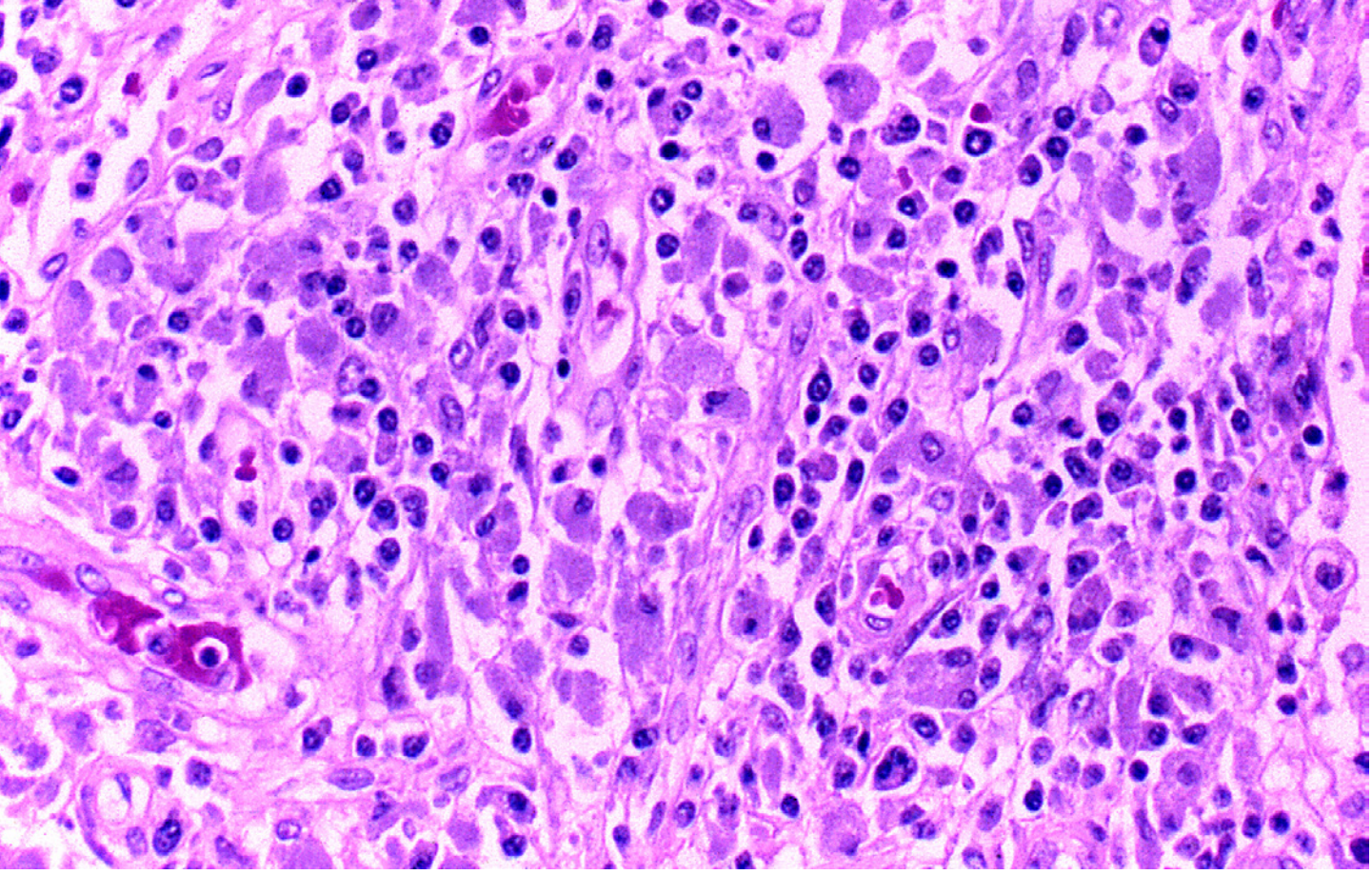

Credit: CDC/ Dr. Edwin P. Ewing, Jr.

Educational aims

- To critically review the literature describing the use of surgery in the treatment of pulmonary disease caused by nontuberculous mycobacteria (NTM).
- To assess the outcomes and complications observed with different surgical approaches used in the treatment of pulmonary NTM disease.

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Surgery in nontuberculous mycobacteria pulmonary disease

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Medical treatment of pulmonary nontuberculous mycobacteria (NTM) disease has highly variable outcomes. Despite the use of multiple antibiotics, sputum clearance is often difficult to achieve, especially in cases with macrolide resistant NTM infection. Immunocompromised patients and those with structural lung disease are at increased risk, although occurrence in immunocompetent patients without structural lung disease is well recognised. Most pulmonary NTM disease involves *Mycobacterium avium* complex (MAC), but with enhanced identification multiple species have now been recognised as opportunistic pathogens. The observed increase in NTM disease, especially infection with multidrug-resistant *Mycobacterium abscessus* complex, is probably multifactorial. Surgery has been used as adjuvant treatment in patients with 1) focal disease that can be removed or 2) bothersome symptoms despite medical treatment that can be ameliorated. Early post-surgical mortality is low, but long-term morbidity and mortality are highly dependent on the degree of lung involvement and the residual lung function, the potency of medical treatment and the type of surgical intervention. In conjunction with antibiotic therapy, reported post-surgical sputum clearance was excellent, although publication bias should be considered. Bronchopleural fistulae were problematic, especially in pneumonectomy cases. Study results support the use of minimal resection surgery, in a carefully selected subgroup of patients with focal disease or persistent symptoms.

