manifest itself, hence the manner of treatment is a still a topic of debate among treating physicians. The mainstay of treatment is surgical intervention and medical options although disappointing at the current stage, require further investigation in light of the newer available anti-fungal agents. The need for surgical intervention is however not as clear-cut as one would like, since many patients have multiple co-morbidities and other diffuse or focal lung pathology, making the decision process indeterminate in certain instances. In this review, we focus on the different surgical options available for the management of aspergilloma across variable clinical settings, and we propose an approach to its management.

KEYWORDS

Aspergilloma; clinical course; surgical management

J Thorac Dis 2014;6(3):202-209. doi: 10.3978/j.issn.2072-1439.2013.12.40

Introduction

The aspergillus fungus is responsible for many clinical entities or a wide spectrum of pathology in the human body. Lung manifestations are quite diverse and include:

- (I) Pulmonary aspergilloma;
- (II) Allergic bronchopulmonary aspergillosis;
- (III) Chronic necrotizing pulmonary aspergillosis;
- (IV) Invasive aspergillosis (1).

This article focuses on pulmonary aspergilloma and the

surgical management thereof.

Aspergilli are saprophytes and are present worldwide. Most human infections (95%) are caused by the species *aspergillus fumigatus* (2).

Thoracic aspergillomas

Most pulmonary aspergillomas are found in the lung tissue. Being saprophytes, they infest a pre-existing cavity in the lung. These cavities may be the result of previous pathology including tuberculosis, healed abscesses, sarcoidosis, pneumoconiosis or cystic fibrosis (3-7).

An unusual presentation of aspergilli infection is endo-bronchial aspergilloma (1,8,9). This is simply the fungus found endo-bronchially and it may occur with or without pulmonary involvement (1).

Pleural aspergillomas are usually found in the scenario of chronic empyemas, where the suppuration produces a conducive environment for the colonisation of the aspergillus (10).

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Submitted Dec 09, 2013. Accepted for publication Dec 24, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

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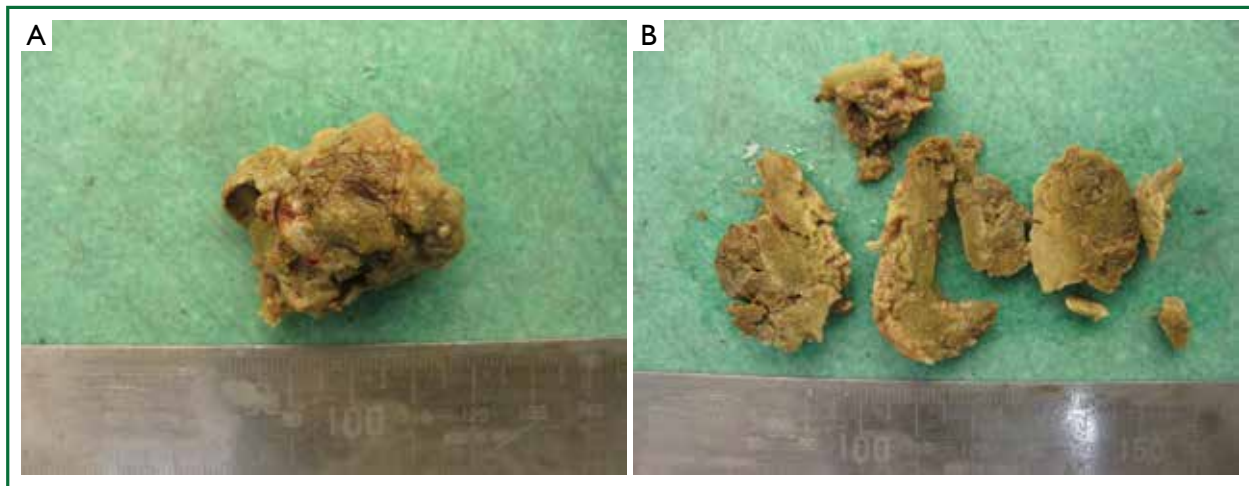


Figure 1. Gross picture of a Mycetoma. (A) Intact specimen; (B) Cross section.

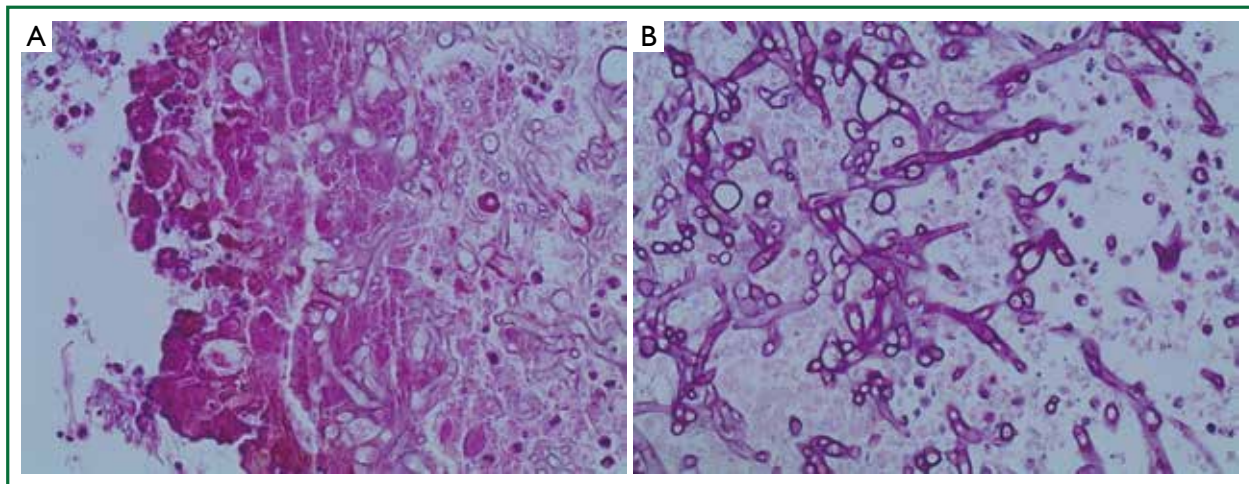


Figure 2. Histology of aspergilloma. (A) Microscopic features of the aspergilloma; (B) Magnified slide to show the acute angulations and the septated hyphae of the aspergillus fungus.

Anatomy

Macroscopically

The aspergillus fungus colonizes a cavity in the lung (mostly upper lobes) (11) and forms a mass of varying size. It is also known as a fungus ball or a mycetoma. Grossly it appears as a clay ball with rough edges (Figure 1A,B).

Microscopically

Classically the fungus has septated hyphae with acute angulations (Figure 2A,B).

Encompassed in the conglomerate mass is fibrin, inflammatory

cells and other altered blood elements (12).

Classification

It is important in the management of aspergillomas to understand the classification fashioned by Belcher and Plummer (13,14) as it has important clinical ramifications.

They divided pulmonary aspergillomas into simple and complex types.

Simple aspergilloma

Here the aspergilloma develops in a thin-walled cavity that has adjacent normal lung parenchyma (Figure 3A-C). Herein

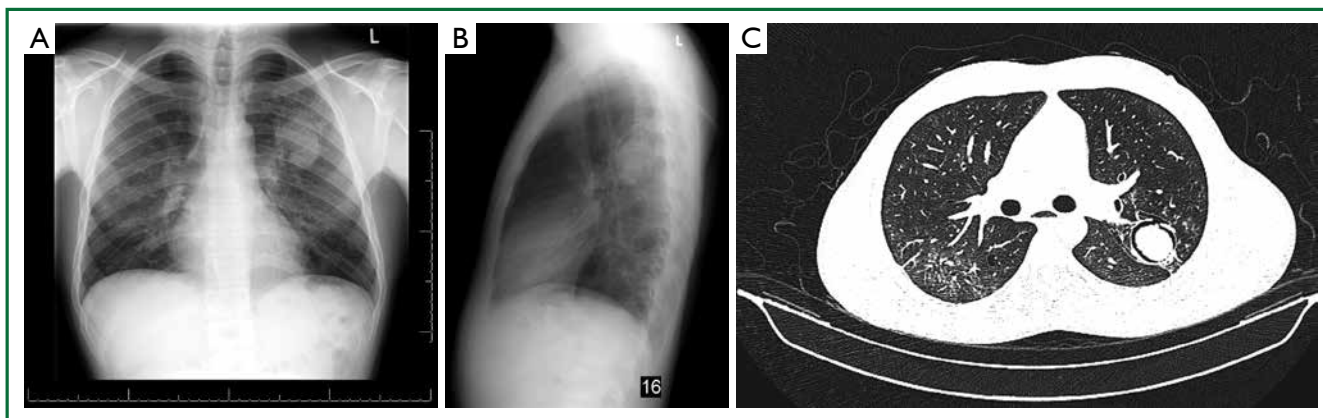


Figure 3. Radiology of a simple aspergilloma. (A) PA chest x-ray; (B) Lateral view. Note the air-crescent sign; (C) CT picture of the same aspergilloma.

the disease process is much more localized. The pleura is not involved in the disease process (3,14-16).

Complex aspergilloma

The disease process is much more aggressive and diffuse. There is much more destruction of the lung parenchyma than a simple cavity. In most instances, the adjacent pleura is also involved in the pathology. The aspergillus fungus has merely colonised this unhealthy destroyed tissue. The lung and pleural pathology is usually due to pre-existing disease processes (most commonly tuberculosis) (3,17) (Figure 4A-D). These patients are not uncommonly sicker and may even have reduced pulmonary function tests. Cavities are usually thick walled due to repeated infections. There may also be more widespread lung pathology in other lobes of the lung and even bilateral disease.

Pathophysiology

The aspergillus fungus is commonly found in sputum cultures (11). They invade the lung through the respiratory tract and colonize the pre-existing cavity which has a direct communication to a bronchiole (18). There may be tissue invasion of the lung causing the more invasive and aggressive forms of pulmonary aspergillosis or a chronic necrotizing form (19).

Predisposing conditions

The most common preceding lung lesion is an open healed TB cavity. The incidence of cavitary TB being affected by aspergilloma formation is 11-17% (3,20). Other conditions include sarcoidosis, abscesses, cysts, bronchiectasis, cavitary tumours and bullae (3,18,21,22).

Chen *et al.* (22) found that the interval between the diagnosis of TB and aspergilloma development varied from less than a year to up to 30 years. They quoted an average of 9.2 years to aspergilloma development.

It is also reported that aspergillomas may develop in healthy lungs, whereby the aspergilli fungi secrete a digestive enzyme in the surrounding lung to create a space for its colonisation (2,23).

Aspergilli can proliferate and easily colonize a cavity as phagocytosis is hindered in cavities found in the lung.

Clinical course of aspergillomas

The natural history has been poorly studied. Moreover, the underlying disease process may confound the natural history of an aspergilloma (21,24,25). There is no consistent variable that can predict the outcome of an aspergilloma (14,22).

Aspergillomas can be extremely variable in its course, ranging from undergoing spontaneous lysis (7-10%) to causing severe haemoptysis (22,26,27).

Up to 30% of patients with minor haemoptysis may go on to develop life-threatening haemoptysis (28).

It is also reported that the severity of haemoptysis is not related to the size, the number of aspergillomas nor to the underlying lung disease, erythrocyte sedimentation rate, eosinophil count or to the response to skin prick tests (29).

Jewkes *et al.* reported a recurrence of aspergillomas post-surgery to be in the region of 7% (29,30).

Symptomatology

This can be diverse ranging from patients being asymptomatic to experiencing life-threatening haemoptysis.

Many-a-times patients present with symptoms related to the

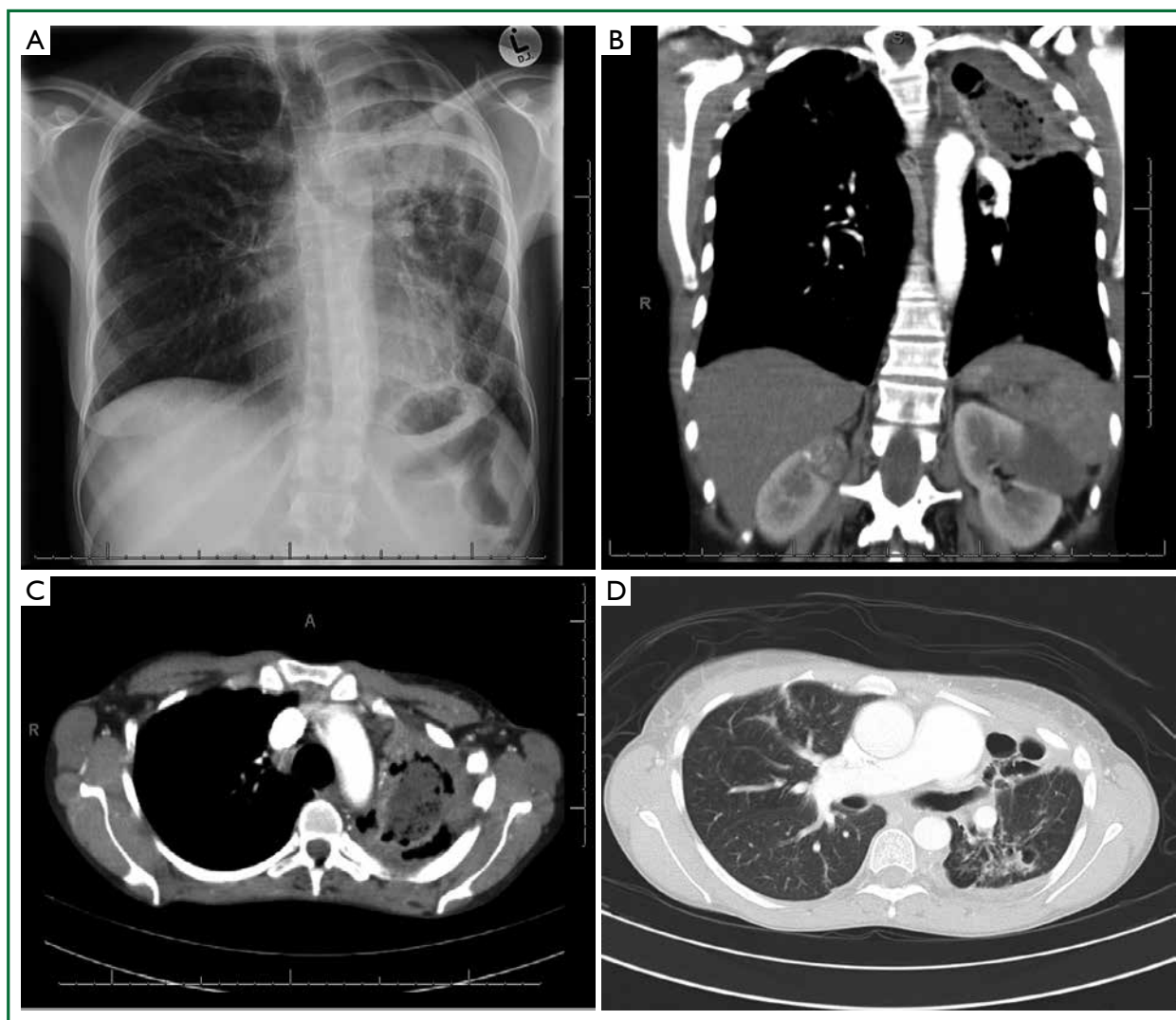


Figure 4. Radiology of a complex aspergilloma. (A) PA chest x-ray showing a complex aspergilloma in the left upper lobe; (B) Coronal CT scan of the complex aspergilloma; (C) Axial CT picture of the complex aspergilloma; (D) CT scan of the same patient showing the diffuse bronchiectasis and cavitation involving the lingula and superior segment of the left lower lobe.

underlying diseased lung.

Most patients present with a productive cough containing either mucus, pus or blood (2). Dyspnoea is usually due to primary lung disease (3,31).

Most series report haemoptysis as being the most common symptom with an incidence of around 80% (21,32).

What causes haemoptysis?

The likelihood of massive haemoptysis in a patient with an aspergilloma is unpredictable, in part because of the lack of prospective data about the natural history of the condition.

The size, complexity of the aspergilloma or a sentinel bleed

cannot predict if patients will progress to massive haemoptysis (11).

Possibilities as to the cause of haemoptysis are (2,13,29,33):

- (I) Erosion (local invasion) of adjacent vessels;
- (II) Mechanical irritation of exposed vasculature in the cavity;
- (III) The release of an endotoxin and trypsin like proteolytic enzyme from the fungus;
- (IV) Presumed acute superimposed bacterial infection.

Radiological signs

The radiological signs are variable and classically the mycetoma is surrounded by a crescent of air in the cavity, but this really depends on how large the aspergilloma is within the cavity. The

Table 1. Early surgical intervention irrespective of symptoms.

Proponents	Opponents
<ol style="list-style-type: none"> 1. Risk of massive haemoptysis (up to 30%) if conservative approach is adopted 2. No identifiable variable predicting complications 3. Better to operate under elective conditions rather than emergent conditions when patients may be more clinically unstable 	<ol style="list-style-type: none"> 1. As symptoms are variable, it is better to offer surgery only if complications manifest 2. Surgery very difficult and fraught with morbidities

walls of the cavity can be either thin or thick walled.

The radiological appearance of an aspergilloma forms a differential diagnosis of a “ball-in-a-hole” which also includes lung abscesses, cavitary carcinomas, and ruptured hydatid cysts, to name a few.

When the cavity is much larger than the aspergilloma, it is seen to be mobile and it assumes different positions in the cavity depending on positional change of the patient. This change of position is gravity dependent.

Additional pleural and lung parenchymal changes dictate whether the aspergilloma is of a simple or complex type.

Treatment

The treatment for aspergillomas remains controversial and there is no consensus amongst the treating physicians. This is mainly because of the variability of the underlying lung disease process. The optimal treatment strategy is unknown.

Medical management

The medical management of aspergillomas has a complementary role and has been fairly disappointing, although there are still ongoing investigations into its role (11).

Anti-fungal agents, whether systemic or intra-cavitary have showed no consistent success.

Likewise bronchial artery embolization appears to be a temporary measure and vascular collaterals tend to develop quite soon after embolization.

Surgical management

There is also no consensus regarding the timing of surgery and the type of surgery needed.

Many earlier reports showed a high mortality and morbidity rate (60%) (13,14,26,34-36) after surgical intervention for aspergilloma. This has obviously influenced the bias towards a more conservative and medical management of this condition.

Newer studies from the year 2000 onwards show much

more favourable results with surgical intervention. Akbari *et al.* showed an operative mortality of 3.3% and a 33.3% morbidity (13,37).

Park *et al.* reported a 0.9% operative mortality and 23.6% morbidity in their series of 110 patients (38).

Lee *et al.* (13) recommended surgery for all patients with an aspergilloma and having adequate pulmonary reserve, even if asymptomatic.

Since the current risk of surgery is less than the risk of a massive bleed, the scale seems to be tilting towards early surgical intervention on suitable candidates diagnosed with an aspergilloma. This however positions the role of surgical timing to be debatable (Table 1) (13,22,34,39).

The predicament arises in patients with unsuitable lung function precluding any pulmonary resection. In these cases, one has to carefully balance the risk benefit ratio and in this subset of patients, the more conservative operative procedures come to the fore. These surgical interventions are offered to prevent massive and disastrous haemoptysis from occurring.

Indications for surgical intervention

Assuming patients are functionally optimal for surgery:

- (I) Symptomatic patients with aspergillomas;
- (II) Indeterminate lesions with a high suspicion of lung malignancy;
- (III) Asymptomatic aspergilloma (still controversial).

Types of surgery

- (I) Wedge or segmentectomy.
- (II) Anatomical resections—lobectomy or pneumonectomy.
- (III) Cavernostomy and thoracoplasty.

Wedge/segmentectomy (26)

Usually reserved for simple aspergilloma that is small and either peripheral (wedge) or lies locally within a segment (segmentectomy).



Video 1. Cavernostomy, removal of aspergilloma and thoracoplasty for an apical aspergilloma.

Since a simple aspergilloma is a relatively benign disease and if the whole aspergilloma can be removed by lesser resections, then lung conserving surgery can be undertaken.

Anatomical resection (lobectomy or pneumonectomy)

These operations are usually reserved for a large simple aspergilloma occupying almost the whole lobe or for complex aspergillomas. It is undesirable to leave diseased lung behind if the patient can functionally tolerate anatomical lung resection.

Sometimes the disease process may bridge the fissure and partly occupy the adjacent lobe. This may then require tailoring the lobectomy to include a wedge of the adjacent lobe.

The same principles are adhered to as for the resection of inflammatory diseased lung. The usual precautions when attending this pathology must be applied and respected. Most morbidities and mortalities of case series arise from operating upon complex aspergillomas and many surgeons have been humbled by complications. Some reasons for these complexities include: obliterated pleural space, very stuck hilum and mediastinal surface, increased collateral circulation and patients that are nutritionally disadvantaged.

Cavernostomy and limited thoracoplasty

This type of procedure is reserved for high risk patients with complex aspergillomas, namely patients who functionally would not be able to tolerate anatomical resection. Whether this operation can be extended to other patients, namely those with good lung functions and simple aspergillomas, is still contentious

and is in need of more evidence. At present anatomical resection remains the gold standard.

The goal of this operation is to remove the culprit lesion namely the aspergilloma, close off the communicating bronchioles, collapse down the cavity (via an apicolysis) and perform a limited thoracoplasty to obliterate the resultant space.

It must be stated that this operation is much less tedious than anatomical resections.

It is based on the assumption that the ongoing haemoptysis is most likely due to the aspergilloma and hence this procedure is concentrated only on removing the inciting lesion (aspergilloma) and leaving the rest of the diseased lung *in situ*.

The steps for an apical lung aspergilloma are:

- (I) Tailored high thoracotomy as for a thoracoplasty operation;
- (II) Pleural space entered and lung cut into, to open the cavity;
- (III) Aspergilloma removed in total and cavity washed out;
- (IV) All bronchial communications sutured closed;
- (V) Apicolysis of cavity or lung to be able to collapse the cavity;
- (VI) Cavity sutured closed. One may introduce intercostal muscles into the cavity;
- (VII) Tailored thoracoplasty to collapse the chest wall, and obliterate the resultant space left by the aspergilloma removal. During the thoracoplasty, the first rib may be left intact;
- (VIII) Apical area drained with an intercostal drain;
- (IX) Wound closed in layers (Video 1).

This procedure is a modification of that reported by Daly *et al.* (40,41), wherein a myoplasty was done. Others have described atrophy of the muscles used, due to inactivity (42,43). Some authors have recommended a 2-stage procedure but we recommend it be done in a single setting (40).

A complementary thoracoplasty is advocated to obliterate the space resulting from collapsing of the cavity. This allows one to refrain from the arduous task of freeing the remainder of the lung in the hope that it will fill the space (3). A thoracoplasty may not be required if the aspergilloma is not located apically.

This operation has to be tailored according to size and location of the aspergilloma.

Surgical approach to different clinical scenarios (Figure 5)

If a symptomatic patient has bilateral disease, then it is advisable to perform a bronchoscopy to confirm the site of bleeding, before performing surgery.

If patients are deemed non-surgical candidates, even with the slightest of surgical interventions, then conservative medical treatment has to be adopted.

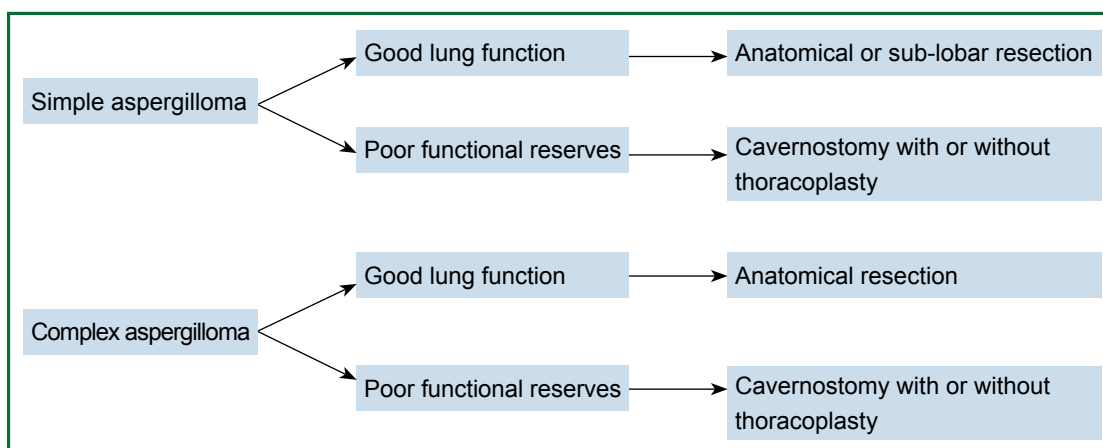


Figure 5. Simplified surgical approach to aspergillomas.

Surgical complications

Surgery for inflammatory lung disease is fraught with morbidity and mortality, hence the earlier, more dated opinion of being conservative with patients having aspergillomas.

Daly *et al.* (41) reported a mortality of 25% and morbidity (including excessive bleeding, residual pleural space, broncho-pleural fistulae and empyema) up to 60%.

Later reports are more favourable (13,28,44).

Summary

Aspergilloma is a result of a saprophytic infection of a diseased lung. The course and prognosis of this subset of patients cannot be predicted with certainty.

There are many surgical options, but one has to carefully choose and tailor the procedure according to the functional stability of the patient (28) (Figure 5).

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Moodley L, Pillay J, Dheda K. Aspergilloma and the surgeon. *J Thorac Dis* 2014;6(3):202-209. doi: 10.3978/j.issn.2072-1439.2013.12.40

Nontuberculous mycobacterial pulmonary infections

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ABSTRACT

Pulmonary infections due to nontuberculous mycobacteria (NTM) are increasingly recognized worldwide. Although over 150 different species of NTM have been described, pulmonary infections are most commonly due to *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, and *Mycobacterium abscessus*. The identification of these organisms in pulmonary specimens does not always equate with active infection; supportive radiographic and clinical findings are needed to establish the diagnosis. It is difficult to eradicate NTM infections. A prolonged course of therapy with a combination of drugs is required. Unfortunately, recurrent infection with new strains of mycobacteria or a relapse of infection caused by the original organism is not uncommon. Surgical resection is appropriate in selected cases of localized disease or in cases in which the infecting organism is resistant to medical therapy. Additionally, surgery may be required for infections complicated by hemoptysis or abscess formation. This review will summarize the practical aspects of the diagnosis and management of NTM thoracic infections, with emphasis on the indications for surgery and the results of surgical intervention. The management of NTM disease in patients with human immunodeficiency virus (HIV) infections is beyond the scope of this article and, unless otherwise noted, comments apply to hosts without HIV infection.

KEYWORDS

Nontuberculous mycobacterium (NTM); mycobacterium avium intracellulare (MAI); bronchiectasis; mycobacterium abscessus; hot tub lung

J Thorac Dis 2014;6(3):210-220. doi: 10.3978/j.issn.2072-1439.2013.12.24

Introduction

Historically, human infections due to *Mycobacterium* were due almost exclusively to *Mycobacterium tuberculosis* (TB); the extensive societal impact of this infection is legendary. More recently, other species of mycobacterium causing clinical disease have been identified and, in many geographical regions, cause greater disease burden than TB. These organisms are referred to by a variety of collective names—anonymous or atypical mycobacteria, mycobacteria other than tuberculosis (MOTT) and nontuberculous mycobacteria (NTM). In this paper, the acronym NTM is used to collectively describe NTM organisms.

Similar to TB, NTM infections can occur throughout

the body. However, pulmonary infections, lymphadenitis, and skin and soft tissue infections are the most commonly described attributable human infections (1). Both host factors and organism characteristics influence the susceptibility and manifestations of infection (1).

Overview of atypical mycobacteria

Mycobacteria are aerobic, non-motile organisms that appear positive with acid-fast alcohol stains (2). They have a lipid rich, hydrophobic cell wall, which is substantially thicker than most other bacteria (2). The thickness and composition of the cell wall renders mycobacteria impermeable to hydrophilic nutrients and resistant to heavy metals, disinfectants, and antibiotics (3).

NTM are ubiquitous in the environment with the heaviest concentrations found in soil and water sources. They are associated with biofilm formation (4), which contributes to disinfectant and antibiotic resistance (3,5). The hydrophobicity of NTM results in preferential aerosolization from water (6), and many of these organisms are resistant to high temperature and are relatively resistant to low pH (7,8).

Given these characteristics of NTM it is not surprising that

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Submitted Jul 12, 2013. Accepted for publication Dec 12, 2013. Available at www.jthoracdis.com

ISSN: 2072-1439

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Table 1. Atypical *Mycobacteria* causing lung disease (not complete list; other species may cause disease).

Slow-growing mycobacteria

Mycobacterium avium complex (includes *avium* and *intracellulare* species)

M. kansasii

M. xenopi

M. simiae

Rapid-growing mycobacteria

M. Abscessus

M. Fortuitium

M. chelonae

drinking water, household plumbing, peat rich soils, brackish marshes, and drainage water are reservoirs of NTM (9). Water systems in hospitals, hemodialysis centers, and dental offices have particularly high rates of mycobacterium colonization (10). When sampling a potential source for NTM colonization, biofilms should be included in the sampled specimens given the organisms' predilection for biofilm adherence (11-13).

Currently, there are more than 150 species of *Mycobacterium* and it is likely that more will be discovered. The rapid increase in identified species in recent years is due to improved culturing techniques and more precise differentiations of species. Species differentiation improved dramatically with the development of molecular techniques that enabled the detection of differences in the 16S rRNA gene (14). This gene is highly conserved amongst species and slight differences characterize different species. A full listing of recognized NTM can be found at www.bacterio.cict.fr/m/mycobacterium.html.

Although mycobacterium organisms other than TB were identified soon after Koch's identification of TB in 1882, it was not until the 1950's when they were recognized to cause human disease (15). Historically, different classification systems have been proposed, but NTM are most commonly classified by growth rate—either slowly growing or rapidly growing (Table 1). By far, the most common organism associated with pulmonary disease is the *Mycobacterium avium* complex (MAC), a slow growing NTM that encompasses many subspecies including *avium*, *silvaticum*, *hominissuis*, and *paratuberculosis*, as well as the species *intracellulare*, *arosiense*, *chimaera*, *colombiense*, *marseillense*, *timonense*, *bouchedurhonense*, and *ituriense*. *Mycobacterium kasassii*, also a slow growing organism, is the second most common cause of pulmonary infections in the United States and is responsible for pockets of infection in England (16,17)

M. abscessus, is the most commonly isolated rapidly growing NTM and is the third most common cause of lung disease (16). Although most NTM lung infections are caused by these three organisms, it is important to recognize that many other NTM may cause pulmonary disease in both immunocompetent and immunocompromised hosts. Thus, the pathogenic significance of a NTM specimen must be determined in the context of a patient's clinical presentation (18,19).

Epidemiology

Over the last three decades, it has been suggested that the incidence of both NTM laboratory isolation and disease prevalence is increasing. This change has been attributed, in part, to improved culturing techniques, coupled with greater disease awareness and a true increase in disease prevalence. However, it is challenging to accurately characterize the incidence and prevalence of NTM pulmonary infections since isolation of the organism does not universally indicate clinical infection. Additionally, NTM infections, unlike TB, do not require public health reporting, which hinders an accurate understanding of epidemiology. Furthermore, nearly all epidemiologic data is reported from the United States, Japan, and Europe, and thus, may not be reflective of changes in prevalence worldwide.

When similar culture techniques are employed, environmental recovery is similar in various geographical regions (20). In Western societies, most laboratories report a dramatically greater prevalence of NTM than TB (21). However, not all positive NTM cultures represent infection. A recent analysis showed that approximately half of those with positive NTM respiratory cultures fulfilled clinical criteria for active infection (22). In Kendall and Winthrop's review, the prevalence of NTM pulmonary infections based on laboratory records coupled with clinical characteristics varied between 4.1 and 14.1 per 100,000 patient years (23). In patients greater than 65 years the prevalence was 47 per 100,000 patient years (24). Women are also more likely to have NTM disease than men (24), the disease prevalence increases with age (25), and it is more common in the West and Southeast (24). In the United States, Caucasians account for 90% of cases followed by Asians/Pacific Islanders and Blacks (24).