@ERSpublications
Minimal resection surgery, in a carefully selected subgroup of patients with focal disease or persistent symptoms can be considered as an adjuvant therapy in the treatment of pulmonary nontuberculous mycobacterium infection. http://ow.ly/ONSC30mesFC

Introduction

NTM are ubiquitous organisms, commonly found in soil and water, that rarely cause human disease. However, in people with underlying structural lung disease such as bronchiectasis, poor sputum clearance as found in cystic fibrosis (CF), or underlying immunodeficiency they do have pathogenic potential. In some instances, lung disease occurs without identifiable underlying "risk factors". Concern has been expressed that the incidence of pulmonary NTM disease is on the rise globally, with Japan having one of the highest incidence rates [1–8]. This is probably multifactorial, especially in patients with CF, with contributions from better diagnostics, increased surveillance sampling and a dramatic increase in life expectancy [9–11].

Despite optimised antibiotic treatment, sputum clearance is difficult to achieve and highly variable in patients with pulmonary NTM disease. Based on current American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA) recommendations, multidrug treatment regimens

of 1–2-years duration yield sputum conversion rates of 54–87% [12–17]. Sputum conversion rates are lower in those previously treated or in patients infected with macrolide-resistant species [14, 18]. The recurrence rate after successful treatment with clarithromycin-containing regimens ranges between 20% and 44% [14–17, 19]. Many antibiotics used in the treatment of pulmonary NTM disease may have severe adverse effects (table 1) [10], resulting in frequent treatment interruptions and a high cost

Table 1 *Common adverse effects of antibiotics used to treat NTM infections in patients with CF*[#]

Antibiotic (delivery route)	Common adverse effects	Suggested monitoring
Amikacin (intravenous; intramuscular)[¶]	Nephrotoxicity Auditory-vestibular toxicity (tinnitus, high-frequency hearing loss)	Trough levels Serum creatinine
Amikacin (nebulisation)[¶]	None described	
Azithromycin (oral)[+]	Nausea, vomiting, diarrhoea Auditory-vestibular toxicity Prolonged QTc	Symptoms Audiology ECG
Bedaquiline (oral)[¶]	Headaches, dizziness, joint aches Prolonged QTc Liver enzyme derangement	Symptoms ECG LFT
Cefoxitin (intravenous)[¶]	Fever, rash Eosinophilia, anaemia, leukopenia, thrombocytopenia Interference with serum creatinine measurement	Symptoms FBC
Clofazimine (oral)[¶]	Discoloration of skin or sclera Enteropathy (can mimic pancreatic insufficiency), nausea and vomiting	Symptoms
Ethambutol (oral)[+]	Optic neuritis	Symptoms, colour vision and acuity
Imipenem (intravenous)[¶]	Nausea, vomiting, diarrhoea Hepatitis	Symptoms LFT
Linezolid (oral)[¶]	Anaemia, leukopenia, thrombocytopenia Peripheral neuropathy, optic neuritis	FBC Symptoms/clinical
Minocycline (oral)[¶]	Photosensitivity, skin discolouration Nausea, vomiting, diarrhoea Vertigo	Symptoms
Moxifloxacin (oral)[¶]	Nausea, vomiting, diarrhoea Insomnia, agitation, anxiety Tendonitis Photosensitivity Prolonged QTc	Symptoms ECG
Rifabutin (oral)[+]	Leukopenia, anterior uveitis (when combined with clarithromycin), flu-like symptoms (polyarthralgia or myalgia)	Symptoms FBC
Rifampicin (oral)[+]	Orange discolouration of bodily fluids, fever, chills, nausea, vomiting, diarrhoea Hepatitis Thrombocytopenia Renal failure Increased drug metabolism	Symptoms LFT FBC EUC
Streptomycin (intravenous, intramuscular)[¶]	Nephrotoxicity	Trough levels, serum creatinine
Tigecycline (intravenous)[¶]	Nausea, vomiting, diarrhoea Pancreatitis Hypoproteinaemia, bilirubinaemia	Symptoms Serum amylase, lipase LFT plus albumin

LFT: liver function test; FBC: full blood count; EUC: electrolytes, urea and creatinine; QTc: corrected QT interval. [#]: based on United States CF Foundation (USCF) and European CF society (ECFS) consensus recommendations [46]; [¶]: primarily used for *Mycobacterium abscessus* complex; [+]: primarily used for MAC. Reproduced from [10] with permission.

from additional investigations and the management of side-effects. [20].

Surgery has been used as adjuvant therapy in the treatment of NTM pulmonary disease [12, 21], to effect higher rates of cure in patients with focal lung involvement. Increased cure and reduced relapse rates have been demonstrated with the use of lung surgery in the treatment of multidrug-resistant tuberculosis (MDR-TB). A recent meta-analysis of the role of surgery as an adjuvant therapy demonstrated that partial lung resections, but not pneumonectomy, were associated with improved treatment success (cure and completion) (OR 3.0; 95% CI 1.5–5.9; I^2_R 11.8%), and that a good outcome was more likely when surgery was performed after initial culture conversion [22]. We critically reviewed the treatment outcomes achieved with surgical management of pulmonary NTM disease.

Studies undertaken in the pre- and post-clarithromycin era

Studies showed that combined medical and surgical management of NTM had low mortality with high rates of sputum conversion [23–27], which was often difficult to achieve with antibiotic treatment alone. With the addition of clarithromycin (in the late 1990s) the success rate from antibiotic treatment increased [12–17]; however, treatment failure rates with clarithromycin-resistant species or with acquired-clarithromycin resistance during treatment remained high. Studies undertaken after the clarithromycin era demonstrated benefit from lung surgery in select patient groups only [19, 28–31].

Table 2 presents an overview of identified studies where surgical intervention was performed and describes the characteristics of the patient cohorts selected for surgery. Other studies where surgery was performed in a small number of the overall cohort did not have sufficiently detailed information about the surgery cases to be included in the table [32, 33]. None of the studies included children and there was a female predominance. Most patients had bronchiectasis and/or lung cavities visible on a chest radiograph or computed tomography scan. A history of cigarette smoking (range 18–97%) or previous pulmonary TB (range 8–26%) was common in the studies where this was mentioned [30, 31, 34–37]. Underlying immunodeficiency was uncommon and absent in six studies where this was mentioned [19, 28, 29, 38–40]. Low body mass index (BMI) was common in studies where immunodeficiency was reported [29–31, 37, 40, 41], and was identified as a predictor of poor prognosis in one study [37]. Most studies included patients with MAC disease and were performed in the USA and Japan. None of the studies included patients with CF.

Indications for surgery

According to ATS/IDSA guidelines, surgery should only be considered in select patients who meet the diagnostic criteria for pulmonary NTM disease [12]. Specifically, they need to have localised disease deemed amenable to resection and be judged to have adequate pulmonary reserve [12]. Generally, the indications for surgery fall into three categories: 1) removing a disease focus to optimise the chances of cure; 2) removing a destroyed part of the lung for symptomatic relief or prevention of a catastrophic bleed; and 3) limiting the rate of disease progression in cases with a poor response to medical treatment.

Nelson *et al*. [38] indicated that in the pre-clarithromycin era, most of the surgical treatments were used at an earlier stage of infection in conjunction with medical therapy to try and cure the NTM disease. However, since newer generation macrolides (specifically clarithromycin) became available, surgery has predominantly been used in the setting of treatment failure (71% of cases) [38]. Poor response to antibiotic treatment has been defined as the lack of sputum clearance and/or ongoing features of active disease and progressive lung destruction on imaging. Clarithromycin susceptibility is an important factor when considering surgical resection, given that clarithromycin-resistant strains have significantly reduced sputum conversion rates (~25%) with antibiotic therapy compared with susceptible strains (~85%) [14].

Excessive haemoptysis can be lethal and is the most common symptom leading to surgical resection. Intractable cough is another symptomatic indication for surgery if this has a major negative impact on a patient's quality of life. In these instances, surgical intervention seeks to provide symptom relief or prevent a life-threatening complication, irrespective of clinical cure. The third indication is to use surgery to protect the unaffected or residual lung by removal of an intractable disease focus that remains a source of infected secretions with risk of intrapulmonary spread [42].

Surgical options

All the surgical interventions were conducted under general anaesthesia with frequent use of a double lumen endobronchial tube. Surgery duration ranged from 1 h to 8 h and blood loss from 10 mL to more than 3 litres, depending on the types of surgical resections performed and the complications encountered [28, 29, 35, 37, 38, 40]. Either a postero- or antero-lateral thoracotomy approach was used, depending on anticipated pleural adhesions. Conversion from thoracoscopic to open surgery occurred when extrapleural dissection was required or because of concerns regarding underlying vital structures. Pre-operative

Table 2 *Overview of patient characteristics in NTM lung surgery studies performed to date*