In a review from Oregon, NTM pulmonary infections were associated with more densely populated areas, suggesting that urban municipal water supply exposure predisposed individuals to disease (26). However, in Japan, NTM was more commonly found in farmers and gardeners than in urban patients with bronchiectasis, suggesting a greater etiologic role for exposure to soil than water sources (27).

Skin testing for MAC antigens suggests that exposure to MAC is not uncommon and varies greatly geographically. Early studies of United States Navy recruits demonstrated reactivity to MAC antigens in 10-20% of recruits from northern and western areas of the United States, but over 70% of recruits from the southeast demonstrated MAC antigen reactivity (28).

Currently, greater than 90% of NTM cultures in the United States are from pulmonary secretions (29). At the height of the human immunodeficiency virus (HIV) epidemic, NTM was more commonly cultured from blood due to disseminated infections, but anti-retroviral therapy and appropriate prophylaxis have substantially decreased the incidence of disseminated disease in this population (30).

For reasons that are not fully understood, some pathogenic NTM organisms tend to cluster in specific geographical distributions. In the United States, *M. kansasii* is most commonly seen in southern and central regions (16). However, even outside of geographically endemic areas for *M. kansasii*, disease prevalence is high in areas with a substantial HIV disease (31). *M. abscessus* is most commonly identified in the southeastern United States from Florida to Texas. However, it has also been identified outside of this region.

NTM culture and Identification

When NTM are sought, care must be taken when processing samples. Specimens from non-sterile sites, such as sputum, require decontamination to avoid overgrowth by bacteria or fungi. NTM are not visible on routine Gram stain, so the fluorochrome technique for staining is recommended (2). Culturing specimens in both broth and solid media is recommended. Broth cultures offer the advantage of greater yield and more rapid growth, but they are more susceptible to bacterial overgrowth. Growth of specimens on solid media allows an opportunity to visualize characteristics of colony growth (32). Cultured NTM should be identified to the species level to guide decisions regarding clinical relevance and appropriate therapy. Speciation of NTM can be achieved with polymerase chain reactions, gene probe assays, and high-performance liquid chromatography (33).

When NTM is cultured from a human sample such as sputum, its clinical significance needs to be determined. In some instances the mycobacterial organisms are pathogenic; but in others they are commensal. Many NTM are less virulent than *M. tuberculosis*. Additionally, since NTM are so commonly identified in water systems (9), it is important to assure that NTM in a clinical specimen, especially when present in low concentration, is not the result of contamination from water sources.

Mechanism of infection

The mode of transmission to humans has not been defined. In many instances the Koch postulates do not prevail. Unlike TB, person-to-person transmission has not been convincingly demonstrated. Although animals may serve as a reservoir for NTM, animal to human transmission is not thought to occur. However, shared drinking water systems with animals may serve as a source of infection (34).

Although the exact route of NTM infection is not established with certainty, based on NTM environmental distribution, it is very likely that the organism is ingested, inhaled, or implanted. Cervical lymphadenitis due to NTM occurs more frequently in children, coincident at the time that they are exploring outdoors and there is trauma to gums due to erupting teeth (35). Thus, it is assumed that NTM enter the tissues via the mouth. Previous infections leading to cervical lymphadenitis were most often due to *Mycobacterium scrofulaceum*; now most are due to MAC (35).

Aerosolization of droplets small enough to enter the alveoli is the likely route of acquisition of pulmonary disease. Bathroom showers have been implicated as a primary source of exposure to aerosolized NTM (36). Households with water heater temperatures ≤ 50 °C are more likely to demonstrate colonization of their water supply with NTM than those with water heater temperature ≥ 55 °C (37). Potting soils, particularly those enriched with peat, have a high concentration of NTM and dust generated from soil may produce particles small enough particles to enter the alveoli (38). However, a case controlled cohort study by Dirac *et al.* looked at "aerosol-generating activities in the home and found that the only activity predictive of the development of NTM lung disease was the use of a spray bottle for watering plants (39).

Contamination of hospital water supplies, medical equipment, including bronchoscopes and endoscopes, and contaminated dialysis solutions, has led to both NTM colonization and nosocomial outbreaks of disease. The site of disease is dependent upon the exposure, but cutaneous abscesses, pulmonary disease, meningitis, and surgical site infections have all been described (10). It is hypothesized that regulations to limit hospital water system temperatures to prevent scalding hinder the control of NTM (40). Advances in DNA techniques have allowed easier and more rapid identification of the source of NTM in the setting of nosocomial outbreaks. However, recognition of nosocomial outbreaks is highly dependent upon clinical suspicion and investigation.

Susceptibility to NTM infection

Nearly everyone is presumed exposed to NTM, yet most do

not develop clinical signs of infection. The factors predisposing to infection are not well understood, but likely are due to an interaction between host defense mechanisms and the load of clinical exposure.

Disseminated disease is most commonly seen in association with profound immunosuppression. In HIV infected patients, dissemination does not typically occur unless the CD-4+ T-lymphocyte count is below 50/uL (41). Structural lung disease, such as chronic obstructive pulmonary disease (COPD), silicosis, pneumoconiosis or prior TB infection, predisposes to pulmonary infection. Nodular bronchiectasis is very strongly associated with NTM infections.

NTM infections are of particular importance in patients who are awaiting or have undergone lung transplantation and those with cystic fibrosis (CF) (42,43). The manifestations of infection are protean and may affect soft tissues, bones, and joints, as well as the lung (44). As in other populations, isolation of NTM organisms is not uncommon among transplant patients, but most have transient colonization and do not require treatment. Knoll *et al.*, reviewed lung transplant recipients from 1990-2005 (45). NTM, especially, *M. avium* was commonly found in the respiratory secretions of this cohort, but a minority of patients fulfilled criteria for active pulmonary infections (45). However, lung transplant patients with NTM after transplantation have a higher mortality (46). In a multi-centered cohort study of 1,582 patients with CF, 6.6% demonstrated sputum positivity for NTM, while 3.3% fulfilled bacteriologic criteria for disease (47). A prior multicenter study showed a 13% prevalence of NTM sputum positivity (48). Molecular typing of the organisms suggested neither person-to-person transmission nor nosocomial spread was common. In study groups, *M. avium* and *M. abscessus* were most commonly identified.

Interleukin-12 (IL-12) and interferon-gamma (INF- γ) are crucial elements of the host defense response to NTM. Defects in these pathways increase susceptibility to NTM infections (49). Abnormalities in INF- γ receptors have been described in association with NTM infections in both individuals and familial clusterings of disease (15). However, therapy with aerosolized INF- γ has been clinically unrewarding.

Increasing therapeutic use of tumor necrosis factor-alpha (TNF- α) receptor antagonist drugs, especially in rheumatoid arthritis and other connective tissue diseases, has been associated with a concomitant increase in NTM infections. In a review of cases reported to the FDA, Winthrop *et al.*, finds that most cases of NTM infection were due to lung infections, but there were significant extra-pulmonary sites of involvement as well (50). *M. avium* was responsible for half of the cases. In a review of 8,000 users of anti-TNF- α agents, the rate of NTM infections was

74/100,000 person years (51).

Measures taken may reduce exposure to NTM, and may be warranted in patients with recognized risk factors such as immunosuppression or structural lung disease. Bathroom showers with large diameter water streams have been suggested as preferable to one producing a fine mist. However, a prospective study examining risk factors for NTM lung infection was unable to correlate infection with shower exposure (52). It is presumed beneficial to use a bathroom vent that can exhaust the aerosol rapidly. Higher water temperatures with water heater temperatures greater than 55 °C are associated with lower NTM recovery. Thus, increasing the water heater temperature may be advantageous. Additionally, access to well water rather than use of a piped supply might reduce NTM levels.

Filtration of water has theoretical advantages in reducing the passage of NTM, but these filters are expensive and require replacement regularly (53). Chemical disinfection of water also has potentially negative ramifications by changing the microbial flora. Avoidance of hot tubs, especially in enclosed areas, may be beneficial.

Diagnosis of NTM pulmonary infections

Unlike TB, the isolation of NTM in pulmonary specimens does not equate with disease.

In an effort to standardize the definition of NTM infection, the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) jointly published guidelines in 2007 (16). The diagnosis of NTM pulmonary infection requires the presence of symptoms, radiologic abnormalities, and microbiologic cultures in conjunction with the exclusion of other potential etiologies. Clinical symptoms vary in scope and intensity but chronic cough, often with purulent sputum, is common. Hemoptysis may also be present. Systemic symptoms including malaise, fatigue, and weight loss may occur often in association with advancing disease. As demonstrated in Figures 1-4, various radiographic patterns may be seen in patients with NTM pulmonary infections. Fibrocavitary disease is commonly identified on chest roentgenograms. Characteristic findings include thin walled cavities with an upper lobe distribution and surrounding pleural abnormalities. There is no radiographic finding to reliably differentiate fibrocavitary NTM from TB. NTM in conjunction with nodular bronchiectasis may be visible on chest radiograph, but is best appreciated on high resolution chest computed tomography (HRCT). Characteristic findings include clusters of small nodules usually less than 0.5 mm—the so-called tree-in-bud sign. Larger nodules, with or without cavitation, may occur, which are suspicious for malignancy.

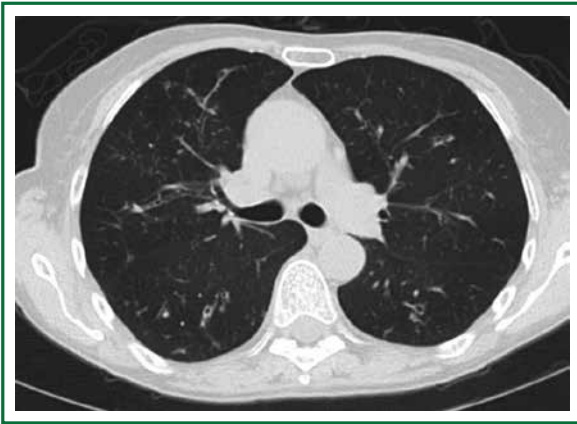


Figure 1. Tree-in bud opacities, most prominent in the right middle lobe due to mycobacterium avium intracellulare (MAI) infection.



Figure 2. Cavitating nodule in the right lower lobe due to *Mycobacterium avium* complex (MAC).



Figure 3. Extensive right middle lobe disease with parenchymal destruction due to *Mycobacterium avium* complex (MAC). After a prolonged course with multiple drug therapy, she underwent a right middle lobectomy with a video-assisted thoracoscopy.



Figure 4. “Hot Tub Lung”-Diffuse consolidation due to hypersensitivity pneumonitis (HP) after repeated exposure to *Mycobacterium avium* complex (MAC) in an indoor hot tub. Surgical lung biopsy demonstrated granulomatous inflammation. The patient had marked clinical and radiographic resolution after cessation of exposure.

Uptake of ^{18}F fluorodeoxyglucose (FDG) on PET scan has been described in nodules due to NTM (54). Infected areas of lung parenchyma may demonstrate atelectasis or cystic or saccular bronchiectasis.

Because NTM are ubiquitous in the environment, especially in water sources, a single positive pulmonary specimen does not fulfill microbiologic criteria for infection. Confirmatory microbiologic findings requires culture growth of NTM from either one bronchoalveolar lavage, two sputum samples, or culture from respiratory tissue demonstrating granulomatous histopathology.

Common clinical scenarios of NTM pulmonary infections

There are two commonly encountered patterns of NTM pulmonary infections. Upper lobe fibrocavitary disease historically had been most well described. It commonly occurs in patients with COPD or other structural lung diseases including silicosis, pneumoconiosis, or prior TB infections. Similar to the historical demographics of COPD, infected patients were often older males with a history of underlying lung disease.

In 1989, Prince *et al.*, described a cohort of 21 patients, 19 of whom were women, with NTM pulmonary infections without known underlying lung disease. They presented with slowly progressive nodular opacities on chest radiograph (55). This report led to the subsequent recognition of NTM infections in association with nodular bronchiectasis. The prototypical patient

Table 2. Required monitoring for patients on drug therapy for nontuberculous mycobacteria (NTM).

Test	Drug(s)
Liver enzymes	Azithromycin, clarithromycin, rifampin, rifabutin
White blood cell count	Rifabutin
Visual acuity/color differentiation	Ethambutol
Peripheral neuropathy	Ethambutol
Decreased hearing	Azithromycin, streptomycin
Renal function	Streptomycin

is an older thin female, often with pectus excavatum, scoliosis, and mitral valve prolapse (56). In these patients, it is uncertain if the NTM infection lead to the development of bronchiectasis, or is a consequence of it.

A presentation suggestive of hypersensitivity pneumonitis (HP) has been reported to occur after exposure to aerosolized MAC, most often in association with indoor hot tub use (57,58). HP has also been suggested to occur in workers exposed to metalworking fluid (59). However, it is often challenging to demonstrate growth of NTM in the workplace (60). Patients with HP often present acutely ill with fevers and pulmonary symptoms in conjunction with various chest radiograph abnormalities. A favorable response to strict avoidance of exposure to the antigen, with or without adjunctive corticosteroid therapy suggests that this is a hypersensitivity reaction rather than true infection (57,58).

Co-infection with different strains of NTM or different organisms is reported. MAC and *M. abscessus* infections may co-exist, making eradication even more challenging.

Treatment of NTM pulmonary infections: medical therapy

There are numerous clinical challenges regarding the treatment of NTM pulmonary infections. The duration and toxicity of antimycobacterial therapy must be balanced against the often indolent clinical course and the patients other co-morbidities. It is often appropriate to observe a patient's clinical course before embarking on therapy. There is currently a paucity of data on the natural history of untreated NTM infections adding to the difficulties of clinical decision-making. Kikuchi et al, have demonstrated that specific genotypic patterns of MAC may predict clinical behavior (61). If confirmed by subsequent

investigations, these data may augment clinical decision making on directed drug therapy.

Once a decision is made to begin targeted NTM therapy, recommendations for medical therapy are limited by a paucity of adequately powered randomized controlled trials. Often consensus opinion, in conjunction with *in vitro* susceptibility testing results, guides therapeutic recommendations. The choice of agents and duration of therapy is based upon the specific organism and extent or disease.

Patients with advanced lung disease in need of transplantation present particular challenges when they develop NTM pulmonary infections. It is debated if listing for transplant should be deferred until completion of therapy. Because of the long duration of therapy for NTM, it is the authors' opinion that listing these patients for bilateral lung transplants should not be delayed, as the involved lungs will be resected at the time of transplantation. Directed NTM therapy should be initiated and continued in the post-transplant period, although the duration of post-transplant therapy is not well defined.

Recommended antibiotic therapy for the most common causes of pulmonary infections is outlined below. For details regarding therapy of other NTM infections, the reader is referred to the ATS consensus statement (16). Monitoring patients for signs of drug toxicity is required during therapy (Table 2). Attention to adequate nutritional intake and weight stability is important as gastrointestinal side-effects, such as nausea and vomiting, are commonly seen in conjunction with the macrolide agents, rifampin, and rifabutin. It is especially important that weight is monitored in patients with nodular bronchiectasis given the propensity of these patients to be quite thin.

M. avium

Newer macrolide drugs such as azithromycin and clarithromycin are central to drug therapy for MAC lung infections. These agents demonstrate *in vitro* and clinical activity (62) against MAC, and are able to achieve penetration into phagocytes and tissue (63). It is imperative that these agents not be used in isolation due to the substantial possibility of the development of resistance. Combination drug therapy with a macrolide (azithromycin or clarithromycin), rifampin or rifabutin, and ethambutol with or without an intravenous aminoglycoside are recommended. Therapy should be continued for at least one year after conversion of sputum cultures from positive to negative (16). The duration of antimicrobial therapy commonly exceeds 18 months or more. In patients with nodular bronchiectasis, thrice weekly "triple therapy" with a macrolide, ethambutol, and rifamycin is typically recommended over daily therapy to

improve drug tolerability and decrease costs. Aminoglycoside therapy is typically not required. Sequential introduction of the drugs over a few weeks may improve patient tolerability. For patients with fibrocavitary disease, previously treated disease, or severe disease daily therapy with the inclusion of either streptomycin or amikacin to the aforementioned agents is recommended. Success, defined as sustained eradication of the organism without relapse for several years after the discontinuation of therapy, is only achieved in 55% of patients treated with a macrolide based regimen (15). The duration of therapy, the suboptimal efficacy, and morbidity of drug toxicity often leads to reluctance to pursue treatment or discontinuation of therapy. In a meta-analysis of studies examining the efficacy of a macrolide containing antibiotic regimen, the patient dropout rate ranged from 11-33% (15). Furthermore, even after completion of recommended therapy, many patients will grow MAC organisms again and require repeated prolonged courses of therapy. In a study of 34 patients treated for 18 months with combination drug therapy, 11/34 (32%) grew MAC in sputum one year following discontinuation of therapy (64). Early reoccurrence of positive cultures suggests relapsed disease, whereas as later reoccurrence suggests a new infection.

Recent evidence suggests that macrolide antibiotics may decrease exacerbations and sputum density in patients with bronchiectasis (65,66). It is known that MAC infection following successful MAC therapy treatment with a macrolide containing regimen is associated with subsequent macrolide resistant MAC (67). Thus, there is great concern that the use of macrolides in patients with bronchiectasis may render subsequent NTM infections resistant to therapy.

M. kansasii

Prolonged triple drug therapy including isoniazid (INH), rifampin, and ethambutol is recommended for treatment of *M. kansasii* infections. Therapy should be continued for 12 months after sputum conversion to negative. Macrolides such as clarithromycin and the fourth generation fluoroquinolone moxifloxacin demonstrate very good *in vitro* activity against *M. kansasii* and may be an alternative to INH (68).

M. Abscessus

Lung infections due to *M. abscessus* are notoriously difficult to treat successfully with drug therapy alone. Chemotherapy in conjunction with surgical resection is often needed in those who can tolerate it. It is important that laboratories specifically differentiate infections with *M. abscessus*, as opposed to reporting

a recovered organism as *M. chelonae/abscessus*, as the potential for success with drug therapy differs.

The role of surgery in NTM infections

The role of surgical intervention in patients with NTM infections has been infrequently studied. Thus, the historical roles of surgery in the management of TB, including diagnostic assistance, an adjuvant treatment option, and the management of complications of the disease have been extrapolated to patients with NTM infections. However, the public health implications for TB clearly differ from NTM. Surgical control of the disease is important in TB on both an individual and societal level because of the substantial risk of disease transmission to other patients and the development of multidrug resistance. These issues do not pertain to NTM.

The optimal procedure, the timing of surgical intervention, the value of debulking the most diseased areas, and expected morbidity and mortality of surgery for NTM infections remain as incompletely answered questions.

Assistance in making the diagnosis

NTM can present with various radiographic patterns including a diffuse ground-glass infiltrate, nodules, and mosaic attenuation consistent with patchy air trapping. Given the lack of specificity of these radiographic findings, surgical biopsies or resections to identify their etiology may fortuitously establish a diagnosis of NTM. An appreciation of the potential for an underlying infectious etiology of radiographic abnormalities highlights the importance of culturing explanted tissue removed at an operative procedure, if a benign diagnosis is provided (69).

The need for medical therapy after a surgical resection identifying NTM is dependent upon the extent of remaining disease, the immune status of the patient, and the pathogenicity of the organism isolated. Patients with remaining areas of infection nodules will presumably benefit from medical treatment post-operatively. The role of post-operative medical therapy and the duration of therapy in patients who have had resection of an isolated solitary nodule are uncertain.

The role of surgery in the management of NTM pulmonary infections

Given the suboptimal outcomes of medical therapy for NTM lung disease (15,70). Surgical resection is considered in selected individuals. However, the role of surgery is not definitively established. The severity and geographical distribution of the disease, responsiveness to antimicrobial therapy, and pulmonary

reserve all influence the decision to pursue surgical management. Ideally, positive sputum needs to be converted and remain negative for at least three months if the infecting organism is susceptible to medical therapy. Optimization of bronchial hygiene with chest physical therapy or mechanical devices is recommended pre-operatively and post-operatively. Some authors recommend resected specimens be "double cultured" with samples sent to two different microbiology laboratories to minimize sampling error (71). Pre-operative or intraoperative bronchoscopy is performed to exclude endobronchial pathology when suspected. Surgical resection is typically indicated in the setting of focal persistent disease amenable to complete anatomical resection. In more diffuse disease, surgery may be indicated to reduce disease burden and systemic symptoms of chronic infection in selected patients. There are not clearly established criteria upon which to recommend surgery in these cases.

Surgical technique

The largest experience with resection for atypical mycobacteria is reported from Denver, USA. These authors have reported both open thoracotomy and video-assisted thoracoscopic surgery (VATS) approaches to pulmonary resection with good results (71). However, in many instances the disease incites an inflammatory response, which obliterates the pleura, making a VATS approach difficult.

Mitchell and colleagues from Denver appear to have a low tolerance for use of muscle flaps (*Latissimus dorsi*) or omentum to fill large spaces or buttress the bronchial stump. One of the present author's (JAO) approaches is to perform a muscle-sparing thoracotomy for any disease process where the risk of bronchopleural fistula and/or empyema is increased. In many instances, a muscle flap is not needed and is preserved and available for use, but only if necessary. The author's experience advocates that dissection should proceed in the intrapleural plane rather than the sometimes easier extrapleural plane, because of excessive bleeding from myriads of small vessels. Lymph node and other tissue surrounding the bronchus should be retained and utilized to cover the bronchial stump. There exists a belief that resection for TB is associated with a high incidence of bronchopleural fistula, but in truth, this complication is infrequent (72).

If a pneumonectomy is performed, drainage is avoided if possible, recognizing that the risk of empyema increases with the duration of the presence of a chest tube. In those with persistent oozing or bleeding, a chest tube is necessary, but should be removed as soon as drainage becomes serous.

In patients with TB, the ipsilateral lung remaining after resection may be abnormal and fibrotic and may not completely

fill the thoracic cavity. Options in these circumstances are to do nothing, with the anticipation and hope that in the post-operative period the space will become obliterated. Pleural tents are often not possible if there have been extensive adhesions that have been freed. In these instances where pleural space problems are anticipated, a multihole catheter alongside the phrenic nerve, with local anesthetic infused so that the hemidiaphragm is temporarily paralyzed is indicated.

Results of surgery

In the Denver experience, the overall operative mortality was low at 2.6%. Eleven patients developed a bronchopleural fistula (4.2%), of whom 10 had positive sputums at the time of surgery (71). In contradistinction to the experience with TB, where left pneumonectomy is undertaken twice as commonly as right pneumonectomy, right pneumonectomy is more commonly performed for atypical mycobacteria (71). Bronchopleural fistulae occurred after right pneumonectomy (71). A similarly high incidence of bronchopleural fistula after right pneumonectomy was also reported by Shiraishi and coworkers (73). These reports suggest that prophylactic muscle flaps are likely necessary in this patient sub group.

In a recent series of 110 patients who underwent surgical resection for right middle lobe or lingual bronchiectasis from NTM, 84% had negative post-operative cultures and smears (74). Eight of the negative patients subsequently became positive again, representing either relapse or reinfection. Sixteen percent did not convert, suggesting failure of surgical therapy. Therefore, 22% in total (24/110) remained positive (74). Although some may suggest these data argue unfavorably against surgical resection, it must be highlighted that symptoms of chronic cough and a feeling of being unwell were relieved in most. The impact of removal of the bulk of disease in those with persistent or subsequent positive sputum cultures on future health is not established, although, excision of a large focus of infection may facilitate medical management of remaining sites of disease (75).

The role of surgery in control of complications of NTM infections

In addition to surgery for control of the disease, surgery may be necessary to deal with complications of disease such as hemoptysis, cavitation with or without fungal ball formation, and empyema. These situations often require urgent treatment precluding the luxury of pre-operative testing, antibacterial therapy, and optimization of the patient's cardiopulmonary and nutritional status.

NTM skin and soft tissue infection

NTM may infect surgical wounds post-operatively. The etiology of these infections is unknown, but it is most likely due to direct implantation or contamination of surgical instruments. Both host and organism characteristics are contributory, as these infections occur more commonly in those who are immunosuppressed, and the causative organisms are usually rapidly growing NTM.

The author (JAO) has noticed some characteristics of these wounds. They tend to appear very clean with minimal slough, and pus does not exude. If there is a liquid component to the wound, it is of low volume, clear, and watery. Granulation tissue is not abundant. The patient may have pain out of proportion to the extent of the wound and, in these patients, magnetic resonance imaging (MRI) or CT scans may identify deep tissue involvement. Curiously, some patients have minimal pain. Under normal circumstances, healing would be expected, as these wounds appear quite clean, but this does not readily occur despite adjunctive therapies such as the use of a wound vac or other similar device. Once the diagnosis is established with appropriate culturing, healing occurs with the institution of appropriate antimicrobial therapy.

Summary

The incidence of NTM infections surpasses that of TB infections in developed countries. Although infection may occur in virtually any organ, pulmonary infections are most common. *M. avium*, *M. kansasii*, and *M. abscessus* are the most frequently identified organisms causing lung disease. The isolation of an NTM organism does not necessarily equate with active infection; clinical, radiologic, and microbiologic parameters are all needed to establish the diagnosis of infection. Eradication of disease with drug therapy requires prolonged combination therapy. Surgical resection is often indicated in localized disease, in the presence of drug resistant organisms, or in some cases, of failure of medical therapy.

There remain significant gaps in our knowledge of the acquisition and management of NTM pulmonary infections. Susceptibility to disease is incompletely understood and, thus, it is unclear what preventative measures may be effective. Additionally, given the difficulty of eradicating NTM and its substantial re-occurrence, identifying appropriate candidates for treatment and the timing of initiation of therapy are clinically difficult decisions. A better understanding of the natural history of untreated MAC infection in association with nodular bronchiectasis, the identification of markers for disease progression, and improved understanding of the risk

factors for re-infection would be of substantial help to clinicians and patients. Additionally, there exists a substantial need for improved pharmacotherapy for *M. abscessus*.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Johnson MM, Odell JA. Nontuberculous mycobacterial pulmonary infections. *J Thorac Dis* 2014;6(3):210-220. doi: 10.3978/j.issn.2072-1439.2013.12.24

Efficacy and safety of moxifloxacin in acute exacerbations of chronic bronchitis and COPD: a systematic review and meta-analysis

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ABSTRACT

Purpose: To evaluate the efficacy and safety of moxifloxacin in acute exacerbations of chronic bronchitis (AECB) and chronic obstructive pulmonary disease (AECOPD).

Methods: We searched PubMed, EMBASE, and the Web of Science for relevant studies. Two reviewers extracted data and reviewed the quality of the studies independently. The primary outcome was clinical success at early follow-up. Study-level data were pooled using a random-effects model when I^2 was $>50\%$ or a fixed-effects model when I^2 was $<50\%$.

Results: Eleven randomized controlled studies were considered. There was no difference between moxifloxacin and comparator agents with regard to treatment success in intention-to-treat (ITT) [odds ratio (OR) = 1.18, 95% confidence interval (CI) 0.98-1.42], clinically evaluable (CE) (OR 1.13, 95% CI, 0.93-1.37) patients, or adverse effects in general (OR 1.00, 95% CI, 0.86-1.17). Moxifloxacin was associated with better microbiological success (OR 1.45; 95% CI, 1.14-1.85).

Conclusions: Moxifloxacin was as clinically equivalent and bacteriologically superior to the antibiotic regimens routinely used in patients with AECB and AECOPD. Moxifloxacin therapy may be a promising and safe alternative to empirical treatment for AECB and AECOPD.

KEYWORDS

Moxifloxacin; chronic bronchitis; chronic obstructive pulmonary disease (COPD); meta-analysis; systematic review

J Thorac Dis 2014;6(3):221-229. doi: 10.3978/j.issn.2072-1439.2013.11.12

Introduction

Acute exacerbations of chronic bronchitis (AECB), including chronic obstructive pulmonary disease (AECOPD), represent a substantial health burden to patients, resulting in reduced lung function, increased morbidity and mortality, and long-term

impairment in quality of life (1-3). Approximately around 40-50% of exacerbations may be attributed to bacteria while other causes include viral infections or environmental irritants (4). Current treatment guidelines recommend antibiotic therapy for patients with a more severe illness and often use acute symptom changes based on Anthonisen criteria of type I (worsening dyspnoea with increased sputum volume and purulence) or II (change in any two of these symptoms) exacerbations to define this group (5,6). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations for antibiotic therapy are based on the severity of exacerbations, the presence of risk factors, and predictors of poor outcome (e.g., comorbid conditions, frequency of AECBs, and previous antibiotic use) (7).

Moxifloxacin is a fourth-generation fluoroquinolone with a broad spectrum of activity against a wide range of the microorganisms isolated in AECB, including Gram-positive and Gram-negative bacteria, atypical pathogens, and anaerobic bacteria (8-10). Furthermore, moxifloxacin may be regarded

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Submitted Jun 19, 2013. Accepted for publication Nov 20, 2013.

Available at www.jthoracdis.com

ISSN: 2072-1439

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as the most excellent tissue penetration ability (11). Several randomized controlled trials have been done to compare the effectiveness of moxifloxacin with various standard antimicrobials in the treatment of AECB (12-20). Most studies suggest that moxifloxacin has been approached as effective as standard antimicrobials (12-20). To date, few trials show clinical or bacteriological superiority of one antibiotic over another in AECB or AECOPD. Therefore, we performed a systematic literature review and meta-analysis to clarify whether the use of moxifloxacin could be associated with improved outcomes in comparison with standard antibiotic therapy in AECB or AECOPD.

Methods

Data sources and search strategy

To identify studies for inclusion in this review, two authors independently searched PubMed, the Cochrane Central Database of Controlled Trials, and EMBASE for relevant studies published up to July 2013. The search was limited to studies conducted with humans. No language restriction was imposed. Search terms were individualized for each database. Search terms used included: (“chronic bronchitis” OR “chronic obstructive pulmonary disease” OR “COPD”) AND (“moxifloxacin”). We also searched the proceedings of major relevant conferences, trial databases, the reference lists of identified trials, and major reviews.

Study selection

Two reviewers (K.X. Liu and B. Xu) independently screened studies for inclusion, retrieved potentially relevant studies, and determined study eligibility. Any discrepancies were resolved by consensus. Analysis was restricted to randomized controlled trials. For this meta-analysis, we considered those randomized control trials (RCTs) that compared the clinical efficacy of moxifloxacin and another antibiotic in patients with AECB and AECOPD. The definition of chronic bronchitis and COPD provided by each study was used. This entity was consistently defined as the presence of productive cough for at least three months in two consecutive years. While the definitions of an exacerbation were more varied, the patients consistently considered for inclusion in these studies were those who presented combinations of the key symptoms of exacerbation: increase in dyspnea, sputum volume, and sputum purulence with or without other minor symptoms. All of the studies considered patients with type I Anthonisen exacerbations for inclusion,

and some also enrolled patients with type 2 or 3 exacerbations accompanied with increased in sputum purulence.

Data extraction

Two authors independently extracted data from all of the enrolled studies. Extracted data included study design (e.g., year conducted, sample size), patient characteristics, study methodology (e.g., eligibility criteria, method of randomization, and blinding), intervention (e.g., antimicrobial agents, dose, route of its administration and duration), and clinical outcomes. The primary outcome was clinical success (cure defined as resolution of all symptoms and signs of the bacterial exacerbation with a return to baseline condition, or improvement defined as subsidence of the ABECEB but with an incomplete return to baseline condition) in intention-to-treat (ITT) and clinically evaluable (CE) patients. Treatment success was assessed at 6-21 days after initiation of antimicrobial treatment in order to avoid confounding due to spontaneous resolution of infection that occurs in half of the patients with AECB 21 days after the onset of infection. Treatment success in microbiologically evaluable patients (defined as the absence of pre-treatment isolated bacteria in sputum cultures) and pathogen eradication (documented or presumed) of the bacteria most frequently implicated in AECB isolates (namely *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*) were considered as secondary outcomes. When determining microbiological outcomes, we elected to assess them at the longest post-treatment time point reported in each eligible trial, in an attempt to capture possible relapses.

Quality assessment

We formally determined the methodological quality of each trial using the Jadad score (21), which incorporates randomization, blinding, and attrition to derive a score of 0 to 5; higher scores indicate higher quality. Two reviewers (K.X. Liu and B. Xu) independently appraised the quality of the included trials. Jadad score more than two was considered to denote good methodological quality of an RCT.