First author [ref.]	Study year(s), location	Patients n	Median (range) age years	Females %	NTM species	Lung involvement and/or comorbidities
Studies without clarithromycin						
Elkadi [23]	1962–1973 Missouri, USA	48	48 (20–72)	33%	*M. kansasii* 54% *M. intracellulare* 42% Rapid grower 2%	Lung cavities 77%
Pomerantz [36]	1983–1990 Colorado, USA	38	50 (33–39)	68%	MAC 87% *M. kansaii* 3% *M. chelonae* 3% *M. xenopi* 3%	Previous lobectomy 18% Previous TB 8% Bronchopleural fistula 8% Chest radiation 8%
Ono [35]	1991–1996 Wakayama, Japan	8	50 (36–72)	50%	MAC 100%	Cigarette smoker 25% Bronchiectasis, 25% Previous TB 25% Sjögren's syndrome 13%
Nelson [38]	1989–1997 Texas, USA	28	Mean±SD 50±11	25%	MAC 100%	Almost all were smokers 67% >20% below weight standard No immunocompromised
Shiraishi [34]	1979–1996 Tokyo, Japan	33	50 (30–69)	48%	MAC 100%	Cigarette smoker 97% Bronchiectasis 21% Cavity 64%; nodule 3% Previous TB 9% Pneumonia 9%
Studies incorporating clarithromycin						
Shiraishi [28]	1993–2001 Kyoto, Japan	21	56 (27–67)	48%	MAC 100%	Bronchiectasis 10% Cavity 76%; nodule 10% Destroyed lung 5% No immunocompromised
Shiraishi [29]	1983–2002 Tokyo, Japan	11	57 (43–69)	73%	MAC 91% *M. abscessus* 9%	Multiple cavities 55% Destroyed lung 46% Bilateral disease 36% No immunocompromised
Watanabe [39]	1990–2005 Tokyo, Japan	22	54 (30–77)	68%	MAC 100%	Bronchiectasis predominant 64% Cavitary predominant 36% No immunocompromised
Mitchell [43]	1983–2006 Colorado, USA	236	54 (23–77)	83%	MAC 80% *M. abscessus* 14%	Focal bronchiectasis 55% Cavitary lung disease 29% Mixed pattern 9% Prior thoracic surgery 20%
Koh [40]	2002–2007 Seoul, Korea	23	45 (24–66)	70%	MAC 43% *M. abscessus* 52% *M. xenopi* 4%	Cavities 70% Bronchiectasis 30% No immunocompromised
van Ingen [19]	2000–2009 Holland	8	52 (41–59)	25%	MAC 88% *M. xenopi* 12%	Cavitary 62% Mixed pattern 25% Bronchiectasis 13% No immunocompromised
Yu [30]	2004–2009 Colorado, USA	128	59 (34–81)	96%	MAC 88% *M. abscessus* or *chelonae* 10%	Bronchiectasis 95% Cigarette smoker 16% Cavitary disease 3% Mixed pattern 2% Prior thoracic procedure 10%
Jarand [41]#	2001–2008 Alberta, Canada	24	Mean±SD 57.7±11.1	83%	*M. abscessus* 100%	Localised bronchiectasis 86% Coexisting/previous MAC 54.2% Cavitary disease 37% Previous smokers 23% Previous TB 8.3%

Continued

Table 2 *Continued*

First author [ref.]	Study year(s), location	Patients n	Median (range) age years	Females %	NTM species	Lung involvement and/or comorbidities
Shiraishi [31]	2007–2011 Tokyo, Japan	60	50 (20–72)	68%	MAC 92% *M. abscessus* 5% *M. gordonae* 2% *M. xenopi* 2%	Bronchiectasis 48% Cavities 42% Cigarette smoker 18% Mixed pattern 7% Diabetes mellitus 6.7%
Asakura [37]	1994–2015 Yokohama, Japan	125	60 (IQR 49–66)	53%	MAC 80% *M. intracellulare* 8% *M. abscessus* 5% *M. kansasii* 3% Others 5%	Cavities 70%; nodules 98% Bronchiectasis 89% Cigarette smoker 29% Old TB 26%, COPD 10% Diabetes mellitus 10%

M. kansasii: *Mycobacterium kansasii*; *M. intracellulare*: *Mycobacterium intracellulare*; *M. chelonae*: *Mycobacterium chelonae*; *M. xenopi*: *Mycobacterium xenopi*; *M. abscessus*: *Mycobacterium abscessus*; *M. gordonae*: *Mycobacterium gordonae*; IQR: interquartile range; COPD: chronic obstructive pulmonary disease. #: compared combined antibiotic and surgical treatment with antibiotic treatment alone.

airway toilet using bronchoscopy was selectively used to reduce the infected secretion burden in the airways and surgeons needed to be vigilant to avoid spillage of infected debris within the pleural space or around the wound site. This type of surgery is best carried out in specialist centres with considerable experience in infectious lung surgery [42]. Some centres involved multidisciplinary teams consisting of surgeons, dieticians, respiratory and infectious diseases physicians specialising in NTM infections in decision making [43].

Table 3 summarises the indication for and type of surgery performed for pulmonary NTM disease. Lobectomies and segmentectomies were the most common procedures performed. Table 4 summarises the outcomes following surgical intervention.

Surgical outcomes

Mortality

Most studies reported no early post-operative deaths [23, 28–31, 34, 35, 39, 40]. Nelson *et al.* [38] reported two (7%) deaths out of 28 patients; one died of a myocardial infarction and the second due to acute respiratory failure. Mitchell *et al.* [43] also reported two early post-operative deaths (out of 236 patients; <1%) with one death secondary to ARDS and another due to bronchopleural fistula with MI.

Long-term mortality varied between 3% and 21% and was mostly due to respiratory failure. Most studies followed patients for 6–8 years, but two studies followed patients for nearly 20 years post-surgery [34, 37]. Two case series conducted in the pre-clarithromycin era demonstrated reduced mortality (0% *versus* 10%) in patients managed more aggressively with earlier surgery [23, 44]. However, these finding are less relevant today, given that the overall mortality rates associated with surgical treatment of pulmonary NTM disease declined from 7% in the 1980s to <1% today [43].

Common complications

In the studies evaluated, post-operative complication rates averaged 28%, but varied widely across the studies (range 0–63%) and most complications occurred post-pneumonectomy. Asakura *et al.* [37] found that pneumonectomy, when compared to other resections, was associated with higher rates of post-operative complications with an odds ratio of 4.1 (95% CI 1.6–10.3; p=0.005). Pneumonectomy was generally associated with higher rates of bronchopleural fistula; up to 27% of cases in one series [29]. Bronchial stumps were often reinforced with muscle flaps (latissimus dorsi, serratus anterior or intercostal) and occasionally omental flaps to try to reduce this risk, but its effectiveness is uncertain, and Mitchell *et al.* [43] found that the risk of bronchopleural fistula was associated with positive sputum at the time of surgery. Other complications included lobar atelectasis requiring bronchoscopy, wound infection, wound dehiscence and haemorrhage (table 3).

Risk factors for poor prognosis

Asakura *et al.* [37] found that, in addition to pneumonectomy, older age, low BMI and remnant cavitary lesions were predictors of poor prognosis. Sputum clearance was higher after pneumonectomy, but with increased morbidity and unfortunately the characteristics of those who may benefit from a pneumonectomy were not identified [37]. Limited resection was generally associated with better outcome [35, 39].

Pomerantz *et al.* [36] compared outcomes of pulmonary resections in those with TB and NTM subjects. Their group found that those infected with

Table 3 *Indication, type and complications of surgery performed for pulmonary NTM disease*

First author [ref.]	Patients n	Surgical indications	Type of surgery	Hospital stay	Complications
Studies without clarithromycin					
Elkadi [23]	48	Medical treatment failure	Lobectomy 67% Segmentectomy 21% Pneumonectomy 6% Wedge resection 4% Extrapleural plombage 2%	2.4–4 months[#]	Total=13% Bronchopleural fistula 4% Wound dehiscence 4% Infection 2% Haemorrhage 2%
Pomerantz [36]	38	Localised disease with complications	Lobectomy 59% Pneumonectomy 41% Both (7%)	Not reported	Total=50% Bronchopleural fistula 21%[¶] Prolonged air leak 11% Respiratory failure 5% Wound dehiscence 3% Pericardial effusion 3% Horner's syndrome 3%
Ono [35]	8	Medical treatment failure Persistent symptoms	Lobectomy 75% +partial resection 25%	Not reported	None reported
Nelson [38]	28	Medical treatment failure Significantly destroyed lung Severe haemoptysis	Partial resection 71% Pneumonectomy 29%	Not reported	Total=32% Bronchopleural fistula 4% Prolonged air leak 14% Atelectasis requiring bronchoscopy 4% Severe post-thoracotomy pain 4% Death due to post-operative MI 4%
Shiraishi [34]	33	Symptomatic localised disease	Lobectomy 79% Segmentectomy 15% Pneumonectomy 3% Wedge resection 3%	Not reported	Total=18% Bronchopleural fistula 3% Residual pleural space 15%
Studies incorporating clarithromycin					
Shiraishi [28]	21	Medical treatment failure or drug intolerance	Lobectomy 76% Two lobes 5% Pneumonectomy 14% (90% right sided)	Not reported	Total=29% Bronchopleural fistula 10% Prolonged air leak 4% Residual pleural space 10% Pneumonia 4%
Shiraishi [29]	11	Multiple cavities or total lung destruction	Pneumonectomy 100%	Not reported	Total=45% Bronchopleural fistula 27% Empyema 9% ARDS 9%

Continued

Table 3 *Continued*

First author [ref.]	Patients n	Surgical indications	Type of surgery	Hospital stay	Complications
Watanabe [39]	22	Medical treatment failure Persistent symptoms	Lobectomy 64%+ Two lobes 5%+ Partial lung resection 27%+ Segmentectomy 18%+ Wedge resection 27%+ Multiple resections 45%	Not reported	Total=9% Residual pleural space 5% Home oxygen for 2 months 5%
Mitchell [43]	236	Medical treatment failure Focal persistent lung damage	Lobectomy 48% Segmentectomy 21% Pneumonectomy 17% Mixed procedures 15%	Not reported	Total=19% Bronchopleural fistula 4% Prolonged air leak 4% Respiratory failure/pneumonia 3% Post-operative bleeding 2% Wound dehiscence 1% ARDS 1% Atrial fibrillation 4%
Koh [40]	23	Medical treatment failure 48% Remaining cavity relapse risk 35% Persistent symptoms 17%	Lobectomy 70% Two lobes 9% Two sides 13% Segmentectomy 13% Pneumonectomy 17%	9 days (IQR 6–15 days)	Total=35% Bronchopleural fistula 9% Prolonged air leak 9% Pneumonia 13% Wound dehiscence 4% Pneumonectomy syndrome 4%
van Ingen [19]	8	Treatment failure Infected destroyed lung	Lobectomy 63% Two lobes 13% Wedge resection 13% Pneumonectomy 25%	Not reported	Total=63% Pneumothorax 38% Atelectasis requiring bronchoscopy 13% Respiratory distress 13% Pneumonia 13%
Yu [30]	134	Localised disease ±cavitation Medical treatment failure Persistent symptoms	Lobectomy 100% Middle 59% Lingulectomy 41%	3 days (1–15 days)	Total=8% Prolonged air leak 4% Wound infection 1% Atelectasis 1% Pleural effusion 1% Atrial fibrillation 1%