Statistical analysis

The meta-analysis was done using Review Manager 5.0 (Cochrane Collaboration, Oxford, UK). We computed pooled odds ratios (ORs) and 95% confidence intervals (CIs) from the adjusted ORs and 95% CIs reported in the observational studies. Potential heterogeneity should be achieved while we performing

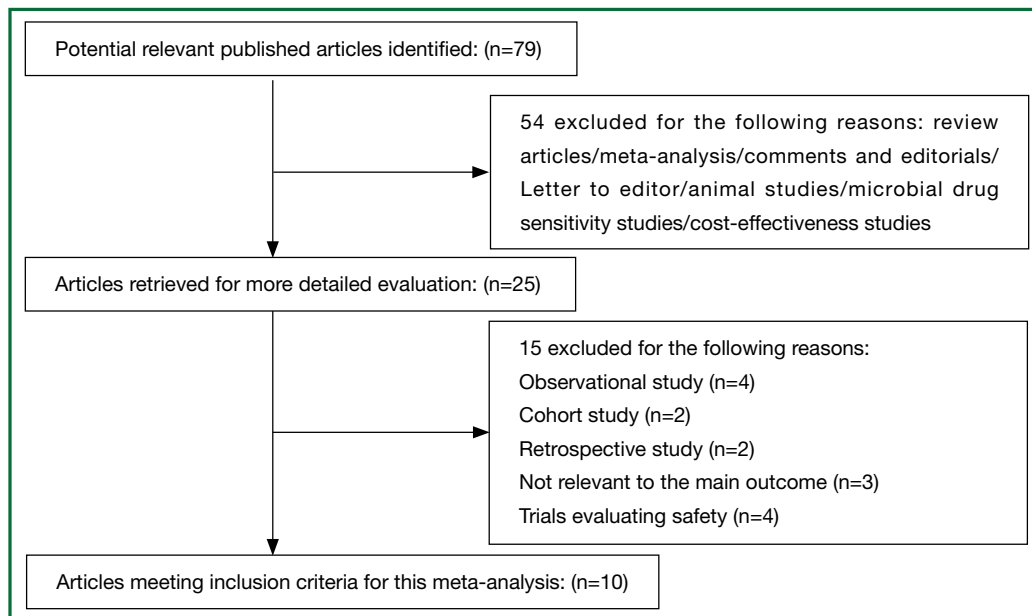


Figure 1. Flow of study selection.

Cochrane Q and I^2 statistics. We predefined heterogeneity as low, moderate, and high with I^2 values of above 25%, 50%, and 75%, respectively. In the analysis of heterogeneity, we considered a P value <0.10 to be statistically significant. Study-level data were pooled using a random-effects model when I^2 was $>50\%$ or a fixed-effects model when I^2 was $<50\%$. A funnel plot approaches of effect size *vs.* SE in the primary analysis of clinical success was employed to evaluate publication bias.

Results

Our search obtained a total of 79 references. Of these potentially eligible studies, 10 met the criteria for inclusion in the meta-analysis (11-20). A flowchart for the studies evaluated and the reasons for exclusion are shown in Figure 1.

Study characteristics

The comparator antibiotics were amoxicillin/clavulanic acid, ceftriaxone, cefuroxime-axetil, clarithromycin and azithromycin (11-20). Five RCTs had double-blind (DB) designs (11,12,17-19), while five RCTs were open-labeled (13-16,20). Most of the studies included outpatients. Characteristics of the included studies are summarized in Table 1. All studies were published from 1999 to 2013. Trials were conducted in a diverse array of countries. The eligible trials enrolled patients experiencing an AECB classified as Anthonisen type I, II, III (11,12,14); or type I, II (13,15-17); or type I (18-20). In nine RCTs, data regarding

the use of systemic corticosteroids before the occurrence of ABECB were provided. The average Jadad score of these studies was 3.5 (range: 1-5, Table 2).

Outcomes of clinical and bacteriological success rates

The primary outcome analysis was the clinical success rate at early follow-up in an ITT and CE populations. Early follow-up was before day 21 in all studies. Tests for statistical heterogeneity were performed for all analyses. Data regarding treatment success in ITT population were available for seven out the ten studies included in current meta-analysis (11,12,14,15,17,18,20). Statistically significant heterogeneity was not observed in the primary outcome of clinical success ($I^2=36\%$, $P=0.16$). No difference was observed between ITT patients with AECB receive moxifloxacin versus the comparator (3,860 patients: OR 1.18; 95% CI, 0.98 to 1.42) (Figure 2). Data on treatment success in CE population were reported in nine of the trials (11-18,20). We found no evidence of statistical heterogeneity for clinical success rate in a CE population ($I^2=0\%$, $P=0.75$). Treatment with moxifloxacin was not associated with statistically significant better outcome when compared with other antibiotics in CE population (3,301 patients: OR 1.13; 95% CI, 0.93-1.37) (Figure 3).

Eight RCTs reported data regarding treatment success in microbiologically evaluable patients (11-13,15-19). No statistically significant heterogeneity was found among the identified studies ($I^2=0\%$, $P=0.79$) (Figure 4). Pooled analysis

Table 1. Characteristics of the study population in various studies.

Study/year	Study design	Population	Enrolled patients/ITT	Regimen used	Systemic corticosteroid before ABECB
Chodosh et al. 2000 (11)	MC DB, RCT	Aged ≥ 18 yrs with CB or COPD with type I,II or III ABECB	936/926	Moxifloxacin 400 mg q 24 h for 5 or 10 days, Clarithromycin 500 mg q 12 h for 10 days	134/614 vs. 74/312
DeAbate et al. 2000 (12)	MC DB, RCT	Aged ≥ 18 yrs with CB or COPD with type I,II or III ABECB	567/567	Moxifloxacin 400 mg q 24 h for 5 days, Azithromycin 500 mg q 24 h on day 1, then 250 mg q 24 h for 4 days	NA
Grassi et al. 2000 (13)	MC RCT	Aged ≥ 18 yrs with CB and type I or II ABECB	476/470	Moxifloxacin 400 mg q 24 h for 5 days, Ceftriaxone 1 g q 24 h for 7 days	136/240 vs. 134/230
Kreis et al. 2000 (14)	MC RCT	Aged ≥ 18 yrs with CB with type I,II or III ABECB	411/399	Moxifloxacin 400 mg q 24 h for 5 days, Azithromycin 500 mg q 24 h on day 1, and 250 mg q 24 h for 4 days	NA
Schaberg et al. 2001 (15)	MC RCT	Aged ≥ 18 yrs with CB and type I or II ABECB	577/575	Moxifloxacin 400 mg q 24 h for 5 days	NA
Starakis et al. 2004 (16)	SC RCT	Aged ≥ 18 yrs with CB and type II ABECB	162/162	Moxifloxacin 400 mg q 24 h for 5 days, Amoxicillin/clavulanic acid 500/125 mg tid for 7 days	38/79 vs. 32/74
Wilson et al. 1999 (17)	MC DB, RCT	Aged ≥ 18 yrs with CB or COPD with type I or II ABECB	750/745	Moxifloxacin 400 mg q 24 h for 5 days, Clarithromycin 500 mg q 12 h for 7 days	160/322 vs. 128/327
Wilson et al. 2004 (18)	MC DB, RCT	Aged ≥ 45 yrs with CB with type I ABECB	733/730	Moxifloxacin 400 mg q 24 h for 5 days, Amoxicillin 500 mg tid for 7 days, clarithromycin 500 mg bid for 7 days, or cefuroxime-axetil 250 mg bid for 7 days	51/354 vs. 40/376
Wilson et al. 2012 (19)	MC DB, RCT	Aged ≥ 60 yrs with COPD with type I AECOPD, a FEV1 < 60% predicted and two or more exacerbations in the last year	1,372/1,352	Moxifloxacin 400 mg q 24 h for 5 days, Amoxicillin/clavulanic acid 875/125 mg bid for 7 days	182/677 vs. 189/675
Zervos et al. 2007 (20)	MC RCT	Aged 40-75 yrs with CB and type I or II ABECB, a FEV1 > 35% predicted	342/342	Moxifloxacin 400 mg q 24 h for 5 days, Azithromycin 500 mg q 24 h for 3 days	NA

Abbreviations: AECB, acute exacerbations of chronic bronchitis; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease; DB, double-blind; FEV1, forced expiratory volume in 1 second; MC, multicenter; NA, not available; RCTs, randomized control trials; SC, single-center.

showed that the use of moxifloxacin was associated with better outcome in ME patients as opposed to control (1,694 patients: OR 1.45; 95% CI, 1.14-1.85). Of the RCTs included in the analysis, five reported data on pathogens isolated at baseline and eradicated. Data on the eradication rates of the three most common pathogens isolated at baseline (i.e., *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae*) were reported in five of the eligible RCTs (11,12,17,19,20). Treatment of ABECB patients

with moxifloxacin was associated with higher eradication rates of *H. influenzae* compared with treatment with comparators (329 isolates, OR 3.48, 95% CI: 1.39-8.73, I^2 51%, $P=0.07$), data from five RCTs (11,12,17,19,20). However, there was no difference between the compared groups on eradication rates of *M. catarrhalis* (248 isolates, OR 0.61, 95% CI: 0.29-1.27), data from five RCTs (1,12,17,19,20) or of *S. pneumoniae* (213 isolates, OR 0.80, 95% CI: 0.40-1.57).

Table 2. Quality of the 12 studies as assessed by the Jadad score.

Study/year	Randomization	Blinding	Description of withdrawals and dropouts	Quality score
Chodosh <i>et al.</i> 2000 (11)	2	2		5
DeAbate <i>et al.</i> 2000 (12)	2	2		5
Grassi <i>et al.</i> 2000 (13)	2	0		2
Kreis <i>et al.</i> 2000 (14)	2	0		3
Schaberg <i>et al.</i> 2000 (15)	1	0	0	1
Starakis <i>et al.</i> 2004 (16)	1	0		2
Wilson <i>et al.</i> 1999 (17)	1	2		4
Wilson <i>et al.</i> 2004 (18)	2	2		5
Wilson <i>et al.</i> 2012 (19)	2	2		5
Zervos <i>et al.</i> 2007 (20)	1	1		3

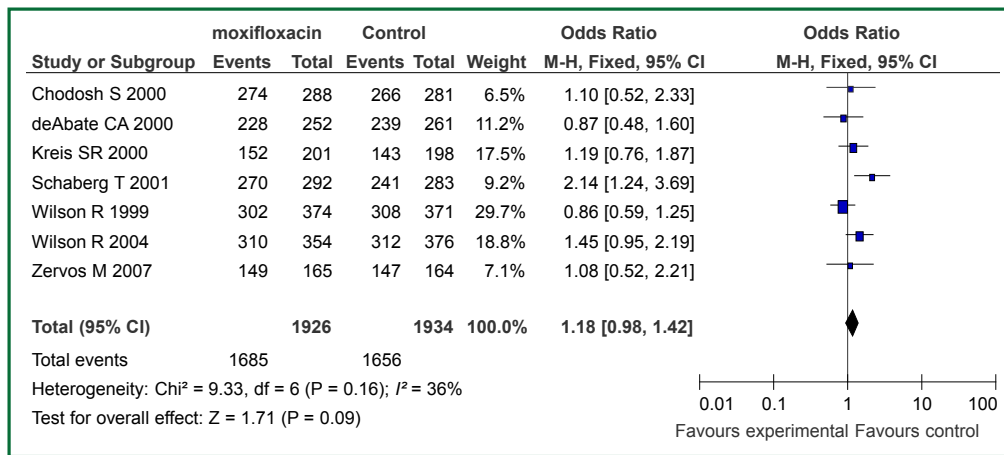


Figure 2. Clinical success in the ITT patients with AECB in RCTs comparing moxifloxacin versus other antimicrobial treatment.

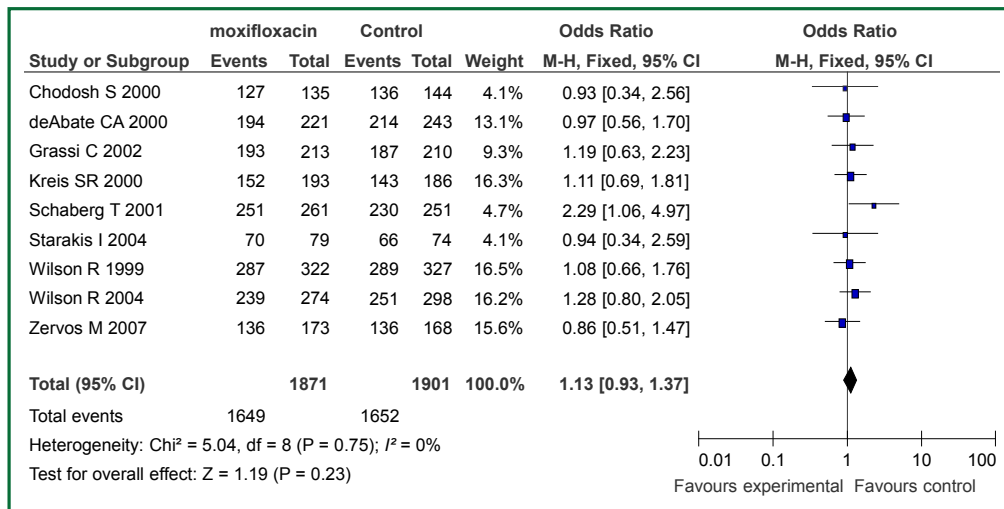


Figure 3. Clinical success in the CE patients with AECB in RCTs comparing moxifloxacin versus other antimicrobial treatment.

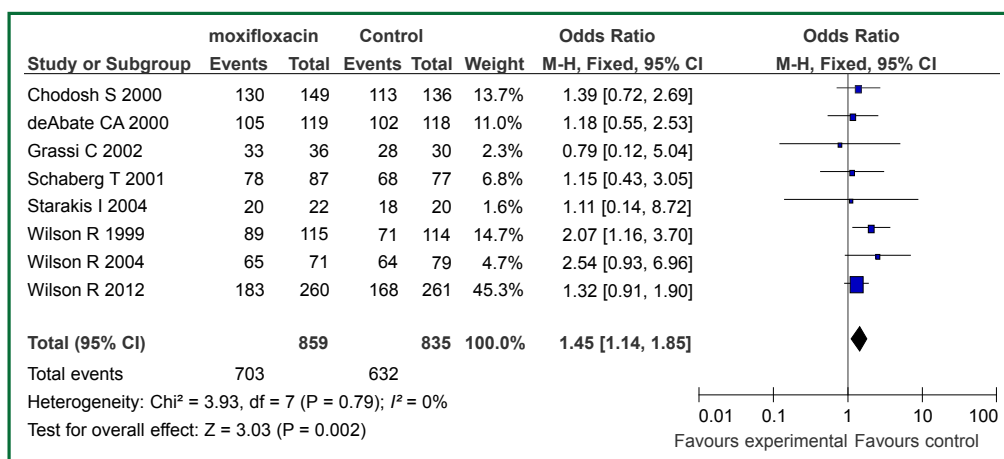


Figure 4. Bacteriological success in patients with AECB in RCTs comparing moxifloxacin versus other antimicrobial treatment.

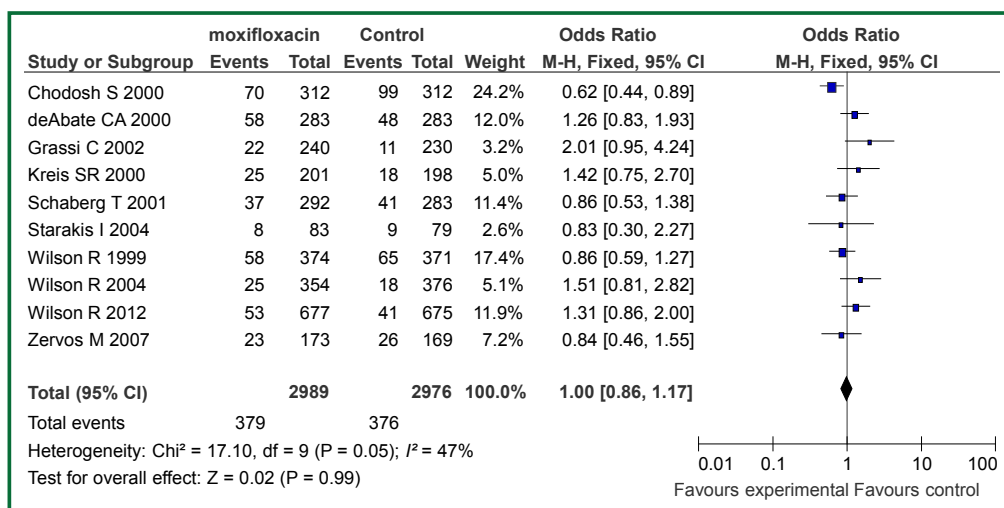


Figure 5. Drug-related adverse events in patients with AECB in RCTs comparing moxifloxacin versus other antimicrobial treatment.

Adverse events

Data on adverse events possibly or probably related to the study medications were reported for all included trials. The most common adverse events included nausea, vomiting, diarrhoea, hypersensitivity, dyspnoea, urticaria and upper abdominal pain. The frequencies of any adverse event were similar for moxifloxacin versus comparator drugs (OR 1.00, 95% CI: 0.86-1.17) (Figure 5).

Publication bias

Upon visual inspection of the funnel plot for the primary outcome, we found evidence of publication bias (absence of small studies in the right lower corner in Figure 6).

Discussion

This systematic review with meta-analysis compared the efficacy and safety of moxifloxacin with that of comparator agents for AECB patients. This meta-analysis indicates that moxifloxacin was associated with similar rates of treatment success and with higher bacteriological success rates compared with comparators (Figures 2,3). The safety analysis regarding the incidence of adverse events proved no difference between the compared treatment arms.

Despite the present evidence suggests that moxifloxacin has a similar efficacy as comparator agents, several unique characteristics make it a superior choice to existing regimens in specific occasions. The results of this study are in agreement with a recent study that was not designed as an RCT. The response to

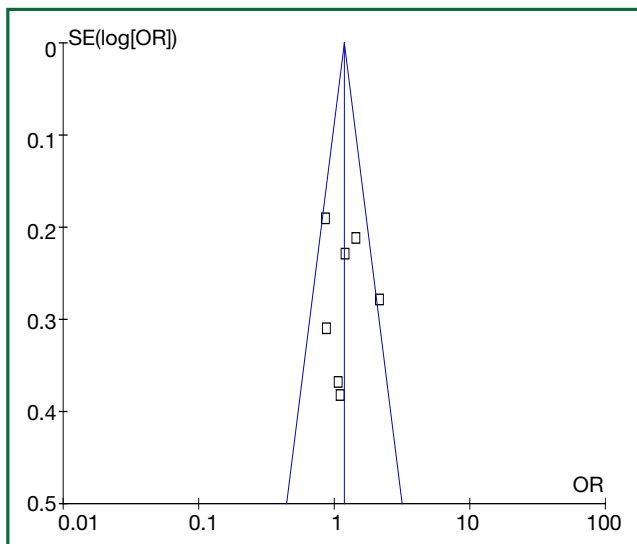


Figure 6. Funnel plot showing the possibility of a small publication bias.

moxifloxacin treatment was broadly independent of the patients' demographic and disease background. First, moxifloxacin has a broad spectrum of antimicrobial activity, ranging from aerobic to anaerobic, Gram-positive, and Gram-negative bacteria. Moreover, it has an excellent effect against drug-resistant *S. pneumoniae*, and respiratory Gram-negative pathogens, such as *H. influenzae*, *Mycoplasma pneumoniae*, *Moraxella catarrhalis*, and atypical organisms (i.e., *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*). Second, moxifloxacin may mitigate the emergence of resistant strains (22). Studies demonstrated a low spontaneous mutation rate for resistance to moxifloxacin, particularly for *Staphylococcus aureus* and *H. influenzae* (23,24). According to the mutant selection window hypothesis, resistant mutants are always selected at antibiotic concentrations above the minimum inhibitory concentration (MIC) but below the mutant prevention concentration (25). Studies determined that the therapeutic concentrations of moxifloxacin lay well above the MPC for *S. pneumoniae* (26). Third, the once-daily dosing of moxifloxacin may offer benefits compared with regimens that require multiple dosing or combination therapy, including patient convenience and comfort and a lower risk of medication errors. Decreasing the duration of antibiotic courses in respiratory tract infections might contribute to a decrease in these resistance rates. Similarly, the meta-analysis by El Moussaoui *et al.* demonstrated that a short course of antibiotic treatment is as effective as the traditional longer treatment in patients with mild to moderate AECB and AECOPD (27).

Pathogen eradication has been shown to correlate with

improved clinical outcomes and decreased relapse rate. It also contributes to the prevention of emergence and dissemination of resistant pathogens (28,29). Although moxifloxacin provided superior bacterial eradication rates than comparator agents, few studies have demonstrated that treatment with moxifloxacin was associated with a prolonged time to recurrence (30). In the included studies, bacterial load was not determined, so it is possible that, although patients were infected with bacteria, a proportion of them would have an alternative cause of their exacerbation. If the bacterial infection is not the major driver of the clinical manifestations of AECB in all cases then it could be one explanation for the dissociation between clinical and bacteriological outcome would be expected. The present meta-analysis showed no difference between moxifloxacin and the comparator antibiotics for the eradication of *M. catarrhalis*, and *S. pneumoniae*. The number of microbiologically evaluable patients was too small to detect differences between them. For patients with AECB due to *H. influenzae*, moxifloxacin provided superior bacterial eradication rates than other antimicrobial treatment. Moxifloxacin has excellent role in vitro activity against *H. influenzae*, that is independent of macrolide resistance mechanisms (31). The predominant bacterial pathogen implicated in AECB and AECOPD is *Haemophilus influenzae*, which is present in 50% of all bacterial exacerbations, with approximately a further one-third of isolates being either *Streptococcus pneumoniae* or *Moraxella catarrhalis*. It should be noted that the causative pathogens of AECB could not be identified in the majority of patients. Thus, correlation of clinical outcomes with bacteriologic outcomes was not possible for most patients.

In terms of safety, no difference was found between compared treatments. Adverse events are usually mild to moderate, in line with the known safety profile of moxifloxacin. A meta-analysis of clinical trial and postmarketing surveillance data for moxifloxacin identified nausea, dizziness, and diarrhea as the most frequent adverse events, which occurred at a rate similar to comparator medications (32,33).

The results of this meta-analysis should be interpreted carefully based on other considerations. First, analysis of any study should critically examine if its endpoints were adequate to demonstrate the potential benefits of the intervention being tested and were clinically relevant. Unfortunately, in the vast majority of antibiotic comparison trials in exacerbations of COPD, end-points used favor the demonstration of equivalence rather than differences among the arms. Clinical studies of antimicrobials in exacerbations of CB such as those performed in the original clinical program have been limited by factors such as inadequate information on patient condition prior to

the exacerbation and lack of long-term follow-up, as well as a lack of prospective control for steroid use, which can positively affect the outcome. Second, the ITT principle overlooks the fact that patients may not always receive all their allotted treatment. ITT analysis of noninferiority trials is not conservative, because the inclusion of patients who violate the protocol will tend to minimize differences between study arms, thereby increasing the possibility of results showing noninferiority. Thirdly, a significant proportion of the RCTs included in the meta-analysis allowed the enrolment of patients with an Anthonisen type III ABECB (mild ABECB) (11,12,14) as well as the enrollment of patients without impaired lung function (i.e., without a decrease in FEV1). It may be expected that less significant differences in the effectiveness would be found between different antibiotics. Finally, most of the studies included in the meta-analysis were conducted in the community, even though at least four studies also included hospital inpatients. However, almost all exacerbations were classified as Anthonisen type I or II, we feel some caution is necessary when applying our findings to patients with severe exacerbations who are admitted to hospital with respiratory failure.

Our analysis has several limitations. First, the majority of the RCTs included in current meta-analysis were not designed to focus on long-term outcome, such as exacerbation-free interval or frequency of exacerbations (recurrences) after the resolution of an initial episode of AECB (34). Second, COPD is a heterogenous disease, and acute exacerbations can be of varying severity, partly dependent upon the type of patients in which they occur (35). Most of the studies lack an objective definition of AECB or AECPD. The small number of studies so far does not allow for stratified analysis according to severity of COPD exacerbation. Superiority outcome clinical studies would require considerably larger sample sizes than non-inferiority studies. We should take the heterogeneity of COPD into account, particularly differences in COPD severity, exacerbation frequency and bacterial colonization. In addition, there is heterogeneity in some of the relevant aspects (the patients and comparative drugs included). The clinical effectiveness was assessed at different days in the various RCTs included in the analysis. Trials usually had a primary end point hence after end of treatment we may have missed early relapse due to inadequate treatment. Third, although we extensively searched for relevant studies using multiple databases and multiple search items, and no language restriction was placed on the search, some degree of funnel plot asymmetry suggested the possibility of publication bias. Fourth, some patients concomitantly received corticosteroids therapy that could probably have had an impact on the examined outcomes. Finally, the quality of the included

studies was not consistent. Some RCTs included in our analysis had major methodological flaws (15,16). Only eight of the included trials were double-blinded. The quality of trials can affect the direction and magnitude of treatment effects when doing a meta-analysis.

Conclusions

In conclusion, despite the limitations of our meta-analysis, we conclude that moxifloxacin has clinical efficacy and microbiological treatment success rates similar to those of comparator drugs in patients with AECB. Moxifloxacin therapy may be a useful alternative to empirical treatment for AECB. Large, well-designed, randomized, multi-center trials warranted to clarify the clinical outcomes (especially long-term outcomes) of patients with AECB receiving moxifloxacin treatment.

Acknowledgements

This research was sponsored by the National Basic Research Program (973 Program) in China (2013CB531402), the Shanghai Subject Chief Scientist Program (07XD14012), Shanghai Leading Talent Projects (No. 036, 2010), and Medical Scientific Research Foundation of Fujian Province (No.2012-CX-23).

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Liu KX, Xu B, Wang J, Zhang J, Ding HB, Ariani F, Qu JM, Lin QC. Efficacy and safety of moxifloxacin in acute exacerbations of chronic bronchitis and COPD: a systematic review and meta-analysis. *J Thorac Dis* 2014;6(3):221-229. doi: 10.3978/j.issn.2072-1439.2013.11.12

Staging lymph node metastases from lung cancer in the mediastinum

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ABSTRACT

Background: The presence of tumor metastases in the mediastinum is one of the most important elements in determining the optimal treatment strategy in patients with non-small cell lung cancer. This review is aimed at examining the current strategies for investigating lymph node metastases corresponding to an “N2” classification delineated by The International Staging Committee of the International Association for the Study of Lung Cancer (IASLC).

Methods: Extensive review of the existing scientific literature related to the investigation of mediastinal lymph node metastases was undertaken in order to summarize and report current best practices.

Conclusions: N2 disease is very heterogeneous requiring multiple modalities for thorough investigation. New research is now focusing on better identifying, defining, and classifying lymph node metastases in the mediastinum. Molecular staging and sub-classifying mediastinal lymph node metastases are being actively researched in order to provide better prognostic value and to optimize treatment strategies. Non-invasive imaging, such as PET/CT and minimally invasive techniques such as endobronchial and endoscopic ultrasound guided biopsy, are now the lead investigative methods in evaluating the mediastinum for metastatic presence.

KEYWORDS

Lung cancer; N2 disease; mediastinal metastasis; lymph node staging

J Thorac Dis 2014;6(3):230-236. doi: 10.3978/j.issn.2072-1439.2013.12.18

Background

Lung cancer has remained one of the most devastating and deadliest cancers worldwide accounting for 18% of all cancer deaths (1). Imparting some of this lethality is lung cancer's aggressive heterogeneous nature, often presenting in advanced stage where the five-year survival is less than 5% (2). This heterogeneity has also conveyed difficulties in properly staging lung cancer.

Now in its 7th edition, lung cancer staging has gone through several revisions collectively overseen by The International Staging Committee of the International Association for the Study of Lung Cancer (IASLC) and based on the “TNM” classification system. The newest edition has called for revisions of the “T” and

“M” components, and after extensive review, found that tumor size had prognostic relevance and that a better differentiation of tumors produced patients with different prognoses (3). However, these evidence-based sub-classifications made no changes to the “N” component, which has remained relatively unchanged through several lung cancer staging revisions.

N2 nodal disease

Current classification of the “N” component sub-divides it into four divisions, no lymph node metastasis (N0), local peribronchial and/or ipsilateral hilar lymph node metastasis (N1), ipsilateral mediastinal and/or subcarinal lymph node metastasis (N2), and contralateral mediastinal and/or supraclavicular lymph node metastasis (N3). However, the N2 classification can be considered the most expansive as it corresponds with lymph node stations of the superior mediastinum (2R, 2L, 3A, 3P, 4R, and 4L) extending to the lower mediastinum [7, 8, and 9] and including those lymph nodes of the aortopulmonary window and para-aorta (5 and 6, respectively). Due to the broad region and number of lymph nodes that N2 disease comprises, it can lead to a heterogeneous mix of lung cancers that can have different survival rates (4,5).

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Submitted Dec 09, 2013. Accepted for publication Dec 10, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

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Although several changes have been proposed for re-classifying the “N” component, the diversity of “N” disease based on global geography and tumor biology, has made it difficult to obtain a consensus validation (3).

Amongst the proposed changes for N2 disease, IASLC has suggested the concept of nodal zones. This classification system arranges 14 lymph node stations into seven lymph node zones (3). Studies supporting this have shown that under this proposed system, patients with single N2 zone positivity have a significantly higher survival rate than patients with multiple N2 zones and have a prognosis similar to patients with multiple positive N1 lymph nodes (3). Other studies have proposed other “N” classification methods based on the number of positive metastatic lymph nodes (6,7), the ratio of metastatic lymph node number to the number of total lymph nodes resected (7-9), and to the combination of both number as well as rate of metastatic lymph nodes (10). Regardless of the kind of reclassification of N2 disease undertaken, any future revision will carry major clinical implications as mediastinal lymph node metastasis is one of the most important factors in determining lung cancer treatment. This is especially true for N2 disease, where metastatic status at time of lung cancer diagnosis can be seen as a “watershed” area between which modality or combination of modalities will be undertaken for treatment.

Moving towards molecular staging

The TNM staging system was established in 1958, and in lung cancer, it is based almost exclusively on determining the anatomic extent of the cancer based on disease burden and spread. Although the American Joint Commission on Cancer (AJCC) was largely responsible for its widespread adoption, the TNM system has now become the gold standard for international reporting of lung cancer staging as shown by its most recent refinement in the 2010 IASLC classification/staging reports (11). Since patient survival has long been associated with the anatomical extent of disease from the primary tumor, the TNM staging system has always proved strongly to correlate with lung cancer long-term survival rates (12). Moreover, not only has the clinical outcome of lung cancer been predicted based on this TNM staging, but also the treatment plans of individual patients have been prescribed by physicians based on anatomical extent of disease. It is generally accepted, for example, that local treatment modalities such as surgery and radiation therapy are inappropriate to administer for curative intent once the disease has spread beyond the surgical margins of resection or the confines of the radiation field, respectively. But, since the TNM staging system is anatomically based with visual inspection of

tissue being critical, these management decisions about options of patient therapy and insights into prognostics have been until recently reliant on the skill of the pathologist and the optical power of a microscope.

In lung cancer staging through the years, histological type, differentiation, and clinical characteristics of patients such as age or race have not been fully incorporated into the TNM staging system. Recently, however, a worldwide effort, led by William Travis of Memorial Sloan Kettering, has re-examined the previous motley classification of adenocarcinoma histology to reveal distinct histological subtypes that do confer prognostic value (13). As others have suspected, this perhaps speaks to a strong correlation between histology and molecular determinants of lung cancer as exemplified in molecular features such as gene-expression profiles (14,15). In fact, the dawn of polymerase chain reaction (PCR) technology and the burgeoning field of molecular diagnostics are proving to be powerful technologies for determining the extent of cancer spread in pathological specimens. It is anticipated that they may fundamentally change the TNM staging system if accumulated evidence persuades their incorporation into the TNM staging system by the AJCC and/or the IASLC.