Continued

Table 3 *Continued*

First author [ref.]	Patients n	Surgical indications	Type of surgery	Hospital stay	Complications
Jarand [41]	24	Localised bronchiectasis 86% Cavitary disease 37% Haeptysis 11%	Lobectomy 83% Pneumonectomy 21% Segmentectomy 10% Wedge resection 3%	Not reported	Total=25% Haemorrhage 4% Bronchopleural fistulae 4% Wound infection 4% Brachial plexus injury 4% Frozen shoulder 4% Respiratory failure/death 4%
Shiraishi [31]	60	Medical treatment failure 87% Persistent symptoms 10% Secondary infection 3%	Lobectomy 90% Two lobes 5% Segmentectomy 7% Pneumonectomy 2% Wedge resections 3%	Not reported	Total=12% Prolonged air leak 6% Atelectasis 3% Respiratory failure 1% Haemorrhage 1% Atrial fibrillation 1%
Asakura [37]	125	Medical treatment failure 56% Cavities; severe bronchiectasis 29% Persistent symptoms 15%	Lobectomy 88% Two lobes 10% Pneumonectomy 25% Segmentectomy 11% Wedge resection 2%	Not reported	Total=22% Bronchopulmonary fistula 6% Bronchopleural fistula 2% Prolonged air leak 1% Wound dehiscence 1% Pneumonia or empyema 7% Bronchial stenosis 1% Diaphragmatic hernia 1% Left atrial rupture 1%

MI: myocardial infarction; ARDS: acute respiratory distress syndrome. ‡: patients were kept in hospital until sputum conversion; ¶: 15% of bronchopleural fistula occurred post-right pneumonectomy; +: primarily as 45% of this cohort had multiple resections.

Table 4 *Pre- and post-surgical treatment with sputum clearance, relapse and mortality (early and total)*

First author [ref.]	Patients n	NTM species	Pre-surgery antibiotics % on antibiotics; duration; macrolide; % sputum clearance	Post-surgery antibiotics % on antibiotics; duration	Follow up duration#,¶	Sputum conversion immediately post-surgery	Relapse	Mortality early and total
Studies without clarithromycin								
Elkadi [23]	48	*M. kansasii* 54% *M. intracellulare* 42% Rapid grower 2%	100%; 1–22 months; no clarithromycin; 54%	Up to 9 months or until sputum conversion	Not reported	85.4% With additional antibiotics 100%	Not reported	None and None
Pomerantz [36]	38	MAC 87% *M. kansaii* 2.6% *M. chelonae* 2.6% *M. xenopi* 2.6%	100%; 3 months; no clarithromycin; 32%	Not reported	Not reported	Not reported	Not reported	2.6% and 21%
Ono [35]	8	MAC 100%	62.5%; 8.1 months (1–30 months); no clarithromycin; 12.5%	Nil treatment post-operatively	20 months# (4–56)	100%	13% 6 months	None and None
Nelson [38]	28	MAC 100%	100%; 1 year (1–6 years); 61% had clarithromycin; 50%	100%; up to 12 months	39 months#	>90% 3 months after surgery: 93% (of those alive)	4% 2 years	7% and 14%+
Shiraishi [34]	33	MAC 100%	85%; 8 months (1–64 months); 4% had clarithromycin; 35%	91%; 13 months (1–96 months)	(1–18 years)	94%	3% 5 years 12% 10 years	None and 6%
Studies incorporating clarithromycin								
Shiraishi [28]	21	MAC 100%	100%; 11 months (2.2–29.1); 100% on clarithromycin; 38%	90%; 6–12 months	35 months¶ (6–99)	100%	10% 2 years	None and None
Shiraishi [29]	11	MAC 91% *M. abscessus* 9%	100%; 57 months (13–109 months); 100% had clarithromycin; Not reported	64%; 6–24 months	2 years¶ (0.6–17)	100%	9% 2 years	None and 18%
Watanabe [39]	22	MAC 100%	100%; 17 months (2–37 months); 82% on clarithromycin; 80%§	100%; 6–35 months	46 months¶ (6–164)	90% 100% after antimicrobials	Not reported	None and None

Continued

Table 4 *Continued*

First author [ref.]	Patients n	NTM species	Pre-surgery antibiotics % on antibiotics; duration; macrolide; % sputum clearance	Post-surgery antibiotics % on antibiotics; duration	Follow up duration#,¶	Sputum conversion immediately post-surgery	Relapse	Mortality early and total
Mitchell [43]	236	MAC 80% *M. abscessus* 14%	100%; 2–6 months; 57% negative sputum prior surgery	Not reported	Not reported	100%	Not reported	2.6% and 2.6%
Koh [40]	23	MAC 43% *M. abscessus* 52% *M. xenopi* 4%	87%; 7.5 months (5–17 months);100% on clarithromycin; 26%	97%; 12 months (6–26 months)	14 months¶ (IQR 6–11)	100% (in 1–2 months)	Not reported	None and 9%
van Ingen [19]	8	MAC 87.5% *M. xenopi* 12.5%	100%; 22 months; Not reported	50%; 9 months	19 months#	88%	0% 19 months	12.5% and 12.5%
Yu [30]	128	MAC 88% *M. abscessus* or *chelonae* 10%	100%; at least 2–3 months; Not reported	100%; duration not reported	23 months# (0–70)	84% 97% sputum negative at final follow up at 34 months	7% 17 months	None and None
Jarand [41]	24	*M.* abscessus 100%	100%; uncertain; % macrolide uncertain; 71%	100%; duration not separately reported for surgery group	34 months (2–82)#	Uncertain Overall 65%	Never converted or relapsed 35%	Uncertain and 17%
Shiraishi [31]	60	MAC 92% *M. abscessus* 5% *M. gordonae* 1.6% *M. xenopi* 1.6%	100%; 14.2 months (3.3–75.2); 100% clarithromycin; Not reported	100%; at least 12 months post-surgery or post-sputum conversion	34 months¶ (13–70)	100%	3% 34 months	None and None
Asakura [37]	125	MAC 80% *M. Intracellulare* 8% *M. abscessus* 5% *M. kansasi* 3% Others 5%	94% treatment before and after surgery; 7 months (IQR 6–18 months); 82% clarithromycin; Not reported	94% (before and after); 7 months (IQR 6–18 months)	7.1 years¶ (IQR 3.5–10.3)	91%	5% 1 year 10% 3 years 15% 5 years 20% 19 years	4% and 4%

#: mean; ¶: median (range); +: 2 patients (7%) suffered late deaths due to unrelated causes; §: only those (5 out of 25) who did not sputum convert were referred on for surgical treatment and joined 17 other patients from another hospital to make up to 22 patients in the cohort.

NTM had poorer results with higher incidences of complications compared with the TB group. They proposed that this might be due to the older age group of those with NTM disease and the indolent nature of disease resulting in more extensive parenchymal involvement at the time of surgery, resulting in more extensive surgical resections [36]. Low BMI (≤18.5 kg·m^{-2}) was associated with worse outcomes (OR 1.91, 95% CI 1.11–3.29) in patients undergoing lung surgery for MDR-TB [45] and pulmonary NTM disease [37].

Sputum clearance

The sputum clearance rates reported across studies ranged from 84% to 100%; with better conversion rates if antibiotics were continued post-operatively [38]. Excellent long-term clearance rates of 95% at 1 year and 87% at 3 years after surgery have been reported in some recent studies [28]. Relapses may be due to occult bilateral disease or infection of the healthy lung around the time of surgical resection; one patient with initial post-surgery sputum conversion required a second lobectomy in the contralateral lung [28]. Relapse rates of 0–20% have been reported with concomitant antibiotic therapy and follow-up periods of 9 months to 19 years. Asakura *et al.* [37] showed that the presence of persisting cavitary lesions after surgery is a significant predictor of microbiological recurrence with an adjusted hazard ratio of 6.73 (CI 1.68–22.7; p=0.0095). Jarand *et al.* [41] compared patients with combined antibiotic and surgical therapy compared with antibiotic therapy alone and showed that the surgical group had a significantly higher rates of culture conversion and remained culture negative at 1 year (57% *versus* 28%; p=0.022).

Lung function

Only one study reported results of lung function after surgery [39]. It showed that vital capacity and forced expiratory volume in 1 s were at 89% and 84% of the pre-operative values, respectively. The study did not assess for ongoing decline after surgery.

Antibiotic treatment

Pre-operative

Despite the introduction of clarithromycin, surgery still assists culture conversion in those who fail medical treatment [28]. Most patients were treated for 6–18 months with multiple antibiotics prior to surgery with some patients on treatment for up to 6 years. Across the studies, sputum conversion with antibiotics alone prior to surgery ranged between 12% and 80% (table 4). Elkadi *et al.* [23] found that patients on the longest treatment course of antibiotics prior to surgery took longer to achieve sputum clearance post-operatively; which may suggest increased acquisition of drug resistance if surgery is delayed for too long, or simply reflect selection bias. On average, studies reported a delay of ~14 months from diagnosis before surgery was performed.

Post-operative

Hattler *et al.* [25] showed that the sputum conversion rate after operative management was 91% compared to 27% with medical treatment