At present, most molecular prognostic markers in lung cancer have principally used only the T component of the staging system to estimate survival, such as recent published examples (Table 1). This concept is based on the hypothesis that the genes or proteins being identified in the primary tumor alone molecularly confer a certain clinical outcome due to their presence and function inherently, and that this is necessary and sufficient to determine tumor behavior. The problem with this approach is that it ignores the time tested benefits of all components of the TNM staging system. Instead of the intense focus on defining molecular signatures solely based on the tumor, strategies should also define molecular characterization of N2 lymph nodes and metastatic disease (serum). Eventually, this may enable more value to be added to the current anatomical TNM system.

Some of the reasons for this shift away from examining molecular determinants of lymph node metastases are that early attempts to correlate molecular markers in mediastinal lymph nodes with clinical survival of lung cancer patients were largely unsuccessful (20,21). One of the largest efforts to date to incorporate a molecular evaluation of the N2 lymph nodes for occult, micrometastatic tumor cells was performed in 2002 by the Cancer and Leukemia Group B Cooperative Cancer Group in the U.S.A. which failed to show any clinic benefit of molecular upstaging to patients (22).

Brock *et al.* recently advanced a step in the direction

Table 1. Recent examples of molecular determinants of prognosis based on lung tumor only.

Authors, reference	Molecular technique	Molecular biology	Year
Claeys <i>et al.</i> (16)	Microarray	31 cell-cycle and 15 housekeeping genes	2013
Ko <i>et al.</i> (17)	Methylation-specific PCR and immunohistochemistry	Co-alteration of <i>RASSF1A</i> and <i>p63</i> genes	2013
Krasnitsky <i>et al.</i> (18)	Immunohistochemistry	PKC η protein	2012
Kratz <i>et al.</i> (19)	Expression array	11 cancer-related target genes (<i>BAG1</i> , <i>BRCA1</i> , <i>CDC6</i> , <i>CDK2AP1</i> , <i>ERBB3</i> , <i>FUT3</i> , <i>IL11</i> , <i>LCK</i> , <i>RND3</i> , <i>SH3BGR</i> , <i>WNT3A</i>) and three reference genes (<i>ESD</i> , <i>TBP</i> , <i>YAPI</i>)	2012

PCR, polymerase chain reaction.

of molecular staging by proposing a set of four genes epigenetically modified that could be used to detect tumor DNA in N1 and N2 lymph nodes without evidence of visually discernible cancer cells, and which could be correlated with disease-free survival (23). Detecting tumor DNA rather than intact cells has an innate advantage because intact cells are needed to be visible in the mediastinal lymph nodes to ascertain the presence of cancer whereas tumor DNA may be present without microscopically observing tumor cells. Intact cancer cells are vulnerable to phagocytosis, especially if immune-inhibitory transmembrane receptors such as CD47 are not overexpressed, they can be fractured or fragmented by stress or trauma, and they can undergo apoptosis or necrosis for failure to implant into the nodal tissue. From any dead or dying cell, tumor DNA would be a residual product in the microenvironment fully available to be identified by PCR and detected for diagnostic purposes. Although molecular staging of the TNM system has not yet reached clinical relevance, the concept behind this approach is still both powerful and appealing. Future studies and more potent molecular marker technology may be needed to derive the full benefits of molecular staging of primary tumor and N2 lymph nodes.

Imaging modalities for evaluating N2 disease

Recent advancements in imaging modalities, such as computed tomography (CT) and positron emission tomography (PET), have drastically improved the detection and evaluation of lung cancer (24,25). CT imaging is now the most widely available and most commonly used imaging technique to assess intra- and extra-thoracic metastases (26). However, CT imaging has been shown to have limited abilities when evaluating the mediastinum for metastases when used as the sole modality. Investigations have shown that the sensitivity and specificity of CT imaging in identifying mediastinal metastases are 55% and 81%, respectively (26).

PET imaging, especially in combination with CT imaging, plays a prominent role in the evaluation of patients with lung cancer and is recommended preoperatively for most patients suspected of having lung cancer (26). Multiple investigations have assessed the validity of PET in identifying and evaluating mediastinal metastases (26-28). In comparison to CT imaging, PET has shown to have significantly better sensitivities and specificities, 77% and 86% respectively, when evaluating for mediastinal metastasis.

However, PET imaging, even when combined with CT, is not without its disadvantages. In areas of endemic granulomatous disease, such as sarcoidosis, HIV infection, and fungal disease, such as histoplasmosis, PET has been shown to increase the rates of false positive malignancy in mediastinal lymph nodes due to the increased metabolic activity these diseases engender in N2 lymph nodes (28-31). False mediastinal lymph node positivity on a PET scan will incorrectly upstage disease, which can erroneously direct patients from curative surgery (26,32). Hence, clinicians must be aware that PET imaging is not a definitive test and tissue confirmation is often needed to confirm PET scan findings. Despite its major positive impact on the stage classification of patients at a higher risk of having distant metastases outside the thorax, when used alone without tissue confirmation, PET imaging has the potential to be harmful if used in less structured settings.

Invasive techniques for evaluating N2 disease

Mediastinoscopy

Confirming mediastinal involvement is crucial in the treatment and prognosis of lung cancer. Non-invasive methods for establishing mediastinal involvement, such as PET/CT, are excellent in detecting disease, but do not provide definitive disease confirmation. A plethora of invasive techniques are now

available to obtain tissue as the next step to confirm mediastinal metastases.

Mediastinoscopy has long been viewed as the “gold standard” for diagnostic evaluation of the lymph nodes of the mediastinum. Performed in an operative suite under general anesthesia, the procedure involves an incision just above the suprasternal notch, with insertion of a mediastinal scope alongside the trachea, allowing for biopsies of the mediastinal lymph nodes. Using this approach, lymph nodes stations 1, 2R, 2L, 3, 4R, 4L, and anterior station 7 lymph nodes can be sampled. The use of a video mediastinoscope may allow for greater sampling, such as access to the posterior lymph nodes of station 7, and possible performance of a lymph node dissection (33).

Mediastinoscopy may also be modified to sample the aortopulmonary lymph nodes of stations 5 and 6, such as in an extended cervical mediastinoscopy. In this procedure, using the same cervical incision as a traditional Mediastinoscopy, the mediastinal scope is directed laterally toward the aortic arch (34). However, due to the grave complications of this technique, extended cervical mediastinoscopies are delegated to the few institutions that routinely preform them (35-37).

Endobronchial and endoscopic ultrasound guided biopsies

Despite its low rates of morbidity and mortality, 2% and 0.08% respectively (38), the role of mediastinoscopy is changing in favor of less invasive techniques, such as endobronchial ultrasound (EBUS) guided biopsy and esophageal endoscopic ultrasound guided (EUS) biopsy. EBUS has been increasingly used in the staging of lung cancer due to its excellent diagnostic performance (26,39-41). EBUS biopsy was found to be significantly more sensitive for detecting malignant lymph nodes than transbronchial needle aspiration, 69% vs. 36% respectively (39). Overall, in patients who had clinical indications for an invasive investigation of the mediastinum, EBUS was shown to have a sensitivity of 89% with a negative predictive value of 91% (26).

Once considered a complimentary procedure of the mediastinoscopy, EUS biopsy has emerged as a viable alternative (39,42-44). Performed with minimal risks of complications, EUS has been shown to be particularly helpful in evaluating the lymph nodes of station 5 and the lymph nodes of the inferior mediastinum. EUS biopsy is also capable of obtaining tissue from outside the thorax to evaluate distant metastases, such as in the liver, celiac lymph nodes, and areas of the sub-diaphragm (44,45). When used for the detection of metastases to the mediastinum, EUS has been shown to have sensitivities and specificities as high as 89% and 100%, respectively (26).

Currently, and with the support of multiple investigations,

EBUS and EUS are now being routinely combined to allow for near complete evaluation of the mediastinum (26,39,46,47). In a meta-analysis of seven studies comprising 811 patients with a lung cancer prevalence of 33%, EBUS plus EUS was able to produce 91% sensitivity and 100% specificity (26). However, despite their high appeal as alternatives to mediastinoscopy as a first line status in evaluating the mediastinum, they both require high levels of expertise to be performed effectively. Additionally, few clinicians are sufficiently trained to do both procedures well, so that two separate qualified clinicians are needed to carry out both procedures.

Intra-operative techniques: lymph node dissection vs. sampling

In the thoracic surgery literature, there has been a long running debate concerning the correct surgical technique of harvesting hilar and mediastinal lymph nodes from lung cancer patients during surgical resection. At the heart of the debate, is whether a small sampling of relevant lymph nodes is adequate or whether a complete dissection of all visible lymph nodes is needed.

Ludwig *et al.* added fuel to the fire with a population-based Surveillance, Epidemiology and End Results (SEER) study from 1990 to 2000 based on 16,800 patients with stage 1 NSCLC treated with surgical resection with curative intent which suggested that patient survival was associated with the number of lymph nodes evaluated pathologically for disease (48). Specifically, those patients with 13-16 lymph nodes examined by a pathologist had the best survival as compared to those with only 1-4 lymph nodes harvested (HR 0.78; 95% CI, 0.68-0.90). Surgical procurement of more than 16 lymph nodes did not seem to confer additional benefit. The authors concluded that this was most likely due to “a reduction-of-staging error”, in other words, that as more lymph nodes are sampled, there is a decreased tendency of a pathologist to miss any positive lymph nodes present.

Others have validated these findings for stage 1a lung cancers surgically resected in California, and in those states recorded in the SEER national registry (49,50). Additionally, complete mediastinal lymphadenectomy has been shown to be the most accurate mode of detecting multilevel N2 disease and skipped metastases (Pathologically positive N2 lymph nodes are present, but there is no evidence of histologically involvement of N1 lymph nodes) (51-55). Moreover, there has been concern that only 57% of patients undergoing major pulmonary resection for lung cancer have mediastinal lymph nodes harvested by their surgeon (56).

Darling *et al.* have largely settled this debate, at least for the

time being, in a large randomized cooperative group trial that showed no difference between the survival of patients whose lymph nodes were procured by either of the two techniques (57). Interestingly, in both the right and left sides of the chest, a median of 18 lymph nodes were harvested per patient (12 N2 nodes and 6 N1 nodes). Based on this study, the cooperative group recommended that a surgeon procure, in addition to the tumor specimen and any N1 lymph nodes associated with it, at least 12 mediastinal lymph nodes during a mediastinal lymphadenectomy from stations 2R, 4R, 7, 8, 9, and 10R in the right chest, and stations 4L, 5, 6, 7, 8, 9, and 10L in the left chest. Finally, as more minimally invasive video assisted thoracic surgery (VATS), (especially VATS lobectomies) are being performed, the cooperative group study suggests a note of caution in that VATS lobectomies in their study were associated with fewer lymph nodes harvested per patient with a median of 15 versus 18/19 lymph nodes from an open thoracotomy (57).

Sentinel lymph node staging

Due to the morbidity of mediastinal lymph node dissection, over the last two decades, there has been an interest in developing a less invasive, more regional mode of determining pathological mediastinal lymph node status by examining a few sentinel lymph nodes. Importantly, this technique has been successful in other solid tumors (58). Sentinel node mapping is very much reliant on lymphatic flow drainage patterns, and the level at which lymph nodes are first impacted by drainage from the primary tumor bed. Recently, a systemic review of the literature on the efficacy of sentinel lymph node staging found that in relation to the proximity from the primary tumor the more distal N2 lymph nodes rather than the closer N1 nodes were the first sites of lymphatic drainage in a wide range of patient distributions ranging from 5% to 95% (59). This exemplifies the difficulty in the sentinel lymph node technique as the current technology of radiotracers and/or dyes shows a large variability in lymphatic drainage among patients as clinically observed with the phenomenon of “skipped metastases”.

Conclusions

Despite the current inadequacies in assessing N2 nodal disease in lung cancer, recent improvements on multiple fronts are allowing better prognostic and predictive information for treating patients. Studies aimed at reclassifying the anatomy, incorporating molecular determinants, improving the technology for imaging and of procuring the nodes, and finally advancing the pathologically assessment of N2 nodes will

continue to push the envelope of science forward. Collectively, these multidisciplinary, cooperative efforts will enable patients to be treated more effectively, and hopefully lead to fewer deaths from this terrible disease.

Acknowledgements

Funding: Supported by Grant Number 3T32CA126607-04S1 and P50 CA058184 from the National Cancer Institute of the National Institutes of Health. Also, the American Association for Cancer Research/Stand Up to Cancer Dream Team Translational Cancer Research Grant, grant number SU2C-AACR-DT0109.

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Terán MD, Brock MV. Staging lymph node metastases from lung cancer in the mediastinum. *J Thorac Dis* 2014;6(3):230-236. doi: 10.3978/j.issn.2072-1439.2013.12.18

Approach to a solid solitary pulmonary nodule in two different settings—“Common is common, rare is rare”

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ABSTRACT

A new solid solitary pulmonary nodule (SPN) is a common feature in the daily practice of physicians, pulmonologists and thoracic surgeons. The etiology and consequently the diagnostic approach is very different in various parts of the world. Identification of malignant nodules is the universal goal to proceed to a potential curable therapy. In countries with a low incidence of inflammatory disease and a high incidence of lung cancer the diagnostic work up includes a positron emission tomography (PET) scan or PET-computer tomography (CT) as a main pillar. In countries with a high incidence of inflammatory and infectious disease and a low incidence in lung cancer this diagnostic work up needs to be adapted. In these settings a PET scan has a limited role and tissue diagnosis, whether with a trans-thoracic, trans-bronchial biopsy or a video-assisted wedge resection is the most targeted approach to determine or exclude malignancy. The evaluation of a solid SPN in the two different situations is outlined in our algorithm. Recommendations stress the value of clinical judgement in different settings, determination of probabilities of malignancy, cost-effective use of diagnostic tools and evaluation of various management alternatives according to the risk profile and the patients preferences.

KEYWORDS

Solitary pulmonary nodule (SPN); diagnostic work up; lung neoplasms; inflammatory lung disease; algorithm

J Thorac Dis 2014;6(3):237-248. doi: 10.3978/j.issn.2072-1439.2013.11.13

Introduction

The differential diagnosis of a solid solitary pulmonary nodule (solid SPN) is broad, ranging from benign tumors, infectious lesions and lung cancer to other malignant conditions. Moreover, incidences vary widely in different parts of the world. While lung cancer is predominant in industrialized regions like Europe and North America, developing areas such as India, Central-, South- and West Africa as well as parts of South America have a high incidence of infectious lung diseases in the near absence of lung cancer: in North America and Europe where lung cancer affects 40-60/100,000 men

and 13-22/100,000 women (1) 11,669 patients were newly diagnosed in 2010 in the Netherlands alone as opposed to only 189 patients with Tuberculosis (TB) in a previous year (2). In contrast South Africa experienced an almost 200 times higher population related incidence of 138,803 new cases of TB in 2008 (2). Conversely, the incidence of lung cancer in India and Central- and West-Africa is the lowest in the world with 0.9-10/100,000 men and 0.6-2.3/100,000 women (1).

Consequently, the approach to a solid SPN needs to happen in the context of geography and its respective socio-economic circumstances. To highlight the resulting diversity of diagnostic processes the approach to a new solid SPN is described in a setting such as Leeuwarden, the Netherlands and Cape Town, South Africa.

Definition SPN

A SPN is a common clinical problem. It may be accompanied by symptoms like cough, loss of weight, malaise or hemoptysis. In most instances the lesion is discovered incidentally on chest X-ray (CXR) or on computer tomography (CT) scan. Nowadays more and more lesions are discovered on CT scan, which is performed

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Submitted Sep 17, 2013. Accepted for publication Nov 20, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

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Table 1. The distribution of the diagnosis in a newly found SPN divided in malignant and benign causes based on various American studies (15).

Distribution	Percentage (%)
Causes of malignant SPN	100
Adenocarcinoma	47
Squamous cell carcinoma	22
Solitary metastasis (i.e., melanoma, sarcomas, carcinomas of colon, breast, kidney and testicle)	8
Undifferentiated, small cell, large cell and miscellaneous rare tumours	23
Causes of benign SPN	100
Healed or non specific granulomas	25
Active granulomatous infections (tuberculosis, coccidioidomycosis, histoplasmosis, cryptococcosis and aspergillosis)	15
Hamartomas	15
Miscellaneous benign lesions i.e., nonspecific inflammation and fibrosis, lung abscess, hematoma, hemangioma, arterio-venous malformation, bronchogenic cyst etc.	45

Table 2. Distribution of etiology of solid pulmonary nodules in a cohort of 242 HIV positive patients (16).

Diagnoses	Patients with nodules, No. [87]
Bacterial pneumonia	30
Pneumocystis Carinii pneumonia (PCP)	3
Lymphoma	10
Tuberculosis	14
Kaposi's sarcoma	11
Non-tuberculous mycobacteria	4
Aspergillus pneumonia	3
Lung cancer	4
Cytomegalovirus	0
Other	8

for various reasons like screening programs, investigations for pulmonary embolism or cardiac function and search for metastases of other cancers than lung cancer (3,4).

For this article the SPN will be defined as a single, spherical, well-circumscribed radiographic opacity of less than 3 cm in diameter with at least 2/3 of its margins surrounded by pulmonary parenchyma. Excluded in this definition are lymph nodes, atelectasis and post-obstructive pneumonia (5,6).

The major question that follows detection of a solid SPN is whether the SPN is malignant or not.

Prevalence of SPN

The detection rate of a SPN is 0.09% to 7% on routine chest

radiographs (5). A study from the 1950's showed that one of 500 CXRs demonstrated a SPN. In 1999 in the Early Lung Cancer Action Project, 7% of 1,000 healthy volunteers were found to have 1, 2 or 3 nodules in CXR screening (5). The failure to recognize lung cancer on the CXR is one of the most frequent causes of a missed diagnosis in radiology.

On CT scans the screening prevalence of at least one SPN is higher. It ranges there from 8% to 51% in the lung cancer screening trials using CT imaging (3,7-9). A positive screen result in the CT arm of the North American National Screening Trial (NLST) was defined as finding a non-calcified nodule of at least 4 mm. Using these criteria 27% had a positive baseline screen (9). The Netherlands-Belgium Lung cancer Screenings Trial (NELSON study) showed a rate of 51% non-calcified nodules at baseline (10).

Prevalence of malignancy in a SPN

As screening programs are typically performed in developed countries, the prevalence of malignancy in single pulmonary nodules reflects their incidences ranging from 1% to 12% in the various studies (11-13).

Differential diagnosis of SPN

As outlined, the differential diagnosis for a SPN is extensive (14,15). The frequency of each etiology varies amongst studies worldwide. Most studies were performed in the United States in specific cohorts. National data from Africa and Asia are scarce or missing. Tables 1,2 show examples from different settings, one from North America and one from Africa.

The distribution of the diagnoses in a newly found SPN is

shown in Table 1, showing the wide spectrum in malignant and benign causes (15).

Another study reflects figures of a more common cohort in Africa [with a high incidence of human immunodeficiency virus (HIV)] and lists etiologies of pulmonary disease in 242 HIV infected patients undergoing a CT of the chest (Table 2) (16). In this cohort, 36% of patients had one or more pulmonary nodules. Four percent of patients had two concurrent diagnoses.

SPN evaluation

There are many approaches to evaluate a SPN. Significant variation exists among institutions influenced by the socio-economic and inherent circumstances of a region (5,14,15,17-21).

We will try to outline the approaches in a setting of high prevalence of lung cancer and a low incidence of infectious diseases, like North America or Europe in contrast to areas with a high incidence of TB, HIV and other infectious diseases and a low incidence of lung cancer. For this article we will limit ourselves to the solid SPN, and leave the field of ground glass nodules and semisolid/subsolid SPN for a discussion elsewhere.

The ideal approach to a solid SPN should result in the resection of all malignant nodules, while avoiding resection of all benign nodules that require no treatment or some form of medical treatment.

Setting I: SPN evaluation in Leeuwarden, the Netherlands

Patients with a newly diagnosed solid SPN undergo an initial diagnostic evaluation based on radiological findings and medical, often interdisciplinary judgment to determine the probability of being a malignant nodule. In this setting this is the most important question as the patients with stage 1A (T1N0M0) lung carcinoma have the best prognosis and the highest potential for cancer cure (1). We follow the guidelines "The Solitary Pulmonary Nodule" published in Chest 2003 by the ACCP and the next version published in Chest in 2007 by Patel and coworkers (5,14,15,19).

The following indices give us guidance in the approach to a solid SPN.

Clinical characteristics

Older age, a history of cigarette smoking, larger nodule size, female gender, asbestos exposure and previous history of cancer all increase the probability that a solid SPN is malignant (22). The presence of underlying lung disease such as emphysema,

fibrotic lung disease (idiopathic pulmonary fibrosis, radiation and asbestosis) are additional risk factors (23).

Radiologic features

Chest radiograph (CXR)

There are no characteristics that can consistently distinguish between a benign nodule and a malignant nodule based on the appearance on CXR. However a solid SPN that is unchanged for more than two years is unlikely to be a malignant nodule. A CXR is less sensitive than a CT scan for detecting changes in size, density and borders of a solid SPN. The first step is to compare the lesion with previous CXRs or CT scans. If that is not available the next step is a high resolution CT scan.

Chest computed tomography (CT)

CT is more sensitive and more specific than CXR for detecting nodules (23). Additionally, the CT detects intra-thoracic abnormalities like enlarged lymph nodes or tumors in the mediastinum or other blind spots (hidden by diaphragm, heart or bony structures).

Features that can be used to predict whether a nodule is malignant include size, border, calcification, density, growth and location (24):

- (I) Size: larger lesions are more likely to be malignant than smaller lesions. Lesions >3 cm in diameter should be considered malignant until proven otherwise (25,26):
Nodules ≤3 mm: 0.2% likelihood of malignancy;
Nodules 4-7 mm: 0.9% likelihood of malignancy;
Nodules 8-20 mm: 18% likelihood of malignancy;
Nodules >20 mm: 50% likelihood of malignancy.
- (II) Border: malignant lesions tend to have a more irregular, lobulated and spiculated border, whereas benign lesions often have a relatively smooth and discrete border (27) (Figures 1,2). The presence of small satellite nodules surrounding a dominant pulmonary nodule is characteristic of a benign nodule, typically a granuloma.
- (III) Calcification: calcification is highly suggestive of a benign lesion, especially when it has an organized pattern (central, laminated or popcorn pattern).
- (IV) Density: the attenuation of a nodule (Hounsfield Units = HU) is a reflection of the amount of calcium within the nodule. The presence of focal fat within a solid SPN is highly suggestive of a benign solid SPN like a hamartoma.
- (V) Cavitation: thin walled cavitating nodules are more likely to be benign. A thick walled cavity (>15 mm) is a feature of a squamous cell carcinoma, but is also present in many TB cases or aspergillomas.



Figure 1. CT of a solid SPN, which was followed up closely and has slightly grown in size (from 1.1 to 1.4 cm) in a 65-year-old heavy smoker from China. With spiculae present, no calcifications and 66 Hounsfield Units it was most likely malignant (high risk category with a calculated probability of 88.1%): VATS wedge, frozen section (Adenocarcinoma), VATS lobectomy with lymph node dissection. Final histology: pT1bN0M0, Stage I NSCLC.



Figure 2. CT of new solid SPN in the right lower lobe, size 1 cm, smooth appearance, no spiculae, HU 26, detected on routine CXR in a 50-year-old from Europe, non-smoker, NIDDM, most likely benign with a calculated probability for malignancy of 2.4%. Control CT in three months.

- (VI) Growth rate: the doubling time for the majority of malignant lesions is 30-480 days (28). The exception of this rule includes slow growing tumors such as adenocarcinoma in situ (broncho-alveolar carcinoma in the old classification) with a doubling time up to 900 days, which is often ground glass in appearance. All malignant, fast growing lung nodules followed up from the baseline CT scan after three months in the NELSON trial (multinational screening trial) had a volume-doubling time less than 232 days (29).
- (VII) Location: malignant lesions are more likely to be in the upper lobes, but the same applies to TB and aspergillomas.

Probability tests

The most frequently used model for assessing the risk of malignancy is the Bayesian analysis, which postulates that the post test probability of disease is linked to pre test probability and the sensitivity and specificity of the test (19). The method is based on estimating the probability of being a malignancy using nodule size, presence of spiculae and location, patients age, smoking history and previous malignancies (30,31). The overall prevalence of malignancy in the population is also important. A recent study shows that the inclusion of nodule volume in the malignancy prediction model increases the proportion of nodules correctly classified (26,32).

Management

The algorithm outlined in Figure 3 is guiding the diagnostic and management decisions [including the probability test (15)] in the approach to a solid SPN. All decisions get based on a multidisciplinary panel consensus that takes the patient's preference into consideration. As such, a patient will fall into one of three groups: High (>60%), intermediate (5-60%) and low (<5%) risk for developing lung cancer.

- A solid SPN that remains stable for more than two years can be considered benign acknowledging that certain low grade adenocarcinomas and carcinoids can be stable for two years or longer.
- A nodule that grows or a nodule in a patient with a high risk probability (>60%) should be biopsied or excised (Figure 1) unless the patient is not fit for such an intervention or refuses it.
- A solid SPN smaller than 8 mm can be followed up by using the guidelines proposed by the Fleischner Society (25). In 2005 the Fleischner Society guidelines for managing pulmonary nodules detected on CT scans were developed

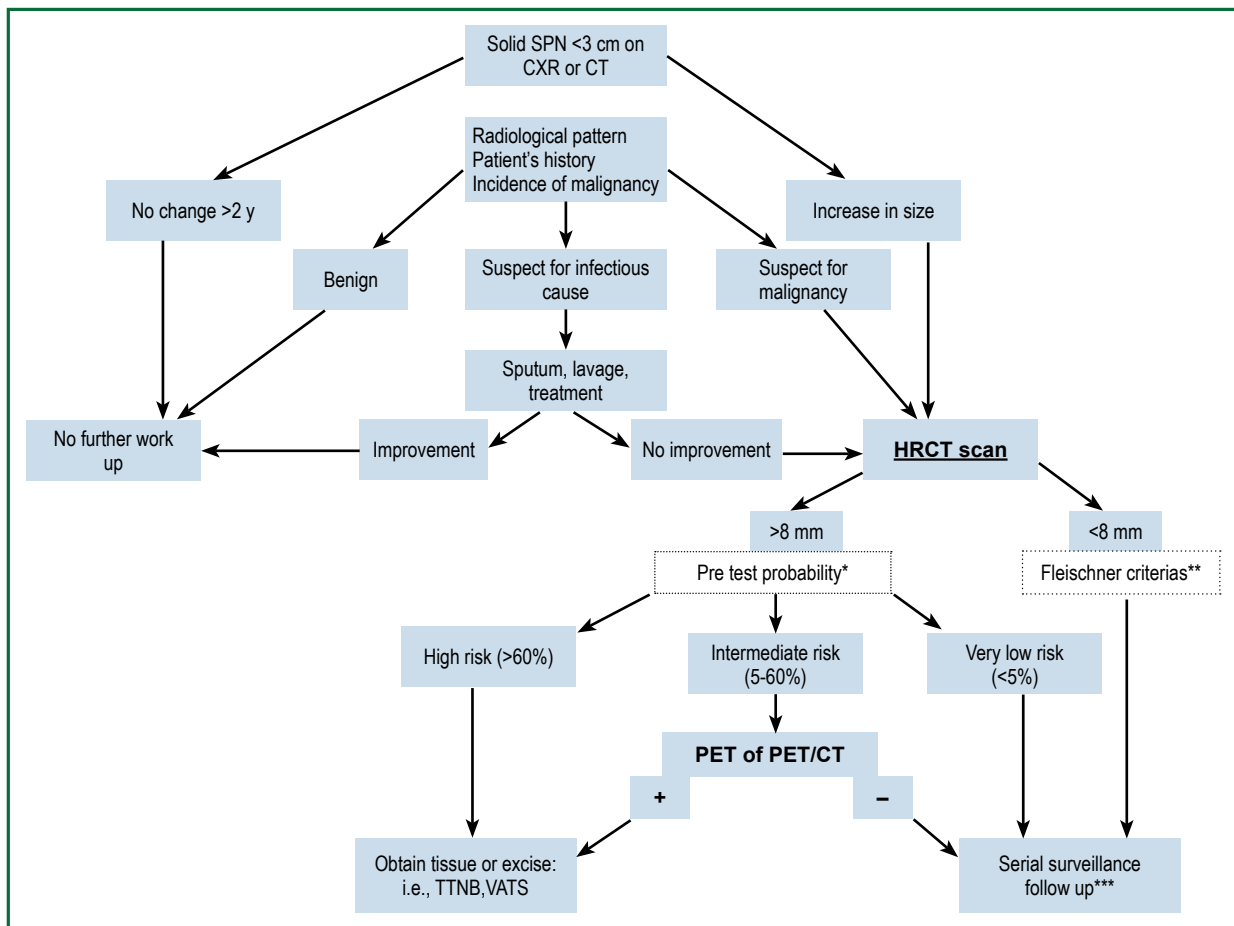


Figure 3. Algorithm solid single pulmonary nodule (SPN), adapted from Patel *et al.* (5). *, Pre test probability. i.e., Swensen *et al.* Factors to determine the probability of malignancy: age, smoking history, previous malignancy >5 y ago, presence of spiculation, upper lobe location. **, Fleischner Society Guidelines (Table 3); ***, ACCP Guidelines 2007: serial CT scan at 3, 6, 12, and 24 months.

Table 3. Guidelines Fleischner Society for the management of small pulmonary nodules detected on CT scans (25).

Nodule size (a)	Patient with low cancer risk (b)	Patient with high cancer risk (c)
≤4 mm	No surveillance (d)	Surveillance CT at 12 months
4-6 mm	Surveillance CT at 12 months. If no significant change, discontinue	Surveillance CT at 6-12 months, then at 18-24 months, if no change
6-8 mm	Surveillance CT at 6-12 months, then at 18-24 months, if no change	Surveillance CT at 3-6 months, then at 9-12 months and 24 months, if no change

a, average of largest and smallest axial diameter of the nodule; b, no smoking history and absence of other known risk factors; c, previous or current smoking history, or other risk factors; d, risk of malignancy (<1%) is substantially lower than for an asymptomatic smoker.

in response to a perceived need for managing incidental small nodules detected on CT scans (Table 3).

- In a solid SPN with an intermediate risk probability a ¹⁸F-Fluorodeoxyglucose positron emission tomography (FDG-PET) is recommended.

Positron emission tomography (PET) CT

It is estimated that 96% of patients with lung cancer will have an abnormal FDG-PET and 78% of patients without lung cancer will have a normal FDG-PET (33-35). PET has a very high

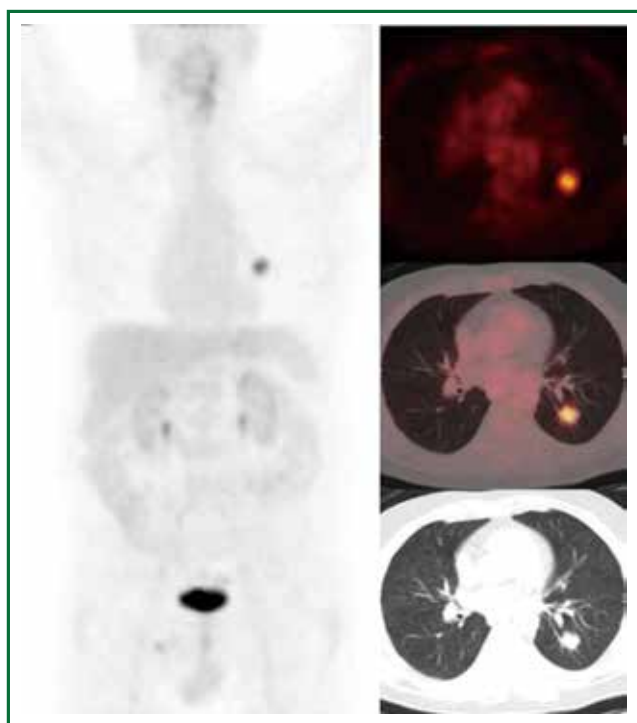


Figure 4. PET positive solid SPN left lower lobe: on the left is a maximum intensity projection (MIP) of the total body F18-FDG PET investigation. On the right there are three transverse slices of the hybrid F18-FDG PET/CT investigation. The single pulmonary nodule (SPN) dorso-caudal of the left hilum shows a maximum standardized uptake value (SUV_{max}) of 12. The corresponding CT slice reveals a hyperdense lesion with a diameter of 2.1 cm, HU 60 and a calculated probability for malignancy of 88.5%. Final histology after resection: pT1bN0M0, Stage 1 NSCLC.

sensitivity (89-100%), but a lesser specificity (69-100%) and an accuracy of 89-96% in a modern combined modality PET/CT (36-38). PET is false positive in granulomatous disease and is usually false negative in lesions of less than 0.8 cm (5,39). Other pitfalls of PET are false negative findings in metabolically low-activity tumors (adenocarcinoma in situ or minimally invasive mucinous adenocarcinoma and carcinoid tumors) and in hyperglycaemia (39).

In intermediate risk patients a PET scan is performed as the next diagnostic step. In case of PET negativity the lesion will be followed up after 3, 6, 12 and 24 months with a low dose CT in line with the recommendations of The American College of Chest Physicians (15).

When the PET scan is positive the probability of malignancy is high in our setting. The following figures are two examples from our daily practice representing newly found solid SNPs.

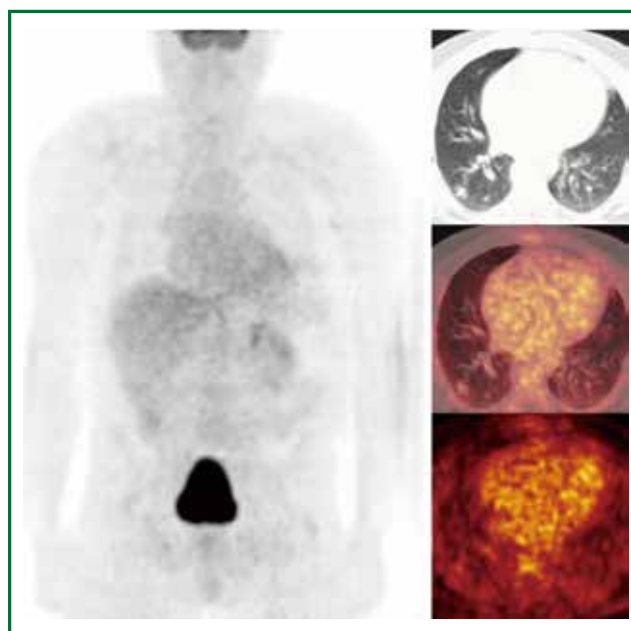


Figure 5. PET scan of a solid SPN in the right lower lobe. On the left: maximal intensity projection (MIP) of the total body F18-FDG PET investigation: no lesion visible. On the right: (above) transverse slice CT in lung settings shows a 2 cm lobulated lesion with ill defined edges and varying densities, HU -55 to +75; (below) two transverse slices of the hybrid F18-FDG PET/CT investigation showing activity not significantly above the background activity [standardized uptake value (SUV) <1.5]. Calculated probability for malignancy: 8.4%.

Treatment follows our algorithm and gets individualized according to the patient's condition and preferences.

The first case is a PET positive lesion in a 54-year-old heavy smoker with chronic obstructive airway disease GOLD II. He underwent a PET scan according to our algorithm as a medium risk patient (Figure 4), followed by a transthoracic needle biopsy (TTNB) (squamous cell carcinoma) and a VATS lobectomy with systematic lymph node dissection (pT1N0M0).

The second case is a 63-year-old ex-smoker (stopped 30 years ago) with a history of a renal cell adenocarcinoma (pT3aN0M0) treated by nephrectomy six years ago, poor left ventricular function and a coronary bypass graft operation in 2012. At the preoperative work up in 2012 a new lung lesion was found. Again according to our algorithm a PET scan was performed (Figure 5). This patient was followed up for three months. On repeat CT scan the lesion had grown. Differential diagnosis included a benign lesion, a metastasis from the renal cell cancer or a PET negative lung cancer such as a carcinoid or some forms of adenocarcinoma. TTNB got some malignant cells compatible

with a metastasis from the previous renal cell (Grawitz) tumor. Due to the overall condition of this patient stereotactic radiation was performed.

A systematic review concludes that the additional information gained from PET imaging in diagnosing a malignant SPN is worth the costs providing good medical indications are applied (40). Implementation of the PET-CT as a combined modality is variable, depending on the health care system and the uncertainty about its cost-effectiveness. In our institution this will become standard next year, at present CT and PET are two machines and get combined by a computer program.

Tissue diagnosis and therapeutic approach

A management decision should be made once the probability that the SPN is malignant or likely to be malignant has been assessed (see algorithm in Figure 3). For high risk patients or PET positive lesions it is mandatory to get a tissue diagnosis but how to obtain the tissue is under debate. There is a lack of published data directly comparing the results from biopsies obtained using different methods. The location of the nodule and the likelihood of complications determine which approach is used. Preferences and expertise of the institution seem to play a role (41).

- Bronchoscopy can be used to evaluate larger or more central nodules (42). However it is much less useful for small (<2 cm) or peripheral solid SPNs.
- Fluoroscopy or endobronchial ultrasound (EBUS) can optimize localization of the solid SPN.
- TTNB: the procedure is reported to have a sensitivity of 64-100% (14). Adding core needle biopsy to the procedure is more likely to establish the diagnosis especially for non-malignant lesions (14,43). A positive result is a reliable indicator of malignancy but a negative result is of limited value in excluding malignancy. Complications are hemorrhage and pneumothorax. In studies of CT guided needle biopsies, non-diagnostic results were seen in 20%.
- Surgery: surgical resection of the solid SPN by thoracotomy or video assisted thoracoscopic surgery (VATS) is common practice for a growing solid SPN, a solid SPN with a high likelihood of malignancy or a proven malignant solid SPN. In combination with a frozen section, the definitive treatment can be achieved in the same session. Whether a wedge resection or a VATS lobectomy with systematic lymph node dissection is necessary is determined by the results of the frozen section. In rare cases the frozen section of the VATS wedge resection cannot differentiate between a metastasis and a primary lung tumor. In these circumstances a staged approach after final histology including

immunohistochemistry is adopted. Radio-guided surgery is the preferable method to locate a sub-centimeter solid SPN and mark it with a wire in order to achieve a successful excision instead of finger palpation (44). Intra-operative ultra-sonography is not available in Leeuwarden.

Setting 2: SPN evaluation in South Africa, Cape Town

The approach to a new solid SPN in endemic areas of infectious pulmonary disease like TB, HIV related disorders (Pneumocystis jiroveci, bacterial pneumonia, Kaposi etc.) and fungal disease is different. The standard algorithms published for setting 1 (19) need to be modified especially in the first phase. This will be outlined in the following chapter.

Clinical characteristics

In these endemic areas of TB and HIV infection the patients' history, symptoms and contact history play a significant role in the diagnostic and therapeutic approach.

HIV positive patients with a CD4 count >200 are treated as any other patient. With lower CD4 counts, however, more emphasis will be put on the search for pulmonary infections. In a study by Jasmer and coworkers 36% of the HIV patients had one or more pulmonary nodules on chest CT. Multivariate analysis identified fever, cough, and a nodule size of <1 cm on chest CT as independent predictors of having an opportunistic infection. Furthermore, a history of bacterial pneumonia, symptoms for one to seven days, and a nodule size of <1 cm on CT independently predicted the diagnosis of bacterial pneumonia. A history of homelessness, weight loss, and lymphadenopathy on CT independently predicted a diagnosis of TB (16).

Search for an infective source

The search for an infective source will include induced sputum, bronchoscopy and lavage and in indicated cases (i.e., for enlarged lymph nodes) EBUS /EUS biopsies. With an incidence of TB being as high as 981/100,000, a new lesion warrants active search for acid fast bacilli (AFB). Sensitivities and specificities for induced sputum smear microscopy lie in the range from 13-40% and 90-99%, respectively (6,45,46). Diagnostic progress was made in the last few years by introducing diagnostic rapid TB tests (e.g., the Xpert® assay). In recent studies the sensitivity of the Xpert® assay using bronchial washings or broncho-alveolar lavage fluid for the diagnosis of pulmonary TB was 81-96%, and the specificity was 98-100% (47-49). The positive predicted



Figure 6. CXR posterior-anterior (PA) on the left: a new SPN in the left upper lobe, size ~2 cm, smooth, vague borders, no calcifications, TTNB positive for AFB's. On the right: after three months of standard anti-TB treatment, the lesion is less dense and decreased in size (1.2 cm).

value and the negative predicted value were 100% and 92.1%, respectively (49).

Management

Results from TB cultures are not available for at least six weeks.

(I) In cases highly suspicious for TB with typical symptoms, positive contacts, younger age, HIV infection etc. empiric TB treatment is started. These patients need to be followed up closely and seen again within six weeks for reassessment of their symptoms. A repeat CXR is obtained to assess the growth pattern of the lesion. In this situation the suggested algorithm (Figure 3) can be followed to the left without a CT scan. Standard anti-TB treatment gets started, culture results obtained and a CXR taken after three and six months to monitor the effect of the applied treatment. In addition, the symptomatology of the patient is very important to ascertain whether there is improvement on anti-TB treatment. Targeted treatment is applied once the sensitivities are known. This approach is also supported by the WHO-TB guidelines (2). In cases of multi-drug resistant TB or a mycobacterium other than Tuberculosis (MOTT) the lesion will not change and treatment needs to be adapted.

(II) In cases of less obvious clinical suspicion for TB or other infectious diseases a high resolution CT scan serves as a basis to gain more information over the exact location, the density and borders of the lesion, over lymph nodes, lung parenchyma or additional small nodules other than the solid SPN seen on CXR.

The following two cases represent our daily practice.

The first case is a 40-year-old black male presenting with a

productive cough, mild loss of weight and general malaise. He was HIV negative and had no TB contacts. CXR revealed a SPN in his left upper lobe. Induced sputum samples on three consecutive mornings were negative, bronchoscopic lavage results only showed mixed organism, TTNB revealed the presence of AFB's and standard anti-TB treatment was started (Figure 6).

The second case is a 65-year-old white male, heavy smoker, HIV negative, pacemaker dependant presenting with a new SPN on routine CXR. CT scan revealed a well circumscribed lesion in his right middle lobe. Bronchoscopic biopsies showed inflammatory cells, no malignancy and cultures showed mixed organism, no AFB's, TB cultures awaiting. He also went for TTNB to establish diagnosis falling into the intermediate risk group on calculations (Figure 7).

If there is a strong probability for the lesion to be a malignant lesion, as previously described, a tissue diagnosis of the lesion is being obtained. Tissue diagnosis is obtained by means of TTNB, VATS wedge or open wedge to distinguish malignancy from inflammatory disease. TTNB is the preferred investigation in our institution as we have a very experienced radiological team and the majority of lesions in our daily practice turn out to be infectious of nature (Figures 6-8). Early tissue diagnosis helps us to plan the further work up and treatment options.

If the diagnosis confirms malignancy the staging of the tumor follows established guidelines (50). Enlarged lymph nodes will be biopsied (via EBUS biopsy, mediastinoscopy or via a VATS approach) in order to stage the tumor.

The PET scan

The PET scan is useful for staging a proven malignant lesion, also in this setting but is not widely available.

In the initial work up to establish a diagnosis and in order to distinguish malignancy from infectious or inflammatory disease the PET scan is less helpful as increased FDG activity on PET scan is found in all three conditions. For the initial assessment of the solid SPN we do not use this modality due to the high incidence of false positive findings with infections and inflammation.

A multi-disciplinary team, including a thoracic surgeon, a respiratory physician and a radiologist discuss the steps outlined above routinely in our own institution as well as in its affiliated satellite hospitals. The area served is spread out over the entire Western Province, with some hospitals being more than 600 km away. This is achieved by regular visits or teleconference. If any doubt exists amongst the treating physicians, the patients are referred to our centre.

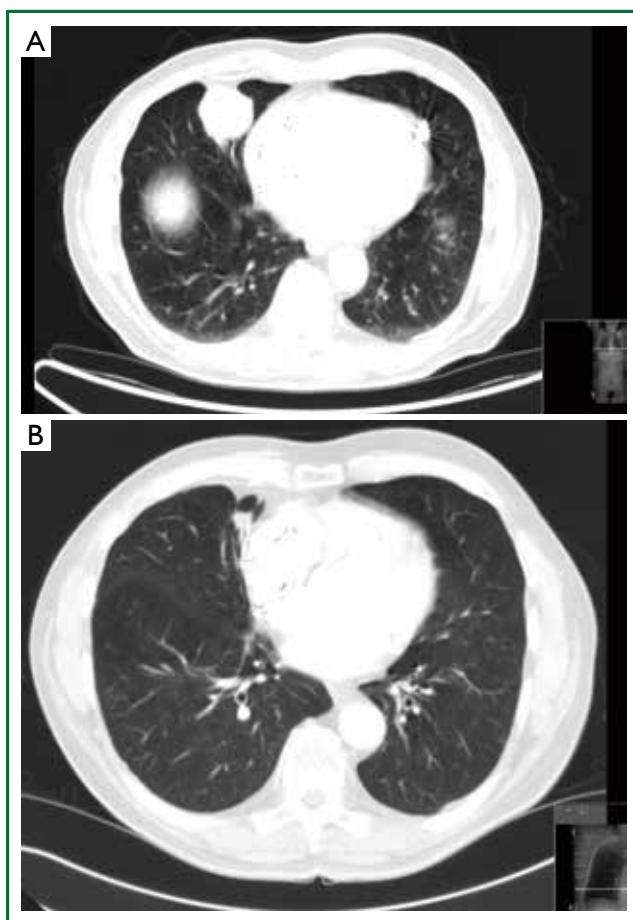


Figure 7. CT scan of a new solid SPN in a 62-year-old smoker with COPD and a pacemaker, calculated probability for malignancy: 55.2%. (A) smooth, homogenous opacity in the right middle lobe, no calcifications, proven to be a caseating granuloma on TTNB; (B) CT scan of the same patient six months after anti-TB treatment. Only a small holer is left in the antero-medial aspect of the right middle lobe.

Discussion

A solid SPN newly diagnosed on routine CXR or on (screening) CT is a common problem. We describe the decision making process in the Netherlands and in South Africa, a country with a high incidence of TB and other inflammatory diseases. It is clear that the general statement: “a new nodule in a smoker aged over 50 is a primary lung cancer until otherwise proven” is too simplistic to be used all over the world.

The differential diagnosis is wide. One needs to know the incidences of different etiologies (malignant, infectious and inflammatory disease) of a solid SPN in the area the patient comes from. In setting 2 a new pulmonary nodule is often

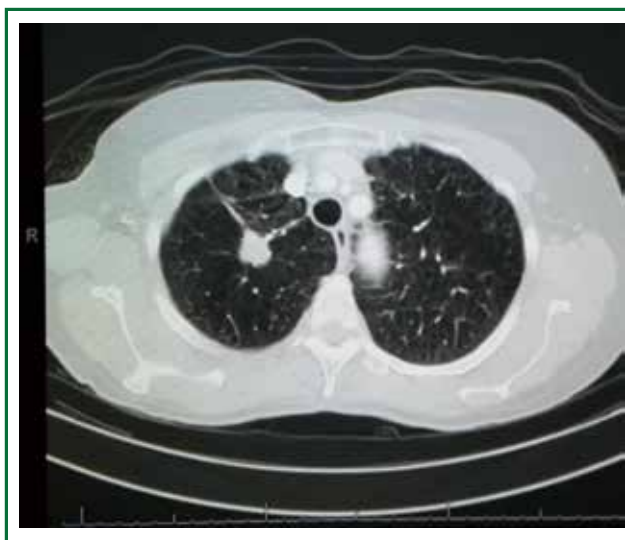


Figure 8. High resolution CT scan of a 60-year-old female, heavy smoker. A solid SPN in the right upper lobe was seen on CXR. CT scan shows a spiculated, ~2 cm lesion without calcifications, calculated probability for lung cancer: 66.4% in the absence of a PET, bronchoscopy and lavage did not reveal a diagnosis. A TTNB only showed necrosis, a wedge excision was performed and frozen section revealed a caseating granuloma compatible with TB.

regarded as TB until otherwise proven, especially in HIV positive patients. Incidence of lung cancer in Africa is very low, partly due the lower median life expectancy in developing countries. People die earlier from other diseases before lung cancer can develop. Hereditary factors may also play a role as well as different smoking habits. Unfortunately exact incidence and prevalence data are not widely available for developing countries (1,2), the most reliable information coming from the World Health Organization: www.who.int. Yet, the general rule: “common is common, rare is rare” applies.

In developed countries more insight in these data is available, also due to data from big screening trials where prevalence, follow up, treatment and outcome data is well recorded. The North American National Lung Screening Trial (NLST) is by far the largest series. So far, the NLST study is the only randomized controlled trial that has shown mortality reduction by using CT screening (10,51). Problems identified with CT screening include false positive, benign nodule resections, over-diagnosis, the exposure to radiation and costs (38,52,53). An estimated expense of 50,000 Euro per life year gained was reported (1,54). In the Netherlands, the prospective randomized NELSON screening trial did not show such a mortality reduction and the discussion is ongoing (12,45,54-58).

For follow up of a solid SPN <8 mm, the Fleischner Society guidelines are used in a flexible manner. Strict adherence to the Fleischner Society guidelines for managing pulmonary nodules detected on CT scans is questionable and it does not seem to have found general acceptance. A review article from 2012 showed that the radiologists in a Large Community Hospital do not always adhere to the Fleischner criteria. In most cases they recommend a closer follow-up (59). We find the same in our clinical practices.

In the evaluation of a new solid SPN we believe that the PET scan is an extremely helpful tool besides its established role in the staging for lung cancer and differentiating it from metastatic disease. It is a cornerstone under the conditions of a developed country as outlined in the algorithm. Not using a PET scan in South Africa has various reasons from limited accessibility of tertiary health care facilities to budget constraints. Another reason is the lack of specificity in glucose uptake to distinguish inflammatory disease from cancer (33,34,36). Therefore, its predicting power for malignancy is limited for such a setting. As such, the value of performing a PET scan as outlined in the algorithm in 'setting 2' is questionable and as a consequence, this step is often skipped. For patients with intermediate risk it very much depends on the individual case. Diagnostic steps are focused on obtaining a tissue diagnosis i.e., TTNB or wedge resection (see Figures 6,7). PET scan (where available) is advisable in the further work up of the patient with a proven malignancy.

The use of calculators for predicting the risk of malignancy is also a very helpful tool (22,30,32). However, one has to take into consideration that the development of such calculators (probability tests) was based on cohorts in countries with high incidence of lung cancer and low incidence of infectious diseases. While they are in principle applicable in all settings, conclusions for countries such as South Africa, India and China should be less strict as TB can mimic the features of lung cancer (Figure 8). Upper lobes are the predilected location for both TB and aspergillomas.

In general, the algorithms available and the risk-calculating methods do help in the decision making process. Physician, nuclear physician, radiologist and surgeon need to judge the probability of a malignancy. The patient and the health authorities play an increasingly important role in the choice of investigations and therapies.

One cannot point out strongly enough that the key issue in a new solid SPN is to establish a diagnosis for the surgical resection of early stage lung cancer. Stage I non small cell lung cancer (NSCLC) has a 5-year survival rate of approximately 60-80% (1). Whether this is achieved via a TTNB or directly via the surgeon, who will first perform a wedge resection and in the same session a lobectomy as the SPN turns out to be malignant, is handled

differently in different institutions, mainly dependent on the expertise available in a center and individual preferences. Minimal invasive techniques are commonly used nowadays and therefore one tends to prefer an established diagnosis on histology rather than relying on frozen section. CT guided biopsies are commonly used with a good diagnostic yield. In case of functional inoperability stereotactic radiation is a good alternative (60,61).

In summary, the evaluation process for a new solid SPN in the two different areas—the Netherlands and South Africa—follows the same principles. Yet, the initial diagnostic steps differ because of the different incidence of the various etiologies of a solid SPN in these two areas. The proposed algorithm is a valuable tool for the teams in day-to-day practice, especially in challenging cases. It provides a framework incorporating many sets of guidelines for the different scenarios also in different countries. There is general consensus that management should be individualized and carefully adapted to the patient's condition and preferences.

The approach to the solid SPN will probably modify with evolving technologies like volumetric imaging and advanced bronchoscopic techniques. Cost-effectiveness will also play an even more dominant role in the future (40,42,62).

Conclusions

To evaluate a solid SPN the physician needs to know what incidences and disease burdens are present in his/her area. Probabilities and risk stratification of being a malignant solid SPN needs to be judged accordingly. Models, calculators and guidelines are helpful tools for the countries with a high incidence of lung cancer.

Despite the difficulties in advising a general algorithm we believe that the stepwise approach outlined above is helpful in the decision making process in the developed and developing world. The team of physicians can use it as a template to provide individualized treatment in a newly diagnosed solid SPN.

Acknowledgements

The authors thank the Department of Radiology and the Department of Nuclear Medicine, Medical Center Leeuwarden for their great contribution regarding the figures.

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Murrmann GB, van Vollenhoven FH, Moodley L. Approach to a solid solitary pulmonary nodule in two different settings—"Common is common, rare is rare". *J Thorac Dis* 2014;6(3):237-248. doi: 10.3978/j.issn.2072-1439.2013.11.13

Surgical indications and optimization of patients for resectable esophageal malignancies

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ABSTRACT

Esophageal cancer is a devastating diagnosis with very dire long-term survival rates. This is largely due to its rather insidious progression, which leads to most patients being diagnosed with advanced disease. Recently, however, a greater understanding of the pathogenesis of esophageal malignancies has afforded surgeons and oncologists with new opportunities for intervention and management. Coupled with improvements in imaging, staging, and medical therapies, surgeons have continued to enhance their knowledge of the nuances of esophageal resection, which has resulted in the development of minimally invasive approaches with similar overall oncologic outcomes. This marriage of more efficacious induction therapy and diminished morbidity after esophagectomy offers new promise to patients diagnosed with this aggressive form of cancer. The following review will highlight these most recent advances and will offer insight into our own approach to patients with resectable esophageal malignancy.

KEYWORDS

Esophageal cancer; indication for surgery; preoperative optimization; review

J Thorac Dis 2014;6(3):249-257. doi: 10.3978/j.issn.2072-1439.2013.11.18

Overview

The American Cancer Society projects that in 2013, 17,990 adults will obtain a diagnosis of esophageal cancer and 15,210 will succumb to the disease. While the incidence of this cancer is relatively low, the long-term prognosis is grim with overall five-year survival rates of 17%. There are, however, promising avenues for further gain—including earlier detection, aggressive adjuvant therapies, greater patient optimization, and augmented surgical prowess in managing diseases of the esophagus. This is supported by the disparity of survival depending upon the stage of the cancer at the time of diagnosis with isolated esophageal disease harboring a substantial survival benefit in comparison to those with distant metastasis (38% and 3% five-year survival, respectively) (1). This considerable difference has empowered

both oncologists and surgeons to work together to uncover the best treatment algorithms with patient-specific paradigms at the forefront of their efforts.

The following review will highlight major risk factors for development of esophageal cancer, recent advancements in the realm of the various imaging modalities utilized in staging, and current trends in medical and surgical management with a focus on patient optimization prior to resection.

Clinical presentation

The unique anatomic structure of the esophagus is the reason most individuals presenting with obstructive esophageal symptoms are diagnosed with advanced disease. Because it lacks a true serosal layer, the smooth muscle of the esophagus can stretch, accommodating a large tumor burden before frank symptomatology is evident. For instance, dysphagia, the most common presenting complaint, is not clinically significant until 50-60% of the esophageal lumen has been comprised by the tumor. Typically, this patient population presents with difficulty in swallowing solid foods which progresses to liquids as the tumor increases further in size. This leads to substantial weight loss, yet another regular complaint in those with esophageal cancer. This baseline state of malnutrition can

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Submitted Aug 05, 2013. Accepted for publication Nov 22, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

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make chemotherapeutic and surgical recovery difficult and the importance of a knowledgeable nutritional team must not be underemphasized (2).

Additionally, patients may complain of painful swallowing (odynophagia) which can further exacerbate the aforementioned anorexia. The root cause of this discomfort is most likely multifactorial, caused in part by overlying ulceration as well as direct mediastinal invasion. A number of respiratory specific findings, while rare, can represent tumor invasion into local structures. For instance, hoarseness is indicative of laryngeal nerve involvement and a recurrent cough generally represents a fistulous communication between the esophagus and the tracheobronchial tree. The combination of symptoms present at diagnosis depends largely upon the location of the tumor along the length of the esophagus and, therefore, is in part dictated by whether or not the tumor represents adenocarcinoma or squamous cell carcinoma.

Adenocarcinoma and squamous cell carcinoma: an overview, including disease-specific risk factors

When discussing cancer of the esophagus, it is crucial to differentiate between the two major subtypes—adenocarcinoma (ACA) and squamous cell carcinoma (SCC)—as the risk factors and disease specific characteristics differ significantly depending upon the cell-line of origin (3-5). While there remains a higher incidence of squamous cell carcinoma worldwide, the occurrence of adenocarcinoma has increased in the past three decades while the former appears to have been stable or slightly decreased (6,7). Although the root cause of this trend is not completely understood, it does correlate with a more thorough understanding of the pathogenesis of esophageal cancer as well as recent advancements in disease detection.

The most thoroughly investigated and significant risk factor for adenocarcinoma is the presence of gastroesophageal reflux disease (GERD) (8). While there have also been associations between morbid obesity, medications that diminish the basal lower esophageal sphincter tone, long-standing tobacco abuse and previous thoracic radiation and the development of cancer, reflux remains the most influential risk factor in the progression to invasive disease (8-13). The basic premise is that reflux disease results in intestinal metaplasia (Barrett's esophagus), which further evolves into dysplasia and eventually includes foci of microscopic or grossly invasive cancer. The biology of this degradation includes alterations in various, universally accepted cancer genes, such as *p53*, *p16*, *APC* and *telomerase*, as well as complex interactions between bile, acid, the *Cdx* gene and the

diagnosis of adenocarcinoma (14-16).

The pathway from normal esophageal mucosa to the appearance of squamous cell carcinoma has not been entirely discerned, but there are, nevertheless, some clear risk factors that have been implicated in the development of SCC. This subtype has been linked both to alcohol consumption and to tobacco abuse, as well as a history of head and neck cancer and previous thoracic radiation. Interestingly, several studies have also established the association between red meat consumption and an increased risk of esophageal SCC, presumably due to the production of *N*-nitroso compounds, which have proven to be carcinogenic in animal models (17-19).

This conversation is not purely academic in nature, as a greater realization of the pathogenesis and biological progression of both SCC and ACA has afforded surgeons and oncologists with an improved understanding of the natural history of esophageal disease, its aggressivity, and its expected response to treatment. There is a general consensus that irrespective of histological tumor type, an R0 resection (microscopically negative margins) and the presence of lymph node metastasis are prognostic factors in patient's undergoing surgical intervention for esophageal cancer (3,20). Historically, the studies which have attempted to further delineate prognosis based on subtype have been divided, with several demonstrating a survival benefit in those with ACA (5,21), several presenting improved outcomes in patients with SCC (22,23), and still others showing no significant difference in either group (24).

As the debate surrounding the true impact of histology on overall survival continues, additional disagreement can be found when examining the response of SCC and ADA to neoadjuvant therapies. A large, single institution series demonstrated that after treatment with similar neo-adjuvant regimens, esophageal squamous cell cancer was associated with a higher rate of pCR than adenocarcinoma (42.8% versus 20%) (25). Cancer histology has been reported to influence post-neoadjuvant prognostic characteristics as well. While the most significant predictor of survival in adenocarcinoma appears to be residual nodal status (26), persistent local disease appears to be the most important element in squamous cell cancer (25). Additional studies have established that after trimodal therapy, patients with ACA frequently had malignant lymphadenopathy in the esophageal specimen, which inevitably results in a shorter time-to-metastasis (4,27,28). A more thorough review regarding the impact of neoadjuvant therapy on overall survival will follow in a subsequent section, but it is valuable to discuss the utility of viewing ACA and SCC as separate but similar entities rather than solely grouping them under the modifier 'esophageal cancer'. While the relevance of these distinctions

to the surgeon might not be initially obvious, preoperative optimization is crucial in order to maximize the overall benefit after an esophagectomy.

Diagnosis and staging

Once definitively diagnosed, a combination of imaging modalities has been utilized to most accurately stage esophageal cancer according to the recommendations of the American Joint Commission on Cancer's 7th edition guidelines, which include its depth of invasion (T), its degree of nodal involvement (N) and its spread to distant sites (M) (29). Accurate staging is instrumental to the treatment team as it dictates which therapeutic approach will become the focus of the management strategy.

Endoscopic ultrasound (EUS) is the preferred mechanism to determine the depth of esophageal invasion with an accuracy of almost 90% (30). Precision in distinguishing between the various 'T' stages becomes critical to the surgical team because advances in radiofrequency and endoscopic therapies have afforded patients with dysplastic disease as well as early stage, superficial esophageal cancer (Tis and T1a disease, respectively) an alternative to radical esophagectomy (30-34). Furthermore, local invasion of unresectable structures such as the aorta, vertebrae and the trachea (T4b) excludes surgery as a feasible treatment option. Due to it being widely accepted that the number of positive nodes in the esophagectomy specimen is prognostic of overall survival, it is also essential that imaging be sensitive enough to accurately detect suspicious lymphadenopathy (29,35). Accordingly, in order to be assured of the nodal status preoperatively, an array of information is obtained from EUS, CT, and PET/CT. Aside from merely offering a mechanism for staging, these tools can dictate whether a lesion is amenable to surgical resection. Positive, or highly suspicious, nodes outside of the typical resection field as well as distant sites of metastasis (M1 disease) denote incurable disease with very poor long-term prognosis (1).

Approach to treatment: the interplay of neoadjuvant, endoscopic and surgical therapies

As mentioned previously, individuals with esophageal cancer typically seek medical attention once the disease has progressed to a more advanced stage, resulting in a treatment strategy of which a multi-modal approach is central (36,37). Patients must be carefully analyzed by the surgery, gastroenterology, and oncology services to determine which therapy, or therapies, will be the foundation of this stage-specific approach.

High grade dysplasia (carcinoma in situ)

The risk of progression from high grade dysplasia (HGD) to invasive cancer has been estimated at 10% per year (38). Historically, esophagectomy had been recommended for patients with areas of HGD because it had been associated with a 40-60% risk of harboring cancer (39). More recent investigations, however, have questioned the need for such aggressive treatment in this population of patients, and have demonstrated instead, that radiofrequency ablation (RFA) provides adequate eradication in those with both high- and low-grade dysplasia (90.5% and 81.0%, respectively) (33). Furthermore, in one large study, only 3.6% of patients had disease progression after ablation therapy and an even small number (1.2%) developed cancer (33). Of note, RFA should be avoided in patients with long segments of dysplasia, nodular features or multifocal disease, since these characteristics have been associated with failure of endoscopic treatment.

Stage I disease

As stated above, superficial lesions involving the lamina propria (T1a) without extension into the submucosa (T1b) are typically responsive to endoscopic mucosal resection (EMR) with five-year survival rates above 90% (30-32,34,40,41). This is attributable to the low rate of lymphatic involvement associated with these early stage tumors (42,43). EMR offers a lower-risk alternative to surgical intervention in applicable tumors with complication rates quoted in some studies to be as low as 7% while simultaneously maintaining similar long-term survival as esophagectomy (44,45). The use of endoscopic therapy is cautioned however, in cancers that have invaded beyond the lamina propria (T1b) as locoregional control can be compromised due to a substantial risk of lymph node involvement. These patients, given they have no appreciable metastases, should be referred for a formal resection with lymph node dissection.

Stage II and III disease

The ultimate goal and interest of the surgeon, however, is being able to select which patients will benefit from surgical resection in terms of overall survival and which ones will not. Consequently, patients with advanced, but resectable, lesions should be presented at multi-disciplinary cancer conferences (MDCCs) in order to ensure that the treatment plan follows the most up-to-date and widely accepted guidelines. Several studies have outlined the benefits of MDCCs in patients with

Table 1. A select number of randomized-controlled trials on the benefit of induction therapy followed by surgery vs. surgery alone in the management of esophageal cancer.

References	Publication	Methods	Results
Bosset et al. (53)	NEJM 1997	282 patients: 139—surgery alone 143—induction CRT	No difference in overall survival Chemoradiotherapy resulted in: longer disease free survival (P=0.003) longer interval free of local disease (P=0.01) lower rate of cancer-related deaths (P=0.002) higher rate of curative resections (P=0.017)
van Hagen et al. (52)	NEJM 2012	366 patients: 188—surgery alone 178—induction CRT	Chemoradiotherapy resulted in: greater incidence of R0 resection (P<0.001) longer overall survival (P=0.003) greater median disease free survival (P<0.001)
Walsh et al. (54)	NEJM 1996	113 patients: 55—surgery alone 58—induction CRT	Chemoradiotherapy resulted in: greater median overall survival (P=0.01) greater 3-year survival advantage (P=0.01)
Burmeister et al. (37)	Lancet Oncol 2005	256 patients: 128—surgery alone 128—induction CRT	No difference in overall survival No difference in progression-free survival Chemoradiotherapy resulted in: greater incidence of R0 resection (P<0.001) fewer positive lymph nodes (P=0.003)

Abbreviations: NEJM, New England Journal of Medicine; CRT, Chemoradiation therapy.

esophageal cancer which include enhanced staging (and thus a greater percentage of patients foregoing esophagectomy in favor of endoscopic therapy), an improvement in the time interval from diagnosis to commencement of treatment, and most importantly, a favorable impact on five-year survival (46-48).

These conferences refer to the National Comprehensive Cancer Network (NCCN) guidelines for esophageal cancer as a framework from which to construct their specific intervention. T1b-T4a cancers (tumors invading the submucosa, muscularis propria, adventitia, or specific adjacent structures—pleura, pericardium, and diaphragm) represent resectable disease (49). For those deemed candidates for esophageal resection and especially in T2-T4a and N + (stage II and stage III) disease, preoperative therapy should be considered. This has been supported in several randomized control trials and a large meta-analysis, which have all demonstrated a distinct overall and disease-free survival benefit in individuals undergoing chemoradiotherapy prior to surgical resection (50-52). In the CROSS study, there was a 34% lower risk of death in patients

treated with combined neoadjuvant and surgical therapy in comparison to those who only underwent esophagectomy without any prior systemic therapy (52). There is always the theoretic concern that radiation-induced fibrosis will complicate an ensuing resection, but this was not supported in the aforementioned study as nearly 94% of patients underwent successful esophagectomy following chemoradiotherapy (52). Table 1 provides a brief overview of a select number of the randomized-controlled trials evaluating the benefit of induction chemoradiation therapy.

Stage IV disease

T4b cancers, or those involving the heart, great vessels, trachea or other adjacent organs (e.g., the liver, pancreas, lung and spleen) are not amenable to surgical intervention unless palliation is sought (49). And although there have been several smaller case reports of subsequent metastasectomy in patients with previously resected esophageal cancer primaries, there

have been no large trials that have exhibited a survival benefit in surgically treated Stage IV disease and, currently, it cannot be universally recommended (49,55).

Patient optimization prior to surgical resection

Esophagectomy is an incredibly demanding operation for patients with cancer of the thoracic esophagus and subsequent morbidity is common following resection. It is imperative, therefore, aside from merely selecting the most appropriate treatment strategy, that the surgical team consults multidisciplinary services to perform a thorough preoperative assessment of the patient's cardiac, pulmonary and nutritional reserves.

With gastrointestinal obstruction and tumor cachexia regularly present in esophageal cancer, almost all patients exhibit some degree of malnutrition. There is substantial evidence that malnutrition is immunosuppressive and has a negative impact on survival (56,57). Accordingly, it is generally recommended that placement of definitive enteral access be considered at the time of resection and that patients who are unable to tolerate at least 50% of their goal calories be started on feeds postoperatively (58). While access is usually secured via the jejunum during the esophagectomy, we support the creation of gastric access prior to induction therapy to ensure that preoperative malnutrition is minimized. This can be performed safely via an endoscopic or laparoscopic approach, but careful attention is needed to avoid injury to the gastropiploic artery, which will supply the gastric conduit during reconstruction.

As mentioned above, patients with relatively more advanced disease are typically treated with a combination of induction chemoradiation followed by a definitive resection. Timing of esophagectomy after preoperative therapy has been under scrutiny as there is a delicate balance between allowing patient recovery while also avoiding progression of disease in the interim. Appropriately, several studies have evaluated this time interval and most centers have now adopted a 6-8-week window after induction therapy during which to schedule an esophagectomy.

Surgical options: trans-thoracic, trans-hiatal, and minimally-invasive approaches

Currently, surgical resection remains the only treatment modality with a chance of oncologic cure in patients with more advanced esophageal carcinoma. The operation can be performed either via a transthoracic or transhiatal approach. The most widely used techniques are the Ivor Lewis esophagectomy (ILE), the transhiatal esophagectomy (THE) and the McKeown

esophagectomy. Minimally invasive esophagectomy (MIE) has recently emerged as a cutting edge option for esophageal resection. Using smaller incisions, MIE harnesses the already well-established open techniques while minimizing the physiologic impact of this large-scale operation.

The ILE begins with a laparotomy for conduit construction and mobilization. A right thoracotomy is subsequently conducted for the esophageal and nodal dissection followed by an intrathoracic anastomosis. The McKeown esophagectomy is similar to the ILE however a cervical anastomosis is created via a left neck incision. It is prudent for the surgeon to select a thoracic approach for: tumors abutting the airway or mediastinal vasculature, large middle third esophageal lesions in which a radical resection may prove necessary, patients with suspected mediastinal fibrosis or in patients with prior gastrointestinal surgery which could lead to technical limitations for conduit mobilization to the neck.

THE commences similarly to an ILE with a laparotomy for gastric mobilization and conduit formation while the lymphadenectomy and mediastinal dissection are performed via the diaphragmatic hiatus. The proximal esophagus is subsequently mobilized via a left neck incision and a cervical anastomosis is fashioned. Patients with marginal pulmonary status can benefit from a THE due to the lack of a thoracotomy resulting in a decreased incidence of ventilator dependence and pneumonia (59,60). This is largely attributed to poor pulmonary toileting postoperatively secondary to pain and splinting. Assessing the outcomes of THE versus ILE, the data show that perioperative morbidity and mortality are roughly equivalent. In a 945 patients study, Rentz *et al.*, showed a mortality rate of 10% for ILE and 9.9% for THE (61). Morbidity occurred in 47% of patients following ILE and 49% for THE (61). Risk factors for mortality following an esophageal resection include a serum albumin less than 3.5 g/dL, blood transfusions of more than four units and age greater than 65 (61). There was no difference noted in the incidence of renal failure, infection, pulmonary failure, bleeding or mediastinitis between the two cohorts (61).

Proponents of the thoracic approaches to esophagectomy argue that ILE has been shown to have fewer anastomotic strictures and leaks as compared to THE (62). Moreover it touts a superior oncologic result due to increased exposure, which allows improved visualization of the tumor and the mediastinum resulting in an increased nodal yield as compared to THE. One study showed that ILE collected a mean of 18.5 nodes as compared to 9 for THE (63). Due to the regional lymphatic basins exhibiting a high rate of nodal metastasis, a more substantial nodal yield is important for staging and prognosis. The results of a European randomized study showed that,

although median overall, disease-free, and quality-adjusted survival did not differ statistically between patients undergoing transhiatal or transthoracic esophagectomy, there was a trend toward improved long-term survival at five years with the extended transthoracic approach (64). This subject remains controversial since the benefit of an extended lymphadenectomy is often outweighed by the morbidity of the operation. It has become our practice, however, to utilize a thoracotomy incision or a minimally invasive strategy in most every patient to ensure an adequate lymphadenectomy, with THE being reserved for multifocal or long segment, high grade dysplasia or T1a disease not suitable for EMR.

MIE has now emerged as a safe and feasible operation to offer patients at high volume centers without the need for special selection criteria (65-67). A multitude of studies, including several meta-analyses and a randomized, controlled trial, have reported equivalent mortality rates between MIE and open esophagectomy (OE) (66,68-70). Moreover, MIE has been shown to be associated with a decrease in morbidity, duration of mechanical ventilation, as well as in ICU and overall hospital stay (67-70).

While MIE has demonstrated sound perioperative outcomes, it is also noteworthy that the oncologic impact of the operation is not changed when compared to OE. With improved visualization, the median nodal harvest is higher for MIE than OE (66). Additionally, margin status is similar between the two groups with 87% R0 resections in the MIE group as compared to 92% in the OE cohort (66). Disease free and overall survival following MIE are also similar to its open counterpart, although these data reflect only short term follow-up (65-67). Another benefit to MIE is the enhanced quality of life (QOL) following the operation. Zeng *et al.* showed that following MIE, patients had improved QOL scores, lower pain scores and increased physical function scores (71). Therefore MIE could be the answer for an extensive esophageal and nodal dissection, without the additional morbidity associated with an open, transthoracic approach.

The extent of lymphadenectomy, however, remains a controversial topic. Three field lymphadenectomy, which adds an extensive cervical dissection, is widely advocated by high volume centers in Japan and other countries in the Eastern hemisphere (72-75). Cervical nodal dissection might improve loco-regional control in aggressive upper esophageal lesions, which happen to be more common in these countries (73-75).

However, because the correlation between the three field approach and improved survival is absent, the extended lymphadenectomy has not garnered much support in the West (76). Additionally, there is the concern that a three-field lymph node

dissection merely results in stage migration with the added morbidity of a neck dissection. The number of lymph nodes harvested during esophagectomy is likely more important than the field of dissection. Several studies have demonstrated that a greater number of lymph nodes removed at the time of resection is associated with progressively increased survival. This associated, however, is not linear and is believed to be stronger for locally advanced tumors (77-79). It is, therefore, recommended that a minimum of ten nodes be resected for T1 cancers, 20 nodes for T2 cancers and 30 nodes for T3/T4 cancers in order to maximize 5-year survival.

Conclusions

While the diagnosis of esophageal cancer remains devastating, a greater understanding of the disease's pathogenesis and the impacts of both neoadjuvant and surgical interventions on overall survival have been encouraging. Due to enhancements in the various modalities utilized in esophageal cancer imaging, improved staging has allowed surgeons to select which patient populations will be afforded the greatest benefit after esophageal resection. Similarly, patients with more extensive disease have profited from a combination of more efficacious radiation and chemotherapy prior to their surgical resection. These numerous facets of the treatment platform have been incorporated into multi-disciplinary cancer conferences, which have permitted a rich dialogue between the numerous departments involved in the management of this complex neoplasm. Areas for future investigation include improved screening in high risk individuals, earlier detection by capturing circulating tumor cells or other malignant markers and more personalized treatment paradigms using each individual's unique genomic targets.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Grimm JC, Valero V, Molena D. Surgical indications and optimization of patients for resectable esophageal malignancies. *J Thorac Dis* 2014;6(3):249-257. doi: 10.3978/j.issn.2072-1439.2013.11.18

Indications and interventional options for non-resectable tracheal stenosis

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ABSTRACT

Non-specific presentation and normal examination findings in early disease often result in tracheal obstruction being overlooked as a diagnosis until patients present acutely. Once diagnosed, surgical options should be considered, but often patient co-morbidity necessitates other interventional options. Non-resectable tracheal stenosis can be successfully managed by interventional bronchoscopy, with therapeutic options including airway dilatation, local tissue destruction and airway stenting. There are common aspects to the management of tracheal obstruction, tracheomalacia and tracheal fistulae. This paper reviews the pathogenesis, presentation, investigation and management of tracheal disease, with a focus on tracheal obstruction and the role of endotracheal intervention in management.

KEYWORDS

Airway stent; laser therapy; rigid bronchoscopy; tracheal stenosis; large airway obstruction

J Thorac Dis 2014;6(3):258-270. doi: 10.3978/j.issn.2072-1439.2013.11.08

Introduction

Large airway obstruction, particularly tracheal disease, is widely believed to be under-diagnosed and under-reported. Recognition of the precipitants to tracheal obstruction and of the common clinical manifestations and investigation findings will facilitate prompt and appropriate management. Rigid bronchoscopy is increasingly popular for the diagnosis and management of tracheal obstruction, and has a role in the delivery of interventional bronchoscopy. Surgical management is often definitive but patient selection and preparation is essential for surgical success.

This paper reviews the pathogenesis, presentation, investigation and management of tracheal disease, with a focus on tracheal obstruction and the role of endotracheal intervention in the management of non-resectable disease. It is intended that this paper will provide guidance for those involved in the care of patients with tracheal disease.

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Submitted May 30, 2013. Accepted for publication Nov 20, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

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Tracheal anatomy and physiology

The trachea extends from the lower body of the cricoid cartilage to the carina and is normally between 110 and 130 mm in length. The tracheal diameter is typically up to 22 mm in males and up to 18 mm in females. Air is a fluid which flows down a pressure gradient, from higher to lower pressure. Airflow can be laminar or turbulent, with the flow rate defined as the amount of fluid moving per second. When flow is laminar, the airflow rate is directly proportional to the pressure gradient but when flow is turbulent, the airflow rate is proportional to the square root of the pressure gradient. Turbulence thus increases airflow resistance, necessitating a higher pressure difference to maintain a given flow rate. Reynolds number is a non-dimensional parameter that governs the change from laminar to turbulent air flow. It is calculated by multiplying mean fluid velocity, density and airway diameter then dividing by fluid viscosity. The diameter of the trachea affects airflow by this equation and any abrupt variation in tracheal diameter produces a transition point which also predisposes to turbulence.

Tracheal obstruction

Congenital or acquired tracheal narrowing may result from intrinsic tracheal stenosis and/or external compression, at any

anatomical level. Variation in the tracheal diameter alters the airflow dynamics in the direction of increased airflow resistance. Tracheal stenosis often results in varying degrees of distortion along the vertical plane in addition to airway narrowing. When the trachea becomes pulled away from or twisted within its normal anatomical path, this further predisposes to airway turbulence and increased resistance.

Congenital

Tracheal stenosis is rarely congenital but may result from posterior fusion of the tracheal rings. By contrast, congenital tracheal webs are well recognised, with 75% occurring at the level of the glottis. Tracheal webs differ from tracheal stenosis due to the absence of a cartilaginous framework. Both may present in adult life.

Congenital cardiovascular anomalies can result in extrinsic compression of the trachea. Most commonly, early bifurcation of the innominate artery compresses the anterior tracheal wall, appearing pulsatile at bronchoscopy. Other causes include anomalies of the subclavian artery and vascular rings, such as congenital double aortic arch, which encircle the trachea causing circumferential compression.

Acquired

Trauma

The cartilaginous trachea has a natural tendency to narrow and fibrose in the face of injury. Tracheal trauma is the most common cause of benign tracheal stenosis and is a feared complication of prolonged endotracheal intubation or tracheostomy tube placement. The presence of tracheal stenosis can necessitate re-intubation and delay respiratory weaning in intensive care unit patients or can present many years later.

The reported incidence of tracheal stenosis following endotracheal intubation ranges from 6-21% and following tracheostomy ranges from 0.6-21% (1-3). With the trend towards early tracheostomy as an aid to respiratory weaning, and increasing numbers of successful discharges from intensive care units, the incidence of tracheal complications is rising.

Stenosis occurs when pressure and friction on the mucosal surface stimulates inflammation and pressure necrosis. Granulation tissue formation is followed by fibroblast proliferation, scarring and contracture. Stenoses can develop after as little as 36 hours of endotracheal intubation but the risk of stenosis rises with duration of intubation. Most strictures occur at the site of the tube cuff, with reduced incidence following the introduction of compliant, large volume, low pressure cuffs (4).

After tracheostomy, stenosis most commonly occurs at the stomal site (3,5). Wound sepsis is a predisposing factor (6). Pre-existing chronic lung disease and airway infection are also associated with tracheal stenosis post endotracheal intubation or tracheostomy (7).

Trauma may also arise from thermal or chemical burns (including chemical warfare agents), resulting in localised stenosis.

Infection

Airway infection alone can result in the development of tracheal stenosis. Tuberculosis is the most common cause of post-infective stenosis but diphtheria, syphilis and fungal infection (e.g., histoplasmosis, blastomycosis) are also recognised causes.

Non-infectious inflammation

Non-infectious inflammatory conditions causing tracheal stenosis include collagen vascular disorders (e.g., Wegener's granulomatosis), sarcoidosis, amyloidosis and chronic atrophic polychondritis. Diffuse inflammatory and infective processes often result in multi-level tracheobronchial stenoses.

Neoplastic

Airway obstruction develops in 20-30% of lung cancer patients (8), however, tracheal compromise occurs in less than 1% of all malignancies (9). Direct tumour invasion of the trachea by a bronchogenic malignancy is more common than metastatic involvement of the trachea. Primary benign tumours of the trachea such as chondromas, fibromas, hemangiomas, and squamous papillomas are rare causes of tracheal stenosis. Extrinsic compression of the trachea can occur from malignant lymphadenopathy, thyroid and mediastinal tumours.

Iatrogenic

The insertion of a tracheal stent (e.g., for tracheobronchomalacia) can, paradoxically, lead to stenosis due to tracheal irritation and the formation of granulation tissue at either end of the stent. Cervico-mediastinal radiotherapy is another recognised cause of stenosis.

Other

Tracheopathia osteochondroplastica is a rare, but increasingly recognised condition in which there is the idiopathic development of focal or diffuse, osseous and/or cartilaginous nodules in the submucosa of the trachea and bronchial walls. The posterior membranous portions of the trachea are characteristically spared. Significant tracheal stenosis and/or tracheomalacia can result.

Superior mediastinal pathology can cause extrinsic tracheal compression. Most frequently this arises from lymphadenopathy secondary to infection, inflammation or neoplasia, but abnormalities of the aortic arch such as dissection or aneurysm can also compress the trachea (10). Thyroid goitre may also cause extrinsic compression, particularly if there is retrosternal extension.

Idiopathic

Idiopathic tracheal stenosis is rare, representing 3-5% of cases. Most commonly these stenoses develop at the level of the cricoid cartilage and are restricted to young women (11). Pathologically there is extensive keloidal fibrosis and mucus glands dilation which may represent a form of fibromatosis (12).

Tracheal fistulae

Any aggressive tracheal pathology can disturb the integrity of the tracheal wall resulting in communication with the mediastinum. Iatrogenic, traumatic and malignant cases are the most prevalent. Infection as an aetiological factor (tuberculosis, HIV infection, mediastinitis) has reduced in recent years. Communication may also be established between the tracheobronchial tree and the oesophagus, resulting in tracheo-oesophageal (or bronchial-oesophageal) fistulae. Acquired tracheo-oesophageal fistulae are frequently the result of mediastinal malignancy. Tumours arising from the oesophagus, trachea, lungs, larynx, thyroid and lymph glands have all been reported to cause fistula formation. Tracheo-oesophageal fistulae can also be congenital. These typically present in the neonatal period but may rarely present in adulthood.

Tracheomalacia

Tracheomalacia is characterised by flaccidity of the tracheal cartilage, leading to airway collapse during expiration. The condition may extend to involve the bronchi (tracheobronchomalacia). Significant airway malacia is defined as a greater than 60% reduction in luminal diameter.

Congenital tracheomalacia results from a developmental defect in the cartilage of the tracheal wall. Tracheomalacia may also develop in the context of congenital conditions such as cystic fibrosis, Mounier-Kuhn syndrome, Marfan syndrome, Ehlers-Danlos syndrome, and congenital trachea-oesophageal fistulae.

Acquired tracheomalacia is associated with prolonged endotracheal intubation and tracheostomy, trauma, head and neck surgery, radiotherapy, and inflammatory conditions such as polychondritis. Intrinsic tracheal disease such as tracheal stenosis and previous tracheal stenting may also contribute to weakening

of the airway support and malacia. When tracheomalacia occurs in the absence of a clear pathophysiology, these patients are often obese, with smoking related lung disease or recurrent/chronic airways infection.

Diagnosis of tracheal disease

The diagnosis of tracheal disease is a recognised challenge because of the broad range of aetiologies and the non-specific nature of presentation, which often has an insidious onset at first. Thus, a detailed patient history and examination is imperative to guide further investigation and management. Sometimes when the patient presents in extremis this is not possible or appropriate, and rapid intervention in a controlled environment with appropriately skilled personnel is central to a successful outcome.

History and examination

Symptoms depend on the location and degree of airway narrowing, additional airway distortion and concurrent thoracic pathology. Most commonly, patients report shortness of breath on exertion, which may progress to dyspnoea at rest. Symptoms occur on exertion when the tracheal diameter is significantly reduced to 8 mm (13). Cough and wheeze are common. Airway obstruction may lead to difficulty with sputum clearance and recurrent infection. The combination of exertional dyspnoea and wheeze is frequently mistaken for chronic bronchitis or asthma. Failure to respond to bronchodilators should not be overlooked.

It is not uncommon for patients with tracheal disease to present with acute respiratory distress, even in benign disease. These presentations are usually triggered by the partial or complete occlusion of the abnormal airway by sputum or haemorrhage.

History taking should focus on potential tracheal insults such as intensive care admission, hoarseness after general anaesthesia (suggestive of traumatic injury), or respiratory tract infections. A full systems enquiry may also reveal information relevant to the underlying diagnosis.

Respiratory examination is often normal until there is severe tracheal stenosis or secondary airway occlusion due to sputum or haemorrhage. Stridor occurs when the tracheal diameter is less than 5 mm (13). Examination should explore the underlying diagnosis, looking carefully for signs such as a tracheostomy scar, goitre, lymphadenopathy or the classical nasal changes of Wegener's granulomatosis.

Investigation

When tracheal disease is suspected, first line investigations

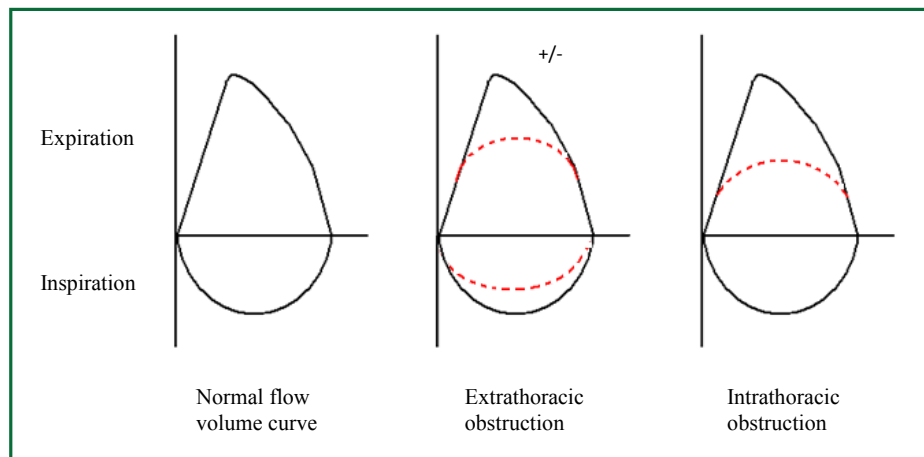


Figure 1. Flow volume curves showing upper airway obstruction.

should include targeted blood tests to look for the underlying diagnosis (e.g., inflammatory markers, autoimmune screen), pulse oximetry and/or arterial blood gas analysis and standard chest radiography. These investigations are often normal.

Lung function testing

When spirometry results are interpreted correctly, ensuring technical requirements are met, they can be the first investigation to suggest the diagnosis of tracheal obstruction. Flow volume diagrams provide an indication of the severity of airflow obstruction and the location of airway obstruction, i.e., intrathoracic or extrathoracic (14).

The pressure surrounding the intrathoracic airway approximates to pleural pressure, which changes during the respiratory cycle. During inspiration, negative intrapleural pressure causes the intrathoracic airway to be splinted open. During expiration, positive intrapleural pressure compresses the intrathoracic airway. Therefore, in intrathoracic airway obstruction (for example in lower tracheal stenosis) typically there is upper airway collapse during expiration and flattened expiratory flow volume curves, but the inspiratory flow volume curve remains normal.

The reverse is true in the fairly compliant extrathoracic airway that is not exposed to intrapleural pressure. Inspiration results in collapse of the extrathoracic upper airway, as the airflow acceleration into the lungs reduces intraluminal pressure. Extrathoracic airways obstruction (upper or mid tracheal obstruction) therefore typically causes airway collapse during inspiration, with flattening of the inspiratory flow volume curve. The force of expiration opens the extrathoracic airway usually resulting in a normal expiratory curve. The expiratory curve may become flattened when there is significant extrathoracic

obstruction, resulting in reduced peak airflow rates. Schematics of the classical flow-volume diagrams are displayed in Figure 1.

Radiological imaging

Computed tomography (CT) is the radiological modality most often used to image the trachea. Dedicated tracheal protocols allow the acquisition of thin slices through the upper airways. With standard chest protocols, tracheal disease is easily underestimated. “Virtual endoscopy” procedures can be performed using CT images constructed during post-processing, with no additional radiation burden (Figure 2). The advantages of virtual endoscopy include the capability to view non-traditional perspectives, to provide volumetric analyses and to apply automatic feature recognition software (15).

CT is useful for diagnosing tracheal disease, identifying the precise anatomical location, the characteristics of the lesion and the extent of disease, including distal airway patency and local vascular anatomy. When tracheal lesions are visualised in cross section, it is possible to assess whether they are circumferential or incomplete, in a single plane (web like) or in three dimensions, like a cork-screw. CT windows also include the wider chest and may provide supportive evidence of an underlying diagnosis.

The combination of axial imaging, multiplanar reformatting, and 3-dimensional rendering is useful prior to tracheal intervention, especially when there is significant anatomical distortion or airway narrowing (16).

Bronchoscopy

Flexible bronchoscopy is often performed in the diagnostic work up for symptoms that are subsequently identified as tracheal in origin. Flexible bronchoscopy is however best avoided due to the risk of precipitating acute, complete airway obstruction



Figure 2. Virtual bronchoscopy images of the normal proximal (A) and distal (B) trachea and tracheal stenosis (C).

or proximal haemorrhage. Rigid bronchoscopy is preferred for evaluating stenotic lesions in the trachea and the advantages over flexible bronchoscopy for diagnosis and therapy which will be discussed further below.

Management

Non-acute airway obstruction

In the non-acute setting, initial management should target ongoing tracheal insults such as inflammation or infection, to retard disease progression. Inflammatory conditions such as collagen vascular disease may respond to steroid or immunomodulatory therapies. Airway infection can be difficult to control and identification of the pathogenic organism is key. Recurrent pathogen isolation may prompt long term antibiotic prophylaxis as oral or nebulised therapy. Airway clearance is crucial and can be enhanced by the use of mucolytic agents such as carbocysteine, nebulised therapy with saline and/or N Acetyl Cysteine and chest physiotherapy.

Acute airway obstruction

When patients present acutely with significant upper airways obstruction, supportive measures may be necessary and include the commencement of an inspired Helium-oxygen (Heliox) mixture. Heliox is less dense than oxygen and nitrogen. In accordance with Reynold's equation, reducing the density of the inspired gas has the effect of predisposing to laminar flow and this can be used to improve airway dynamics in the short term.

Definitive management

Most significant tracheal stenoses necessitate interventional bronchoscopy or surgical resection. Definitive management should be planned with the input of the multi-disciplinary team.

It is the nature of patients with tracheal pathology that their underlying disease or history of intensive care admission may make them high risk surgical candidates; thus, endotracheal intervention is often preferable (17). All patients should, however, be considered for tracheal surgery.

Interventional bronchoscopy does not preclude future surgery in most cases and may optimise potential surgical candidates. Lower surgical success rates are evident if the patient has had previous tracheal surgery, but previous laser therapy does not affect surgical outcome (3).

The most frequent complication of tracheal resection and reconstruction is granulation tissue formation at the anastomotic site. Since the introduction of novel suture materials in 1978, the complication rate has fallen to 1.6% (18). It is possible to treat granulation tissue at the anastomotic site with endotracheal therapy.

Interventional bronchoscopy

Background

Interventional bronchoscopy should ideally be performed in specialist centres, with the support of experienced, consistent multi-disciplinary teams. Globally, interventional bronchoscopy is most commonly performed using intravenous awake sedation, local anaesthesia and the flexible bronchoscope. Rigid bronchoscopy under general anaesthesia has increased in popularity over the last two decades (19,20) but widespread adoption of the technique is limited by relative operator inexperience and a lack of available training. Rarely, if a tracheal stenosis is high, in close proximity to the vocal cords, a laryngeal mask and flexible bronchoscopy is indicated to visualise and treat the trachea.

Strengths and potential limitations of rigid bronchoscopy

Unlike flexible bronchoscopy, which relies upon the patient's own, potentially unstable airway and ventilation, rigid

bronchoscopy offers a controlled, ventilated airway under general anaesthetic, with the support of a cardiothoracic anaesthetist (21). Rigid bronchoscopy is therefore preferable for patients with severe respiratory disease who can be poorly tolerant of flexible bronchoscopy. The use of general anaesthesia also has the benefit of creating an immobile field, free from cough, allowing intervention to be performed more safely (22).

Biopsy or airway intervention during flexible bronchoscopy risks airway haemorrhage with potential compromise of both lungs, rendering the patient hypoxic. Rigid bronchoscopy offers a potentially safer means of obtaining a tissue diagnosis (23). Using the rigid bronchoscope it is possible to apply direct pressure to bleeding lesions, and to apply adrenaline soaked gauze using rigid forceps to tamponade the bleeding source, if direct application of adrenaline solution is not sufficient. Single lung isolation with the rigid bronchoscope can also be used to protect the non-bleeding lung if significant haemorrhage occurs.

The bronchoscope barrel can be used to dissect tissue or dilate tracheal stenoses directly, with excellent access for instrumentation with dilators or stents under direct vision. Rigid bronchoscopy minimises procedure times for endotracheal intervention. The median time to stent deployment is 12 minutes at our institution using rigid bronchoscopy (24).

In a specialist centre with a highly trained and experienced team, low complication rates are seen with rigid bronchoscopy. Potential complications include dental trauma, vocal cord trauma/inflammation and airway haemorrhage. Pneumothorax is a risk due to tracheal instrumentation and positive pressure ventilation but our local experience suggests rates of pneumothorax are less than 1% (based on review of >500 rigid bronchoscopy procedures) (24).

Performing rigid bronchoscopy

The rigid bronchoscope is a hollow, tapered metal tube, with distal side-holes along the body for optimal ventilation. The patient is positioned supine with their neck extended. The pharynx, larynx and trachea are aligned in order to insert the rigid tube, taking care to protect the teeth and vocal cords from trauma.

The lumen of the rigid bronchoscope is used for direct vision. Intervention is performed using rigid instruments passed through the rigid bronchoscope. A flexible bronchoscope is passed through the lumen of the rigid bronchoscope to better visualise segmental airways or to see beyond a narrowed trachea. Some centres use special thin flexible bronchoscopes for this purpose (25). The flexible bronchoscope is also utilised for laser therapy.

Endotracheal intervention

There is an overlap between the techniques used to treat tracheal and bronchial obstruction (26). Options include airway dilatation, tissue destruction and stent insertion, each of which is detailed below.

Airway dilatation

Dilatation is achieved with lubricated bougies of increasing diameter applying radial pressure circumferentially to the narrowed airway. Balloon dilatation is an alternative method. The flexible then rigid bronchoscope can also be used to perform blunt dissection and dilatation of stenosed areas under direct vision.

With all dilating techniques, it is imperative to identify the path of the true airway lumen. It is easy, especially when the trachea is distorted, to lose sight of the true lumen, risking airway perforation. Pre-operative imaging is useful to define patient anatomy.

Dilatation alone is very rarely a definitive therapy and re-stenosis usually occurs. Dilatation may be used in combination with other therapeutic techniques such as laser ablation and stent insertion, and can be repeated as necessary (NICE guideline IP938).

Tissue destruction

Once the true airway lumen has been identified, it is usually preferable to destroy and physically remove diseased tissue (Figure 3). The most rudimentary method of tissue destruction uses forceps to mechanically remove tissue from the trachea. Techniques used to effect tissue destruction include laser therapy, argon plasma, brachytherapy, electrocautery and cryotherapy. Most centres prefer laser therapy, of which the neodymium:yttrium-aluminum-garnet (Nd Yag; Nd: Y3Al5O12) laser is the most commonly used (19,27-29).

Nd-Yag laser energy is delivered via fibres inserted into the working channel of the flexible bronchoscope, using the rigid bronchoscope as a stable airway. The fibres can either be contact or non-contact and are used to devitalise or resect diseased tissue whilst assisting with haemostasis. Nd-Yag laser has a wavelength of 1,064 nm, which is in the invisible photo spectrum. A red light is therefore used to direct application. The bronchoscopist should always apply laser energy parallel to the central airway to avoid unintended trauma to local structures. Energy should be applied in a circumferential motion (Figure 4), using 1-5 seconds laser pulses. A circumferential as opposed to radial approach is preferred to open the airway in malignant and benign disease, to ensure good visualisation of the distal airway whilst improving

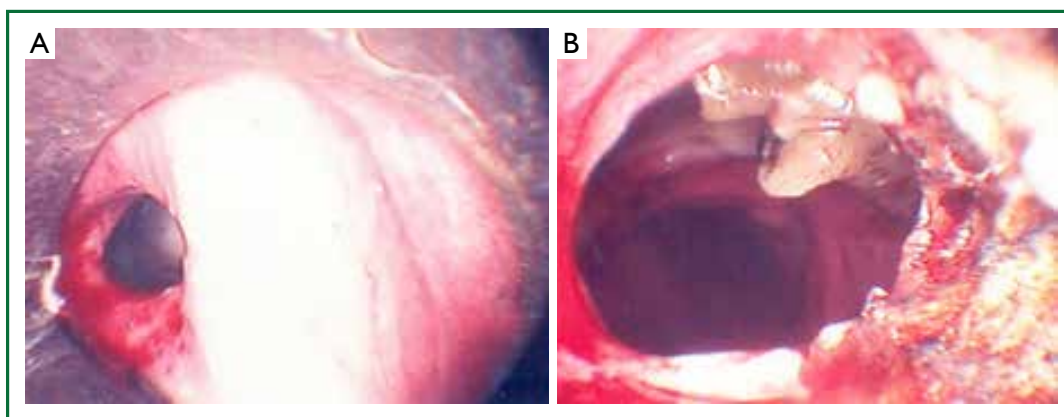


Figure 3. The endoscopic images of tracheal stenosis before (A) and after (B) Nd Yag laser therapy.

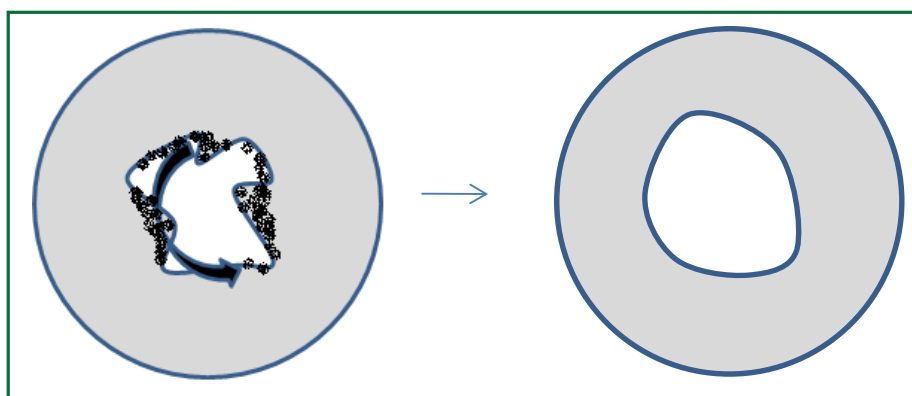


Figure 4. The technique of Nd Yag laser therapy. The laser fibre is moved in a circumferential fashion, starting from the centre of the airway.

airflow. The lowest possible power is recommended. Our recommended practice is to use a power of 15-20 watts in the trachea, and lower power distally.

Following laser treatment, the airway lumen may still appear narrowed. The effects of the treatment continue for days to weeks after the initial application. The bronchoscopist must therefore refrain from being too aggressive with laser therapy. During and after laser treatment, it is important to clear devitalised tissue from the trachea and distal airways. Aspiration is usually sufficient but manual forceps can also be used. The patient will cough up any remaining or further tissue that sloughs away over the coming days.

Personnel should be trained in the use of laser and a committee responsible for laser usage, maintenance and safety should be established and meet regularly. All staff within the potential laser field should wear protective eyewear. The operating room should be adapted for laser therapy with protective curtains, barriers and warning signs at all entry points, and a laser fume extraction device used (Figure 5). Inspired oxygen concentration should

be less than 40 percent and ventilation should be ceased during laser pulses to reduce the risk of airway fire. If a laryngeal mask is used during laser therapy this should be inflated with saline rather than air, to reduce fire risk.

Reported complications of laser treatment include haemorrhage, airway perforation and airway fire. However, published case series report overall complication rates below 1% in approximately 7,000 treatments (27). With safety measures in place, laser therapy is an excellent and reliable way of treating tracheal stenosis.

There is no limitation to the amount of times laser therapy can be performed. Nearly all patients require more than one endotracheal treatment to achieve long term airway patency. Tissue regrowth can be significantly slowed or halted by serial treatments, with the chance of success increasing after each treatment (30).

Endotracheal stenting

Endotracheal stents are used to provide structural support to

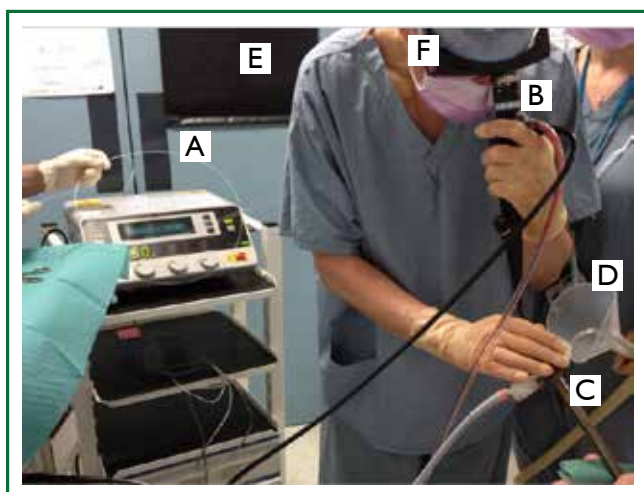


Figure 5. Nd Yag laser therapy. Laser fibre (A) to be inserted through the working channel of the flexible bronchoscope (B), passed through the lumen of the rigid bronchoscope (C). Laser fume extraction device (D), protective curtain (E) and eye wear (F) can be seen.

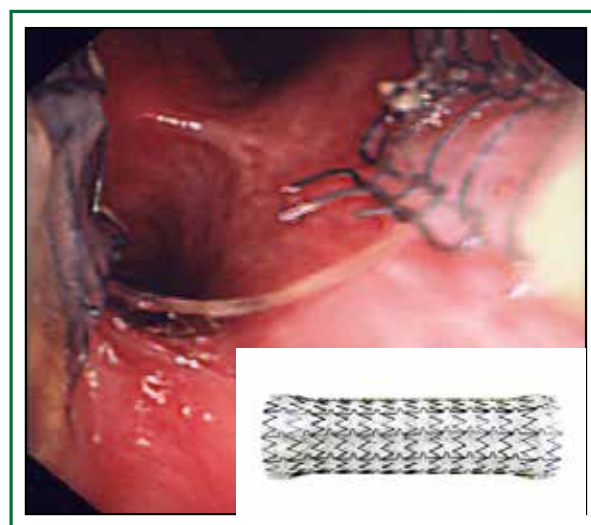


Figure 6. Tracheal metal stent fracture. Endotracheal view of a fractured covered metal tracheal stent and inset picture demonstrating an expanded metal airway stent.

Table 1. Potential complications of endotracheal stent insertion (27,31-39).

Potential complications of endotracheal stent insertion

Mucous plugging

Stent migration

Halitosis

Cough

Obstructing granulation tissue formation

Stent fracture (Figure 6)

Bacterial colonisation/recurrent infection

Fistula formation

Airway malacia (after removal)

the airway and to maintain airway patency. They are, however, foreign bodies in the airway and disrupt mucociliary clearance. The complications of stent placement are listed in Table 1 and stent fracture is displayed in Figure 6.

Metal and silicone stents are available. Metal stents come with or without a silastic or polyurethane covering which is used to minimise tissue growth when intrinsic tracheal disease is present. The covering is purposefully absent at either end of the stent to allow the stent to anchor to the mucosa and reduce stent migration but re-growth or new tissue growth may occur in these areas.

Historically, metal stents expanded in an unpredictable and

uneven manner, resulting in local airway ischaemia, granulation tissue formation, airway perforation and stent migration. The titanium stents in current use are lighter, easier to insert and demonstrate more uniform self-expansion. The application of a more consistent radial force to the airway means perforation, ischaemia and migration are less common and stronger forces can be withstood. There is also a greater availability of stent sizes.

Silicone stents result in a lesser local inflammatory response than metal stents, reducing granulation tissue formation. Silicone stents are therefore easier to remove but have a high risk of stent migration which limits their use (40,41).

When selecting a tracheal stent, it is desirable to use the greatest diameter stent possible. Selection will depend on patient size and disease extent after optimal airway remodelling. In general, airway stents deployed in tracheal disease are between 40-120 mm in length and 14-24 mm wide.

A stent should not be placed when there is active infection as this will promote granulation tissue formation. Treatment of bacterial colonisation in long term airway stents appears useful (42). Our centre routinely offers five days prophylactic oral antibiotics post stent placement.

Stent migration, especially in proximal lesions approaching the vocal cords, can acutely threaten the airway. External fixation of silicone stents has been trialled but with limited success and use, mainly due to cumbersome techniques (43,44). With careful prospective surveillance of metal tracheal stents there is usually minimal risk of migration and no requirement for stent fixation.

Concurrent tracheal and bronchial disease can be managed using Y-shaped silicone stents. The use of Y-shaped stents is limited by recurrent stent obstruction and infection. It is believed the stent structure results in excessive airway friction and mucociliary clearance disruption, with granulation tissue overgrowth and mucus impaction (45). Simultaneous stenting of the trachea and bronchi can be performed with metal stents, when necessary.

Following stent insertion, surveillance bronchoscopy is indicated in both malignant and benign disease (46). This facilitates early identification and management of complications. Relying on history and examination alone for surveillance is potentially hazardous due to the paucity of symptoms and signs before severe tracheal disease development. Treatment of peristent granulation tissue is most commonly addressed by laser therapy (20,31). Timely identification and treatment of airway infection is also crucial.

Indications for stent insertion

In malignant tracheal disease, stenting (with a covered stent) is used to reduce the occurrence of rapid, life threatening disease progression (47). Stenting is also indicated in malignant tracheal fistulae, even if there is no luminal compromise due to tumour bulk. Stents are used to physically obstruct the fistulae, palliating symptoms and protecting the large airway. Stenting for benign tracheal fistulae may be performed in non-operable disease.

Indications for tracheal stent placement in benign disease are less clear than for malignant disease, with varying practices seen worldwide. This is due to the better long term prognosis of individuals with benign pathology, the difficulty removing airway stents, and the reported complications of their use. Endotracheal stent insertion for benign disease should only be considered after airway remodelling by tracheal dilatation and/or tissue destruction has failed to effectively sustain airway patency.

The US Food and Drug Administration recommended in 2005 that metal stents should not be used for benign disease unless absolutely necessary (48). A major concern raised was turning operable cases into inoperable cases (36). Nevertheless, stenting does have a role as a bridge to surgery, enabling optimisation of a patient's functional and physical state prior to surgical intervention.

Tracheal stents for airway malacia should only be considered when patients are symptomatic and airway collapse is greater than 60%. The dynamic radial forces in malacia lead to higher stent complication rates, including metal fracture (49). A further problem with stenting these patients is recognising where to stent, as often long segments are involved. Extensive

airway stenting risks higher occlusion rates due to widespread disruption in mucociliary clearance. When a stent is too short for the involved segment this risks displacing airway collapse to the distal unsupported airway, failing to improve or worsening airway dynamics and symptoms.

Stent removal

Metal stents should be considered permanent as they remodel into the airway by granulation tissue growth and epithelialisation (9,32,50). The longer a stent remains *in situ*, the lower the chance of successful removal. Nevertheless, stent removal has been performed successfully in tracheobronchial disease using both rigid bronchoscopy (51-53) and flexible bronchoscopy (54).

Silicone stents are more easily removed than metal stents and so may lend themselves to short term placement if planned, despite their high migration rates. Research is on-going to produce a fully degradable tracheal stent which can remain *in situ* (55).

Airway management with a tracheal stent *in situ*

Great care should be taken to avoid damaging any tracheal stent if intubation is necessary. It is recommended to use a flexible bronchoscope to ensure that the endotracheal tube is sited above or within the stent lumen (56).

Strong consideration should be given to using rigid bronchoscopy to guide placement of percutaneous tracheostomy in complex tracheal disease (including tracheal stenosis or when a tracheal stent is *in situ*). Percutaneous tracheostomy using rigid bronchoscopy has been previously described (57,58) including where the endotracheal tube is removed and replaced by the rigid bronchoscope (59). The benefits to this approach include better visibility of the complex airway and/or stent, guide wire location, reduced risk of cuff rupture during cannulation and ease of haemostatic control.

Long term tracheostomy

Long term tracheostomy may become necessary for patients with complex tracheal disease. Commonly a Montgomery T tube is placed through a tracheostomy which serves as both a tracheal stent and tracheostomy tube. Tracheostomy is usually reserved for non-surgical candidates, after endotracheal therapy has become complicated and/or requires too frequent procedures, produces suboptimal clinical response or is anatomically too complex to perform safely. Tracheostomy can also be used as a bridge to tracheal surgery or as an adjunct to surgery. Our practice suggests patients are disinclined to tracheostomy, mainly due to negative cosmetic effects, and consider this a last resort.

Interventional outcomes in tracheal obstruction

Malignant disease

There is no randomised controlled trial evidence regarding the use of tracheal intervention in malignant disease due to the ethical challenges in patients requiring life-saving intervention or palliation. The impact of tracheal intervention on survival cannot, therefore, be quoted accurately. Studies have, however, consistently demonstrated that stenting can improve symptoms of breathlessness, quality of life and lung function in malignant disease. Data supports the use of metal covered stents to achieve success rates from 82-97% in these parameters (9,34,40,46,50,60-64). Importantly, improvements in performance status following stenting can open avenues to other therapies for malignancy, potentially improving outcomes further.

Benign disease

Successful short and long term outcomes using a combination of controlled dilatation and/or Nd-Yag laser therapy to destroy endotracheal tissue in tracheal stenosis have been published (28,30,65-68). Despite concerns regarding the use of tracheal stents in benign disease, there are a number of supportive case series and reports in the literature (31,32,35,68,69).

Early studies suggested that endotracheal treatment was less effective for circumferential disease and for stenoses greater than 1 cm in length (70). Recent studies have demonstrated that involvement of the cricoid cartilage and stenoses over 3 cm are associated with a reduced chance of success (71). Time from tracheal stenosis development to first intervention is also important. One study in post intubation tracheal stenosis established that 90% of patients who had intervention within six months of extubation had a positive outcome compared to 61% of those with a longer delay before intervention (72).

Galluccio *et al.* proposed the classification of tracheal stenosis into simple and complex, with simple stenoses defined as those less than 1 cm in length with no associated tracheomalacia or loss of cartilaginous support. Using this classification, silicone stent insertion as part of an endoscopic approach achieved airway patency in 96% of simple lesions at two years follow up but only 69% of complex lesions (30). When considering the removal of short term silicone stents, higher success rates have been seen when sizeable air pockets (longer than 1 cm) between the stent and tracheal wall are visualised at CT (in post tuberculosis tracheobronchial stenosis) (73).

Although our centre strongly advocates the use of rigid bronchoscopy for endotracheal intervention, other centres have

described using flexible bronchoscopy to intubate, dilate and stent patients with tracheal stenosis without complication, in limited patient series (74).

Patient selection for airway stenting in tracheobronchomalacia is crucial as there must be limited disease and a strong enough, supported airway distal to the stent to avoid collapse. As discussed the complication rates of stent insertion in tracheomalacia are higher and when there is malacia from loss of cartilaginous support in tracheal stenosis this reduces the chance of a successful outcome (30,70). However, when patients are carefully selected, studies have demonstrated that patients can achieve relief from breathlessness and an improved quality of life (75,76).

Benign tracheal stenosis has been successfully treated with tracheostomy at long term follow up, including tracheostomy tube placement through tracheal stents remodelled into the airway (36,77).

Summary

Tracheal disease resulting in upper airways obstruction can be life threatening and is an important diagnosis to consider early. A thorough history to identify predisposition to tracheal disease is necessary, with a high clinical index of suspicion directing comprehensive investigation. Prompt treatment of concurrent airway infection is crucial.

Due to the aetiology of tracheal obstruction, the patients are often poor surgical candidates and patients seldom wish to pursue long term tracheostomy. Fortunately, non-resectable tracheal disease can be successfully treated with interventional rigid bronchoscopy to restore airway patency using debulking and/or dilatation techniques. Tracheal stenting is often performed in malignant disease to protect the airway but should be carefully considered in benign disease as stent removal can be difficult. We advocate the use of covered metal stents when stenting is required for tracheal stenosis, due to their infrequent migration ahead of silicone stents. With regular follow up, including surveillance repeat bronchoscopy, endotracheal intervention can achieve long term success for patients with tracheal disease.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Bacon JL, Patterson CM, Madden BP. Indications and interventional options for non-resectable tracheal stenosis. *J Thorac Dis* 2014;6(3):258-270. doi: 10.3978/j.issn.2072-1439.2013.11.08

The anticipation and management of air leaks and residual spaces post lung resection

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ABSTRACT

The incidence of any kind of air leaks after lung resections is reportedly around 50% of patients. The majority of these leaks doesn't require any specific intervention and ceases within a few hours or days. The recent literature defines a prolonged air leak (PAL) as an air leak lasting beyond postoperative day 5. PAL is associated with a generally worse outcome with a more complicated postoperative course and prolonged hospital stay and increased costs. Some authors therefore consider any PAL as surgical complication. PAL is the most prevalent postoperative complication following lung resection and the most important determinant of postoperative length of hospital stay. A low predicted postoperative forced expiratory volume in 1 second (ppoFEV1) and upper lobe disease have been identified as significant risk factors involved in developing air leaks. Infectious conditions have also been reported to increase the risk of PAL. In contrast to the problem of PAL, there is only limited information from the literature regarding apical spaces after lung resection, probably because this common finding rarely leads to clinical consequences. This article addresses the pathogenesis of PAL and apical spaces, their prediction, prevention and treatment with a special focus on surgery for infectious conditions. Different predictive models to identify patients at higher risk for the development of PAL are provided. The discussion of surgical treatment options includes the use of pneumoperitoneum, blood patch, intrabronchial valves (IBV) and the flutter valve, and addresses the old question, whether or not to apply suction to chest tubes. The discussed prophylactic armamentarium comprises of pleural tenting, prophylactic intraoperative pneumoperitoneum, sealing of the lung, buttressing of staple lines, capitonage after resection of hydatid cysts, and plastic surgical options.

KEYWORDS

Prolonged postoperative air leak; postoperative apical space; prevention; management; infectious conditions

J Thorac Dis 2014;6(3):271-284. doi: 10.3978/j.issn.2072-1439.2013.11.29

Air leaks

Definition and quantification of air leaks

A postoperative air leak is defined by air escaping the lung parenchyma into the pleural space after any kind of surgery in the chest. As simple as this definition may look like, its clinical implementation very often is based on pure individual

judgement. In fact it is not easy to quantify the amount of air bubbling through a water seal of any closed chest tube drainage system, which all go back to an invention made by Gotthard Bülow, a popular German internist, who lived and worked in Hamburg between 1835 and 1900 (1,2). Bülow used a pleural drainage system with a tube draining fluid and air under water in order to maintain a negative pressure inside the pleural cavity. Bülow used this method to treat pleural empyema since 1875 and published his technique 1891. Since surgery of the chest was not possible at the time, Bülow certainly could not anticipate the paramount importance of his idea for thoracic surgery.

Given the difficulty of a quantitative judgment, qualitative evaluation of air leaks can be attempted by differentiating active leaks-originating from bronchiolo-alveolar districts-from passive leaks due to limited lung compliance and space problems. If traditional closed chest tube systems with water-seal are used, this differentiation is quite susceptible to individual experience

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Submitted Sep 18, 2013. Accepted for publication Nov 27, 2013. Available at www.jthoracdis.com

ISSN: 2072-1439

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and expertise of medical and nursing personnel. In addition different opinions exist among physicians about qualitative and quantitative aspects of air leaks.

The most widely used technique for qualitative assessment of air leaks is asking the patient to cough while observing the water column and the water-seal. No air bubbles in the water-seal during this maneuver attest an air-tight lung; the presence of bubbles simply indicates air in the pleural space, but does not allow judgment regarding active or passive leakage. If the appearance of bubbles remains in the same intensity at repeated coughs the leak is very likely to be an active one. If the intensity is reduced with each cough and maybe stops after a few coughs the background may be a small active leak or a passive leak. Hence, before deciding to pull this tube the physician is well advised to repeat this test after about an hour to exclude any active leaks. If bubbles occur at normal breathing or while the patient speaks, there is a significant active air leak present.

To complement these considerations the strategy to apply suction to chest tubes varies among surgeons and institutions and puts drain management and drain removal algorithms even more on an intuitive basis.

A possible way out of this dilemma is offered by modern electronic chest tube systems allowing for a quantitative assessment of air leaks not just at a given moment, but over a defined period of time (3,4). The digital and continuous air leak measurement and the ability to plot the amount of air escaping the chest over a couple of hours provides solid information for quality assessment and straightforward clinical decisions leading to shorter hospital length of stay (LOS).

Different systems are available today, which directly measure air leaks or calculate the air loss from secondary parameters. Although the introduction of numerical data and trends has put chest tube management on a quantitative basis this quite young technology still has limitations and further development potential.

In order to anticipate and prevent air leaks intraoperative assessment is of importance. After any parenchymal resection the surgeon may want to check all resection lines and bronchial reconstructions for air tightness. This is realized through a water-submersion test. Warm sterile physiological saline solution is instilled into the chest cavity and the anesthesiologist is then asked to gently re-inflate the atelectatic lung gradually up to a peak pressure of 30 mmHg, which pressure is then held for a couple of seconds. All areas of interest are submerged and thoroughly inspected under water to identify major air leaks for further surgical measures. To facilitate the decision making for surgical interventions, a simple quantification test can be used during this assessment, which was suggested by Macchiarini *et al.* (5):

- grade 0 (no leak);
- grade 1 (countable bubbles);
- grade 2 (stream of bubbles);
- grade 3 (coalesced bubbles).

The incidence of postoperative air leaks depends on the timely distance to lung resection. While an air leak is present in 28% to 60% immediately after completion of the surgery, it is reported in 26% to 48% of patients on postoperative day 1 (POD1), 22% to 24% on POD2 and still 8% on POD4 according to the literature (6-10).

Prolonged air leak (PAL)

Generally about 50% of all patients present with at least minor air leaks after lung resections and the majority of these leaks stop spontaneously after a few hours up to three days. The definition for the term PAL varies in multiple published studies and proposed definitions of PAL range from an air leak lasting four days to greater than ten days postoperatively (11). Based on recent literature several authors have recommended defining a PAL as an air leak lasting beyond postoperative day 5, which is an average LOS after pulmonary lobectomy. This definition is consistent with The Society of Thoracic Surgeons (STS) database definition for a PAL as an air leak exceeding the otherwise necessary LOS.

Clinical impact of PAL

There is no amount of air leak that is ever good, says the thoracic and cardiovascular surgery team from the Cleveland Clinic Foundation. The presence of air leaks predicts a worse outcome with prolonged hospital stay and more complicated postoperative course. As a consequence any air leakage should be considered as a surgical complication, not simply those lasting seven days or more (6).

PALs are the most prevalent postoperative complication with a reported occurrence of 18-26% (12,13) up to higher rates of 45-58% of surgeries (6,14). PAL is the most important determinant of length of postoperative hospital stay (12).

Its effect on LOS is significantly stronger than that of any other causes including suboptimal pain control, nausea and vomiting (15,16).

Prolonged postoperative air leak has been and still is considered a complication only when it persists five days or beyond the normal hospital stay. This ignores the potential impact of the vast majority of air leaks (6). Despite the fact that it is the most common postoperative pulmonary complication followed by pneumonia, acute respiratory failure and hemorrhage, the mortality rate of PAL is surprisingly high

and has been reported between 1-12% (12,17,18). Brunelli A and colleagues have reported a significantly increased rate of empyema in patients with air leaks lasting more than seven days as compared to patients with lesser air leaks (8.2% to 10.4% versus 0% to 1.1%) (19). In addition to empyema Varela G *et al.* have found air leaks lasting longer than five days associated also with other kind of pulmonary complications like atelectasis and pneumonia (20).

These conditions led to a prolonged hospital stay of up to six days and a financial loss to the health care provider of approximately 39,000 Euros. The relation of PAL, LOS and costs is confirmed by a number of other publications (6,19,21,22). The consequences for the individual patient and the whole healthcare system are manifold:

- prolonged chest tube drainage causes prolonged pain (15,23,24);
- restricted ventilation leads to increased risk of pneumonia (22);
- decreased mobility through chest tubes and related pain (25);
- decreased mobility results in increased risk of thromboembolism (24);
- necessity of pleurodesis, mechanical ventilation, and reoperation (25);
- higher readmission rate to intensive care units (22);
- prolonged hospital stay (6,12,15,22) and related higher overall costs (12,23).

Risk factors for prolonged air leakage

In a very recent study from Liverpool, UK, the authors have retrospectively analysed a total of almost 2,000 patients undergoing lung resections between 2002 and 2007 with the aim to define risk factors for the development of postoperative air leaks (14). A logistic regression model including various potentially relevant factors revealed a low predicted forced expiratory volume in 1 second (ppoFEV1, $P < 0.001$), upper lobe lobectomy ($P = 0.002$) and surgical technique ($P = 0.02$) as significant risk factors for developing prolonged postoperative air leak. The consequences of PAL were increased LOS ($P < 0.0001$), higher in-hospital mortality ($P = 0.003$) and more ICU readmissions ($P = 0.05$).

Gómez-Caro A and coworkers have found incomplete or fused fissures to be a risk factor for PAL (26). In a prospective study enrolling 119 patients after lobectomy those with incomplete or fused fissures ($n = 63$) were intraoperatively randomly assigned to receive either the traditional technique or the fissureless technique to approach the fused fissures. The incidence of PAL was significantly higher among patients with incomplete or fused fissures, however, the application of the fissureless preparation technique avoiding dissection of the lung

parenchyma over the pulmonary artery was significantly superior in terms of preventing PAL and reducing hospital stay.

Emphysema and other underlying lung disease have been identified as significant risk factors involved in developing air leaks (27). The severely rarefied lung tissue may be a too weak support for the staples during lung volume reduction surgery (LVRS) and the increased negative pleural pressure together with higher mechanical forces in the proximity of the staple lines predispose the lung to rip. In the NETT trial (22) the occurrence and duration of PAL was higher in patients with lower diffusing capacity ($P = 0.06$), upper lobe disease ($P = 0.04$) and important pleural adhesions ($P = 0.007$), whereas surgical variables were not found to be predictors.

Infectious conditions and chronic inflammation like tuberculosis and aspergillosis (28-30) but also cystic fibrosis (31) have been reported to increase the risk of PAL. Of 23 out of 71 patients with PAL and/or residual air space after resections for pulmonary aspergillosis, complications were observed more frequently in patients with greater cavitation near the chest wall (32).

Some authors have found a different prevalence of PAL for different lobes. Okereke and coworkers retrospectively analysed 319 patients after lobectomy and found PAL less frequently after left lower lobectomy ($P < 0.0001$) (6). In contrast to other studies the occurrence of PAL was clearly surgeon dependent in their series ($P = 0.007$) and not associated with lung function parameters.

Prediction of air leaks

Specific analyses of clinical data performed by different groups revealed a prevalence of PAL exceeding seven days postoperatively of 14% to 18% of lung resections. Knowing the quantitative risk of this complication beforehand may assist the surgeon in deciding on preventive intraoperative measures such as the use of sealants, buttressing staple lines, or pleural tenting.

In their paper published 2004 in the *Ann Thorac Surg* Brunelli and coworkers found a prevalence of 15.6% PAL in a cohort of 588 patients operated on between 1995 and 2003 (33). Logistic regression analysis led to the identification of a set of risk factors for the development of PAL, which was used to further generate a score for the prediction of PAL. This set of predictors consisted of ppoFEV1, presence of pleural adhesions and upper lobe resections.

In 2010 Brunelli *et al.* published a second paper with an updated version of their scoring system based on the analysis of 658 patients undergoing lobectomies between 2000 and 2008 without the use of sealants, pleural tent, or buttressing material (34). Again potential predictors were identified by univariate analysis and subjected to stepwise logistic regression analysis to generate a scoring system, which was then validated on

patients operated on in a different center.

The set of predictive variables and their scores were:

- age greater than 65 years, 1.0 point;
- presence of pleural adhesions, 1.0 point;
- FEV1 less than 80%, 1.5 points;
- body mass index less than 25.5 kg/m², 2.0 points.

Four risk classes according to their aggregate scores were significantly associated with incremental risk of PAL in the validation process in 233 patients.

Another recent paper by Lee and coworkers from Montreal, Canada, analysed single institutional data from 580 patients after pulmonary resection between 2002 and 2007 following a similar algorithm to establish a predictive risk model for PAL (35). They validated their scoring system in a consecutive set of 381 patients operated on at their institution after 2007. The rate of PAL was 14% in the derivation set and 18% in the evaluation set, which is in good accordance with other reports.

Their set of predictors building a simple scoring system, with the total number of points indicating the probability of PAL, consisted of:

- pleural adhesions, 2 points;
- FEV1, 1 point per 10% below 100%;
- DLCO, 1 point per 20% below 100%.

Concluding from the published evidence it becomes clear that lung function as expressed by preoperative (FEV1) or predicted postoperative (ppoFEV1) is the strongest predictor of PAL. This view is supported by another recent paper from the UK by Elsayed H and coworkers (14).

However, individual prediction of air leaks is difficult even after considering the proposed scores and may not be very useful in a day-to-day setting at a thoracic surgery clinic. The delayed decision to reoperate on a patient to close a significant air leak which didn't stop within a week leads to unnecessary prolongation of the postoperative hospital stay in the referring patient.

Only few publications have specifically addressed this issue in order to assist surgeons in this decision. At least modern digital chest drainage systems with air leak meters allow for quantifying the air loss over time and visualisation of a trend. Billé A *et al.* from Torino have reported that 75% of patients with an air leak greater than 180 mL/min had PAL exceeding five days, however the number of patients studied is too small to serve as a reliable basis for clinical decisions (36).

Cerfolio and colleagues found that patients with an early postoperative air leak of 5 or greater on a 7 graded scale are more likely to develop PAL ($P < 0.001$) (37). In the absence of a clear cut-off magnitude of an air leak each surgeon or institution has to base their indication to reopen upon own experience with a certain drainage system (15).

Apical spaces

Ethiology and pathogenesis of PAL and apical spaces

There is surprisingly sparse literature addressing postresection spaces, probably because this condition is an expected finding after lobectomy and rarely clinically significant unless infected or large enough to cause symptoms. Furthermore there is no standard definition of postresection apical spaces.

Following most lobectomies a variable volume of the pleural space is initially unfilled by extension of the remaining lung tissue. This is a common finding on plain chest radiographs and can almost always be seen by CT scan. After lung resection different physiologic mechanisms including expansion and hyperinflation of the remaining ipsilateral lung, mediastinal shifting, narrowing of the intercostal spaces and elevation of the diaphragm contribute to minimize the residual pleural space consequently. Hence, any restrictive process of the lung and chest wall like restrictive lung disease, previous thoracic operations or induction chemo- or/and radiotherapy may increase the likelihood of postoperative residual pleural space.

Persistent residual air spaces are more common in restrictions for inflammatory or infectious diseases, LVRS, upper lobe resections and resections of any type performed in patients with emphysema or fibrotic processes. In these processes the rarefied or poorly compliant remaining lobes fail to regularly fill the void left in the hemithorax (38). If allowed to persist large undrained postresection fluid collections may lead to trapping of the remaining lobe preventing adequate re-expansion and resulting in a fixed space even when drainage is ultimately attempted. Shields and colleagues in 1959 reported an incidence of persistent residual air space after resection for the management of tuberculosis as high as 21% and 33% in patients with pulmonary segmentectomy for TB. Upper lobectomies and bilobectomies have a higher incidence of postoperative air leaks and residual pleural spaces (15,38).

The vast majority of apical spaces may be unproblematic without impacting on the clinical course of the patient. Asymptomatic spaces usually resolve through resorption of the air, better expansion of the remaining lung, mediastinal shifting, elevation of the diaphragm and diminution of the intercostal spaces. However, in the presence of a significant broncho-pleural fistula spontaneous healing and resolution of an apical space is unlikely, especially when complicated by an empyema. In these cases surgical reintervention including filling of the space with viable material like muscle flaps or omentum, sometimes upper thoracoplasty or combinations may be indicated (39).

Barker WL emphasizes in his review paper of 1996 (40) a

cautious, thoughtful and more conservative approach to residual apical spaces for mainly two reasons. Firstly premature surgical interventions may lead to iatrogenic complications and secondly, surgical intervention will not be required for several months after the occurrence of an apical space in most cases, irrespective of cause. He proposes careful observation based on appropriate clinical, physiologic, and radiologic criteria to achieve a favorable outcome in these patients, who may be widely asymptomatic over long periods of time even with persisting vented or unvented spaces. Decision making may not always be easy and straight forward and requires an individualised approach. Like in any other kind of surgery a number of factors have to be taken into account before surgical treatment is considered, including performance status, respiratory reserve, quality of lung tissue, underlying disease and prognosis, problems with maintaining the drainage, local or systemic effects of chronic infection as well as social and even economic aspects.

This view is in part contradicted by a more recent publication. In a prospective study from Istanbul, Solak O and coworkers identified 58 patients who had a postresectional residual pleural space on the first postoperative day and followed them by chest X-ray, recording any complications and reoperations up to twelve weeks (41). The majority (76%) of residual spaces were completely resorbed within the observation period. 10% had an uncomplicated persistent apical space and 14% developed complicated residual spaces requiring re-drainage or reoperation. The authors identified persistent air leak and infection as the major complications of residual pleural spaces and favour early surgical intervention for complicated spaces. Since the onset of infectious complications was not observed after four weeks postoperatively, routine follow-up of uncomplicated spaces beyond the first month may not be necessary.

Treatment of PAL and apical spaces

Before considering any surgical measures in the initial management of PAL it is of paramount importance to separate two clinical entities: does the leak originate from the alveoli through a peripheral lesion in the visceral pleura or from bronchial structures, or in other words do we face an alveolar air leak or a bronchopleural fistula. If a significant air loss is encountered and there is suspicion of a problem at the bronchial anastomosis or stump early bronchoscopy should be indicated. The management of bronchopleural fistulas is substantially different from that of alveolar air leaks, however, in the vast majority of PAL the background is an alveolar air leak and initial management should be aimed at treating this entity (11).

Cerfolio RJ and coworkers have based their prospective

algorithm for the management of air leaks after pulmonary resection on four qualitative categories of air leaks (7):

- grade 1: forced expiratory only;
- grade 2: expiratory only;
- grade 3: inspiratory only;
- grade 4: continuous.

Initially all chest tubes were put on 20 cm H₂O of suction until POD2 and were then converted to water seal. If an air leak was present together with a pneumothorax on POD3, suction was installed again with 10 cm and with 20 cm if a pneumothorax was present without an air leak. 25% of patients presented with air leaks on POD1. A low FEV1/FVC ratio, increased age, increased RV/TLC ratio, increased RV, and an increased FRC were predictors of having an air leak on postoperative day 1. The majority of patients with air leaks on POD4 still had air leaks on POD7 and were effectively treated with talc slurry. This group recommends conversion from suction to water-seal to allow spontaneous sealing of expiratory PALs without significant pneumothorax.

Conservative approaches include prolonged chest tube drainage, provocative chest tube clamping or permissive chest tube removal, physiotherapy, application of various agents for pleurodesis like tetracycline, talcum or silver nitrate through the chest tube, or outpatient management with a chest tube and a Heimlich valve (42).

Pneumoperitoneum

The principle of using pneumoperitoneum to treat PALs and space problems after lung resections is not new and has been described since the 1980s (43-45).

In the era of fast-tracking surgery its value has been rediscovered and the technique adapted. Unlike the more commonly used percutaneous method designed for basal spaces after lower lobe lobectomies as described by Carbognani *et al.* (46), a paper by Alper Toker (47) describes a method to induce pneumoperitoneum intraoperatively through a transdiaphragmatic route in patients with insufficient filling of the chest cavity by the remaining lung. After the resection, in these series mainly upper lobectomies, the lung is ventilated at a peak pressure of 30 mmHg and expansion is monitored. If full expansion and complete filling of the chest cavity is considered unlikely, the anterolateral part of the diaphragm is punctured with a Veres needle and 800 mL of air are injected into the abdomen. The small diaphragmatic lesion is closed by a prepared purse-string suture. No complications related to this method were observed, all air leaks and apical spaces resolved in a few days and the peritoneal air was reabsorbed within 3.5 weeks. If

not applied intraoperatively, these authors recommend making use of this measure at an early postoperative phase when the lung still is mobile enough to shift to the apex of the chest cavity.

Blood patch

Instillation of autologous blood into the pleural space through the chest tube is another nonsurgical option to induce pleurodesis in the management of postoperative PAL. The sclerosing effect of blood may not be as potent as that of other agents and may be explained by non-infectious inflammatory reactions of the pleura together with the occlusion of alveolar leaks by fibrin formation leading to early re-expansion of the lung with an additional sealing effect.

In 1987 Robinson (48) reported an 85% success rate with this method in the treatment of chronic and recurrent spontaneous pneumothorax. This first report was followed by several reports published in the 1980s. In 1998, Cagirici *et al.* (49) demonstrated the efficacy of autologous blood pleurodesis in a prospective study in 32 patients following tube thoracostomy for spontaneous pneumothorax. 84% of air leaks closed within 72 h and no recurrence was seen in the 48-month follow-up. Only minor complications like fever and pleural effusion were observed in one third of patients. However, this paper does not focus on PAL after lung resection. Rivas de Andrés (50) reports a 100% success rate using a blood volume of 100 mL to induce pleurodesis to treat PAL after surgery for non-small cell lung cancer in a small group of six patients. Similar results are reported in a prospective analysis by Lang-Lazdunski and Coonar (51), who assessed the effect of 50 mL of blood for pleurodesis after lung resections in 11 patients. The aspired result was achieved in 72.7% within 12 h and in 100% within 48 h. In a series of 21 patients with PAL mainly after lobectomies and LVRS Droghetti (52) reported a 100% success rate in all patients with blood pleurodesis. After a single injection of blood the air leak ceased in 81% within 12 h and in 100% within 24 h. The authors recommend an instillation of 150 mL of blood in a 32F chest tube and raising the tube above patient niveau instead of clamping in order to avoid chest tube occlusion.

The first prospective randomized controlled study comparing blood pleurodesis with conventional management in 22 patients after lobectomy was published by Shackcloth *et al.* (53) 59% of the observed air leaks were successfully treated, with no statistical differences between both groups. However, blood pleurodesis significantly reduced the time to air leak cessation, chest tube removal, and hospital discharge by six days. Similar results were found by Andreotti and colleagues (54) who compared 50 and 100 mL of blood instillation with conventional chest

tube placement for the management of air leaks after lobectomy. 50 mL of blood reduced the time to air leak cessation by four days, 100 mL by five days. Most recently, Ozpolat (55) reports the efficacy of blood patch pleurodesis for PAL following pulmonary hydatid cyst operations. Air leaks ceased in 21 of 24 patients with chest tube removal within 24 h if no leak was observed (20 patients).

In a meta-analysis of the relevant literature and a best evidence article to answer the question whether blood pleurodesis was an effective measure in the management of PAL, Chambers A *et al.* (56) found more than 43 papers addressing this topic, of which ten represented the best evidence to answer the clinical question. They conclude that autologous blood pleurodesis has a superior outcome as compared to conservative management of postoperative PAL. 70-81% of PAL resolved within 12 h and 95-100% within 48 h *vs.* a mean of 3-6.3 days with simple chest drainage. These rates did not differ between lung resections compared to surgery for pneumothorax. Blood patching decreased the rate of recurrent air spaces from 35-41% for conservative chest tubes to 0-29%. Complications including pleural effusions, fever and empyema occurred in only up to 18%. In patients with ARDS and pneumothorax, blood patching reduced overall mortality as well as duration of ICU stay.

In conclusion, few studies mostly comprising a small number of patients suggest blood pleurodesis to be beneficial though there is no consensus on the optimal volume of blood instilled as well as on the usage of antibiotics to prevent possible complications such as infection and empyema.

Suction or no suction

It is common practice among many surgeons to apply suction of -20 cm H₂O to chest tubes directly after pulmonary resections to enhance pleural apposition and to switch to a plain water seal as soon as there is no further evidence of an air leak. However, this routine has been questioned by evidence from patients undergoing LVRS in whom suction of -20 cm H₂O was found to prolong air leaks (57,58). This is probably due to increased air flow preventing leaks from sealing as well as by possibly creating new tears in the emphysematous lungs of those patients. In uncomplicated cases many experts nowadays use water seals without suction in LVRS.

These findings of a possible negative effect of suction in LVRS prompted interest on the application of suction also after other pulmonary resections in patients without severe emphysema.

In 2005 Alphonso *et al.* (8) published data on 239 patients undergoing lobectomy or wedge resection either via thoracotomy or VATS who were randomized to receive either water seal alone

or low-pressure suction (2 kPa). The protocol started directly after the operation in the operating room, so that patients in the water seal group never received any suction. The cumulative persistence of air leaks showed no significant difference between the groups by Kaplan Meier curves and log rank test, prompting the authors to adopt an algorithm without routine application of suction unless clinically indicated. However, a multivariate analysis to identify possible factors associated with PAL was not performed in this trial.

Brunelli *et al.* (59) report similar findings in a prospective randomized study on 145 patients who underwent lobectomy due to lung cancer and were assigned either to water seal or -20 cm H_2O suction on the morning after surgery. There was no statistically significant difference between groups concerning duration of air leak and number of cases with PAL, also after correction for site of resection and length of stapled parenchyma. The complication rate tended to be higher in water seal patients (32%) than in the suction group (18%), but the difference did not reach statistical significance. The authors conclude that the use of water seal only was safe but did not improve outcome.

In contrast to the findings of Alphonso and Brunelli, Cerfolio *et al.* (37) published a prospective study in favour of a non-suction protocol in a small number of patients [33] without severe emphysema. Patients with an air leak on the first post-operative day were randomly assigned to receive water seal only or -20 cm H_2O suction. The difference between groups concerning air leak sealing was highly significant favouring the water seal group (67% by postoperative day 3) to the suction group (7%). However, 22% in the water seal group had to be switched to at least -10 cm H_2O suction due to a clinically relevant pneumothorax.

Similar favourable data for a non-suction protocol were provided by Marshall *et al.* (9) They prospectively randomized 68 patients to water seal or -20 cm H_2O suction after leaving the operation theatre, with all patients receiving at least a short time period of suction inside the OP. The time to air leak sealing was significantly shorter in the water seal group (1.5 days) compared to the -20 cm H_2O group (3.3 days). However, time to chest tube removal did not differ between groups unless corrected for length of stapled parenchyma, then also favouring the water seal group. 27% of patients in the water seal group had to be switched to -10 cm H_2O due to a pneumothorax of at least 25%. In these patients, suction continued only for up to 24 hours before returning to water seal.

The different results of these studies may be explained by various facts. Brunelli *et al.* (59) studied lobectomies and bilobectomies only, while Cerfolio (37) and Marshall (9) included also lesser parenchymal resections. Hence, water seal

may be efficient only in small parenchymal resections. However, Alphonso *et al.* (8) included a wide range of procedures from lobectomy to lung biopsy and surgery for pneumothorax showing no benefit for either water seal or suction, but there was no subset analysis provided. Concerning the type of procedure, no definitive recommendation can be based upon the data currently available. Another difference between the studies discussed is the performance of pleural tenting in 80% of Brunelli's patients, which has not been routinely done by the other authors. Since pleural tenting is an effective method to avoid air leaks, it might superimpose a possible benefit of water seal versus suction for air leak sealing. Furthermore, the time point of randomization to water seal or suction varied between studies from directly after closure of the thorax inside the operating theatre with patients on water seal never receiving suction to the morning of the first postoperative day. Thus, initial application of suction varied.

Finally, Brunelli *et al.* did not routinely perform chest X-rays after switching to water seal and might have missed a not negligible number of relevant pneumothoraces with the need for intermittent suction, which was around 25% in Cerfolio's and Marshall's trials. That might account for the negative outcome of the Brunelli trial as well as for the slightly increased complication rate among patients with water seal only. Alphonso *et al.* performed chest X-rays on days 1, 3 and 7, but only report 1.6% of patients in the non-suction group to have been switched to suction due to clinical considerations. As in Brunelli's trial, they might also have missed some relevant pneumothoraces, possibly accounting for the missing effect in the water seal group. The fact that patients in the water seal group in this study did not even receive a short period of initial suction since randomization to water seal or suction was already done in the operating theatre, might also have influenced the negative result of this trial. Furthermore, the different and often not clearly defined radiographic and clinical criteria for applying intermittent suction in the water seal group may be another factor explaining the inconsistent results of the four studies cited.

Brunelli *et al.* conducted a second study (60) introducing an alternative algorithm of intermittent suction termed "alternate suction". This algorithm consisted of -10 cm H_2O during the night and water seal only during daytime and was studied against water seal only in 94 patients after lobectomy with an air leak at the morning of the first postoperative day. There was no difference concerning duration of air leaks and complications, but chest tube duration and duration of hospital stay were significantly shorter in the "alternate suction" group. However, chest X-rays were not routinely performed, hence a not negligible number of pneumothoraces in the water seal only group may have been missed as in the previous trial by Brunelli.

The possible advantage of the “alternate suction” algorithm might be comparable to a switch to intermittent suction in case of a pneumothorax as performed in the studies of Cerfolio (37) and Marshall (9).

In conclusion, from the five cited prospective randomized trials the optimal algorithm concerning the application of suction in patients without severe emphysema undergoing lung resection remains unclear. There is evidence that an initial short period of suction followed by water seal only or the “alternate suction” protocol proposed by Brunelli (60) are safe and can reduce air leak or chest tube duration in the absence of a relevant pneumothorax, progressive subcutaneous emphysema or cardiorespiratory deterioration. In a water seal only protocol, a chest X-ray is mandatory after switching to water seal to detect a relevant pneumothorax, which is an indication for applying suction of at least -10 cm H₂O. A water seal protocol might not be advisable or even contraindicated in patients with highly restrictive lung disease and in those with a substantial risk of bleeding. In restrictive lung disease re-expansion of the lung will probably be not achieved without suction. In bleeding, tube patency is of utmost importance and should not be risked by avoiding suction.

In patients with severe emphysema and FEV₁ <40% predicted undergoing other procedures of lung resections than LVRS, clinical evidence and expert consensus suggest a water seal protocol in the absence of clinical conditions that require suction. In these cases, a level of suction not exceeding -10 cm H₂O is reasonable.

Intrabronchial valves (IBV)

Endoscopic valve therapy has been recently introduced as a potential less invasive treatment option. After initial case reports of the successful use of one-way endobronchial valves designed for the treatment of emphysema in the closure of a persistent distal bronchopleural fistula this idea was studied and further developed by other authors (61).

In a multicentric analysis of 40 patients over a period of four years the “Endobronchial Valve for Persistent Air Leak Group” reported a complete resolution of the air leak in almost 50% of patients and an improvement in 45% after placing one to nine endobronchial valves per patient (62). However, this early series comprised patients with different underlying diseases with a majority of recurrent spontaneous pneumothorax. Only seven patients had prolonged postoperative air leaks.

Although in 2001 an ACCP consensus statement did not see a role for bronchoscopy in the treatment of PAL, today numerous reports provide ample evidence that endobronchial

valve treatment of prolonged postoperative air leaks can be successfully used in selected patients (63).

More recently a larger single center experience specifically focussing on PAL was published by Firlinger *et al.* (64). In patients with high comorbidity where a second operation has to be avoided transbronchial selective deflation of the leaking lung segment was successfully used in clinically relevant PAL exceeding seven days. The source of the air leak was identified by stepwise blocking subsegmental bronchi by a ballon catheter and monitoring of the air leak using a digital chest tube system. Endobronchial one-way valves were then deployed into the orifice of the referring segment or subsegment resulting in an immediate improvement or cessation of the air leak. Valves were removed some weeks after successful management of PAL.

Flutter valve (Heimlich valve)

In order to reduce the length of hospital stay strategies have been developed and successfully used by many surgeons during the past decades allowing early discharge and home care management of PAL. The chest tube is left in place, shortened properly and attached to a so called flutter valve, named Heimlich according to its inventor. Henry Jay Heimlich (born 1920) was an American physician. In 1963, Heimlich introduced a chest drainage flutter valve. He claims his inspiration came from seeing a Chinese soldier die from a bullet wound to the chest during World War II.

The principle of the flutter valve is a one-way valve and bases on a rubber sleeve within a plastic case where the rubber sleeve allows air passing through the valve in one direction when the sleeve opens and prevents air flowing backwards when the sleeve closes off. The patient has to be checked up regularly for air leak dynamics and possible complications in the outpatient service. Data from six trials comprising a total number of 148 patients show that all but five (3.4%) air leaks resolved with an outpatient one-way valve system. Hence, the usage of a one-way valve in the outpatient setting is safe and effective in handling a stable and uncomplicated PAL.

The efficacy of the flutter valve has been studied in a recent systematic review screening nine electronic databases for studies reporting the use of HV for adults with pneumothorax. Eighteen studies were included comprising 1,235 patients with primary or secondary spontaneous pneumothorax (SSP). The authors concluded that high-quality data to support the use of the Heimlich valve for ambulatory treatment of pneumothorax is sparse, however was successful in about 80% of patients with very few severe complications (65).

Surgical revision

If a significant PAL persists in a patient despite above mentioned conservative measures surgical revision may be considered. In order to minimize the risk of pleural space infection or partial obstruction this decision should be made as early as possible within a few days, when it becomes evident that bedside pleurodesis is ineffective. VATS may be used to accomplish pleural symphysis with application of sclerosing agents under vision, pleural abrasion or pleurectomy. Early surgical reintervention also increases the chance of completing any procedure by VATS including over stapling of parenchymal lesions and application of sealants. In delayed surgical reinterventions and complicated PAL or apical spaces thoracotomy together with muscle or omental flaps are good options to obliterate the pleural space.

Prevention of PAL and apical spaces

PALs are a common problem following lung resections and have led to the development of various surgical methods to prevent this complication. However, routine performance is not advisable since not all patients are expected to profit from these rather costly and time-consuming adjuncts. A careful selection of patients and the most reasonable method to be performed is recommended.

Pleural tenting

The idea of using a pleural tent to seal possible parenchymal air leaks is not new and was first proposed by Miscall in 1956 (66) and Hansen in 1957 (67). A few more recently conducted prospective randomized trials have renewed the interest in this method. Okur *et al.* (38) published data on 40 patients undergoing upper lobectomies or upper bilobectomies randomized 1:1 to pleural tenting being performed or not. In the pleural tenting group, chest tube duration and mean hospital stay were significantly shorter than in the non-tenting group. Furthermore, cumulative drainage volume was significantly less. PAL with the need for intervention (apical chest tube) only occurred in the non-tenting group in 15% of cases. In the tented group, 15% of patients had an asymptomatic apical space. A more recent study by Allama (68) had a similar protocol for upper lobectomies, assigning 23 patients to pleural tenting and 25 to no tenting. There was a significantly lower incidence of air leaks from postoperative day 3 on in the pleural tenting group. However, chest tube duration and hospital stay did not differ between groups in this study. PALs occurred significantly

less in the pleural tenting group. Regression analysis showed pleural tenting to be associated with decreased risk for PAL, while COPD increased the risk. Brunelli *et al.* (69) investigated pleural tenting in 200 patients undergoing upper lobectomy, with a 1:1 randomization to the tenting or no tenting group. In this study, the mean air leak duration, chest tube duration, length of hospital stay, and hospital costs per patient were significantly reduced by pleural tenting. Regression analysis identified pleural tenting to be the best predictive factor for occurrence and duration of PALs. The beneficial effect of pleural tenting manifested before POD4.

In conclusion, pleural tenting seems to be a safe and effective method to prevent air leaks in upper lobectomies and bilobectomies.

Prophylactic intraoperative pneumoperitoneum

Prophylactic intraoperative pneumoperitoneum has been suggested as another method to prevent PAL. This procedure involves a catheter to be placed under the diaphragm intraoperatively to allow for air insufflation into the peritoneal cavity. In a recent prospective randomized study by Okur *et al.* (70) 60 patients undergoing lower lobectomy or bilobectomy were assigned to either achieve interoperative pneumoperitoneum or not. Chest tube duration and hospital stay were significantly shorter and drain volume lower in the pneumoperitoneum group. Furthermore, residual air spaces occurred in only one case in the pneumoperitoneum group compared to eight in the control group. Though the trial involved only a small amount of patients, data suggest intraoperative pneumoperitoneum to be a safe and effective method of preventing PAL in lower lobectomy and bilobectomy.

Sealing of the lung

Different sealing material has been studied for preventing air leaks after lung resections, and each of these different products has its specific properties and indication fields. A huge number of randomized and non randomized studies were performed with every single product over a period of at least 40 years demonstrating variable feasibility of these products for routine clinical use.

The indications for the use of surgical sealants are controversial. In the absence of consistent evidence for the efficacy of these products for preventing air leaks after pulmonary resections in patients with lung cancer three Cochrane Reviews were undertaken in 2001, 2005 and 2010. For the recent Cochrane Review to this topic published in 2010 (71) the electronic databases were screened from 1966 to 2008 including randomized controlled

clinical trials in which standard closure techniques plus a sealant were compared with the same intervention with no use of any sealant in patients undergoing elective pulmonary resection. Sixteen trials with a total of 1,642 randomized patients were included. Only six trials were able to demonstrate a significant reduction of postoperative air leaks by the use of sealants and three trials showed a significant reduction in time to chest drain removal in the treatment group. In two trials the percentage of patients with PAL was significantly smaller and in three trials a statistically significant reduction in length of hospital stay was found with the intraoperative use of sealants. The authors of this review conclude that surgical sealants reduce postoperative air leaks and time to chest drain removal but this reduction is not always associated with a reduction in length of postoperative hospital stay. Therefore, systematic use of surgical sealants with the objective of reducing hospital stay cannot be recommended at the moment.

Buttressing of staple lines

Staple lines are the obvious sources of air leaks after pulmonary resections, hence buttressing of staple lines might help to prevent PAL. In one prospective randomized multicentre trial by Miller *et al.* (72), 80 patients undergoing lobectomy or segmentectomy were assigned either to receive buttressing with bovine pericardial strips or standard treatment. No advantage of this technique could be noted concerning length of ICU stay, time to chest tube removal or hospital stay. Only a trend towards shorter air leak time was found. Since there were only a small number of patients included in this trial, further studies are needed to clarify whether buttressing might be an effective method for preventing PAL in selected patients.

The STS guidelines on the intraoperative and postoperative management of alveolar air leaks, published 2010 by Singhal S *et al.* (11) recommend buttressing staple lines in performing non-anatomic pulmonary resections in patients with moderate to severe pulmonary emphysema (FEV1 <60% predicted) to prevent postoperative air leaks. For anatomical resection in the same group of patients buttressing is reasonable, particularly in patients undergoing segmentectomies and those with incomplete fissures. In patients with emphysema less than moderate the use of buttressed staples is not well established and should be avoided given the increased costs of treatment.

Special considerations for infectious conditions

Pneumothorax and infection

SSP associated with an underlying infectious disease has been

found to be a more complicated situation than SSP due to a non-infectious condition. Chen *et al.* (73) retrospectively studied the outcome of SSP due to different conditions managed by pigtail catheter. Of the 168 cases included, 38 were associated with infectious diseases. Only 50% of these were successfully treated with a pigtail catheter, compared to 75-81% due to COPD or malignancy. Furthermore, length of hospital stay was significantly longer in patients with underlying infectious diseases than in the other conditions.

Rare cases such as one published by Chaudhry *et al.* (74) involving bullous disease with bilateral pneumothorax due to tuberculosis might even call for sophisticated surgical intervention in addition to medical treatment in order to lead to re-expansion of the lungs and clinical improvement.

Capitonnage after resection of hydatid cysts (Invited comment)

The surgical treatment of pulmonary echinococcosis might necessitate extensive resections of destroyed lung parenchyma such as lobectomy. Although there is no consensus yet, surgery of pulmonary hydatidosis should be as lung sparing as possible and include capitonnage to avoid postoperative complications like air leakage at an excellent long-term outcome regarding freedom of recurrence (75,76). Size and even bacterial superinfection of a cyst does not seem to be a contraindication to lung sparing surgical treatment including capitonnage and only one percent of patients of this series underwent lobectomy for completely destroyed lobes. Capitonnage may not be necessary in cysts facing the diaphragmatic pleura.

Residual spaces after lung resection for infectious disease

Solak *et al.* (41) studied the long-term outcome of residual postoperative pleural spaces (RPPS), which occurred in 58 cases of a study cohort of 140 patients after partial lung resections. Chest X-ray was routinely performed on days 1 and 7, as well as in weeks 4 and 12 to document duration of RPPS and possible complications. In week 12, RPPS still persisted in 10.4% of patients. Major complications included PAL and infection and occurred in 13.7% of cases, half of which had to undergo re-operation, while the other half was managed by re-drainage. Complications were associated with prolonged additional hospitalization (13 days in re-operated compared to 58.5 days for re-drained patients). Infection of pleural spaces occurred after weeks 3 to 4, while pleural spaces that were uncomplicated after one month remained so. The authors conclude that early re-operation should be performed in complicated pleural spaces, while there is no need to follow-up uncomplicated spaces after

one month.

De Giacomo *et al.* (77) describe the successful treatment of an infected pleural space by an autologous platelet-leukocyte gel administered via a chest tube. These gels have previously been shown to stimulate and accelerate healing of soft tissues and bones and could also be effective for treatment of complicated air spaces after lung resections.

Plastic surgery

Even though surgical repair techniques are rarely indicated, they have been proven to be safe and effective when conventional tube thoracostomy has failed to solve the problem of PAL. A combined latissimus dorsi-serratus anterior transposition flap has been proposed by Woo *et al.* (78) The authors studied this method on five cases with PAL. The latissimus dorsi and the proximal part of the serratus anterior were exposed by a lazy-S incision, and both muscles were mobilized as pedicled flaps. The pleural cavity was filled with the latissimus dorsi through a thoracic window in order to seal the fistula, while the serratus anterior was used to close the rib cage. The method was effective in all five cases studied. The air spaces resolved and the chest tubes could be removed after a mean of five days. In a follow-up period of one year no recurrence of air leaks was noted.

Especially in situations with a combination of PAL with an infected apical space, the use of flaps can be crucial for a successful management. Surgery for pulmonary cavity associated with fungus ball is challenged by chronic lung disease. Rergkhang C *et al.* (79) found tuberculosis (70%) as the most common underlying pulmonary disorder very often complicated by massive hemoptyses. Lobectomy was successfully performed in 55% of patients and 30% had a cavernostomy with transposition of muscle flap. An emergency setting and cavernostomy with transposition of muscle flap increased the risk of a compromised postoperative course. The authors propose elective surgery with formal pulmonary resection as the therapeutic option of choice for low risk patients. Cavernostomy with transposition of muscle flap should be reserved for patients with poor pulmonary reserve.

Apical spaces after operations for tuberculosis

Lung surgery for tuberculosis is indicated in special situations and complications such as failure to respond to chemotherapy in multidrug-resistant disease, destroyed lung, concomitant or subsequent aspergilloma, hemoptysis, persistent cavities and pleural spaces and others. Surgical interventions for pulmonary tuberculosis and its sequelae range from wedge resections to pneumonectomy, with cavernostomy, pleural partition by muscle

flaps and thoracoplasty being special procedures in rarer cases. Complications after lung surgery for tuberculosis including apical spaces and PAL have been reported to be more common than in pulmonary resections for other underlying diseases.

In a study by Mohsen *et al.* (28), of 23 patients being operated on for multidrug-resistant pulmonary tuberculosis, 52% had a lobectomy and 48% a pneumonectomy, followed by chemotherapy. PAL occurred in four patients (17%). In another paper by Olcmen *et al.* (29), who retrospectively studied the outcome of 57 patients with a total of 72 thoracic surgeries for pulmonary tuberculosis, 28 complications in 18 patients are reported. Of these, PAL (21%) and residual spaces (12%) were the most common. In line with these studies are the data by Lang-Lazdunski *et al.* (30), who also report a high rate of PAL (28%) after lung resections for Mycobacterium xenopi infection.

Though all these reports conclude lung surgery for tuberculosis to be effective and associated with acceptable morbidity and mortality, duration of hospital stay is longer and complication rates are higher than for similar procedures due to other underlying diseases.

A special situation following pulmonary tuberculosis is pulmonary aspergilloma or aspergillosis. Al-Kattan *et al.* (80) compare the outcome of lung surgery for aspergilloma on the basis of tuberculosis (20 patients) to aspergilloma due to acute myeloid or lymphoid leukemia (10 patients). The indication for a surgical intervention in the tuberculosis group was hemoptysis in all cases. Interventions performed ranged from lobectomy to pneumonectomy. In the leukemia group, lobectomy and wedge resections were performed. 10% of patients in the tuberculosis group had PAL, and there was one postoperative death reported due to massive hemoptysis. In comparison, there was no postoperative morbidity and mortality in the leukemia group.

Csekeo *et al.* (32) report on the outcome of 84 patients with 71 undergoing pulmonary resections, 12 cavernostomies and one lung biopsy for aspergillosis. In about half of the cases tuberculosis was the underlying disease leading to aspergillosis. The authors report the post-operative occurrence of PAL or residual spaces in 23 patients (32%), which were more frequently observed in patients with cavernae near the chest wall. Even though lung surgery for aspergilloma due to tuberculosis is followed by a higher complication rate than similar interventions for other conditions, a surgical approach often remains the ultima ratio for aspergilloma.

Special techniques to resolve persistent pleural spaces after lung surgery for infectious diseases such as tuberculosis include pleural partition with intrathoracic muscle tent and thoracoplasty. Rocco (81) describes the method of pleural partition with muscle transposition which has been used to

successfully treat residual spaces after lung resections in three patients in his report. After removing parts of the second or third rib the latissimus dorsi and serratus anterior muscles are transposed into the thoracic cavity and sutured to the pleura or periosteum and intercostal muscles to form a muscle tent covering the lung and resolving the air space.

Thoracoplasty as salvage option for the rare cases of treatment-refractory complicated residual pleural spaces was studied by Hopkins *et al.* (82). They report 30 cases in a 14-year period, where 23 patients had tuberculosis as the underlying disease for their complications. Persistent air space associated with PAL after lung resection was the most common indication for thoracoplasty. Destroyed lung due to tuberculosis was the main reason for persistent pleural spaces in four patients, and local infection of long-term pleural spaces after therapeutic pneumothorax for tuberculosis was the indication for the procedure in another four cases. Thoracoplasty was successful in 73%. A total of four deaths and six failures of the procedure were reported. The authors conclude that thoracoplasty as the final strategy can be an effective tool for resolving complicated pleural spaces in carefully selected patients.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Mueller MR, Marzluf BA. The anticipation and management of air leaks and residual spaces post lung resection. *J Thorac Dis* 2014;6(3):271-284. doi: 10.3978/j.issn.2072-1439.2013.11.29