Self-evaluation questions

1. What is the role of surgery in the treatment of pulmonary NTM disease?
   a) Surgery is the main treatment for localised pulmonary NTM disease
   b) Surgery has no role in the treatment of pulmonary NTM disease
   c) Surgery should be considered as an adjuvant treatment in selected patients with localised pulmonary NTM disease
   d) Surgery should be only considered in the treatment of pulmonary NTM disease if antibiotic treatments have failed
2. What initial factors are important to consider when evaluating the role of surgery for the treatment of NTM pulmonary disease?
   a) Age, sex and BMI
   b) Localised disease that is amenable to resection in a patient with adequate underlying pulmonary reserve
   c) Localised disease due to *Mycobacterium avium* complex (MAC)
   d) Irretraceable coughing and recurrent haemoptysis
3. Which of the statements around the indication for surgery in the treatment of pulmonary NTM disease is false?
   a) In the post-macrolide era, most surgical treatment of pulmonary NTM disease was due to medical treatment failure
   b) Surgery might be indicated to prevent further spread NTM pulmonary infection
   c) Haemoptysis is the most frequent indication for surgery
   d) At times, surgery might be indicated early to optimise chances of cure
4. Which of the following statements is true?
   a) Pneumonectomy is the most common type of surgical procedure used
   b) Bronchopulmonary fistulae are the most common major post-operative complication and occur most often after lobectomy
   c) Post-operative mortality rates are high
   d) Bronchopulmonary fistulae occur more commonly after pneumonectomy
5. With regards to post-operative outcomes, which of the following statements is false?
   a) Sputum clearance is high post-operatively
   b) Sputum clearance improves with pre- and post-operative antibiotic treatment
   c) Persisting cavitary lesions after surgery is a significant predictor of microbiological recurrence of disease
   d) Antibiotics can be reassuringly ceased after sputum clearance post-pneumonectomy

alone, while Corpe [24] found that bacteriological cure was 2–3 times greater with combined surgical and medical treatment; however, both studies were conducted in the pre-clarithromycin era. Most studies continued antibiotic treatment after surgery, which was associated with greater sputum clearance [39, 40]. The duration of antibiotic treatment ranged from a few months to several years. Current ATS/IDSA guidelines advocate treatment for 12 months after culture conversion [12], which was mostly achieved following surgery. Some centres recommended treatment for 2 years after pneumonectomy, since stump breakdown or infection of the remaining lung can be fatal [29].

Limitations and future directions

It is challenging to accurately assess the impact of surgical interventions, since no randomised controlled trials (RCT) have compared the benefits of surgery to antibiotic therapy alone [46]. RCTs are required to draw firm conclusions about the role of surgery in this setting but are problematic due to low patient numbers and variability in the mycobacterial species and drug susceptibility patterns of individual patients. No studies have been performed in children or in patients with CF. Specific to CF, the United States CF Foundation and European CF society urge caution when considering surgical treatment for CF pulmonary NTM disease as localised disease is rare and it is difficult to differentiate NTM changes from the underlying disease process [46]. The studies performed to date have largely focused on subjects with MAC disease and the impact of NTM species on outcomes remains unclear. Hopefully improved standardisation of NTM treatment and identification of candidates for surgery following the publication of consensus guidelines from the ATS/IDSA will facilitate easier comparison of future surgical case series.

Conclusion

The results of studies to date suggest that lung surgery may have value in the management of NTM pulmonary disease. However, its role requires further clarification and there must be careful consideration of the risks and benefits. While surgery is associated with low rates of post-operative mortality the long-term mortality and morbidity is highly variable. The value of surgery in children and patients with CF with pulmonary NTM disease remains unclear, but should be considered with caution.

Conflict of interest

None declared.

References

1. Adjemian J, Olivier KN, Seitz AE, *et al*. Prevalence of nontuberculous mycobacterial lung disease in U.S. medicare beneficiaries. *Am J Respir Crit Care Med* 2012; 185: 881–886.
2. Prevots DR, Shaw PA, Strickland D, *et al*. Nontuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems. *Am J Respir Crit Care Med* 2010; 182: 970–976.
3. Thomson RM. Changing epidemiology of pulmonary nontuberculous mycobacteria infections. *Emerging Infect Dis* 2010; 16: 1576–1583.
4. Marras TK, Daley CL. Epidemiology of human pulmonary infection with nontuberculous mycobacteria. *Clin Chest Med* 2002; 23: 553–567.
5. Ringshausen FC, Apel RM, Bange, FC, *et al*. Burden and trends of hospitalisations associated with pulmonary non-tuberculous mycobacterial infections in Germany, 2005–2011. *BMC Infect Dis* 2013; 13: 231.
6. Lee SK, Lee EJ, Kim SK, *et al*. Changing epidemiology of nontuberculous mycobacterial lung disease in South Korea. *Scand J Infect Dis* 2012; 44: 733–738.
7. Marras TK, Chedore P, Ying AM, *et al*. Isolation prevalence of pulmonary non-tuberculous mycobacteria in Ontario, 1997 2003. *Thorax* 2007; 62: 661–666.
8. Namkoong H, Kurashima A, Morimoto K, *et al*. Epidemiology of pulmonary nontuberculous mycobacterial disease, Japan. *Emerging Infect Dis* 2016; 22: 1116–1117.
9. Whittier S, Olivier K, Gilligan P, *et al*. Proficiency testing of clinical microbiology laboratories using modified decontamination procedures for detection of nontuberculous mycobacteria in sputum samples from cystic fibrosis patients. The Nontuberculous Mycobacteria in Cystic Fibrosis Study Group. *J Clin Microbiol* 1997; 35: 2706–2708.
10. Lu M, Saddi V, Britton PN, *et al*. Disease caused by non-tuberculous mycobacteria in children with cystic fibrosis. *Paediatr Respir Rev* 2018; in press [https://doi.org/10.1016/j.prrv.2018.05.001].
11. Qvist T, Pressler T, Høiby N, *et al*. Shifting paradigms of nontuberculous mycobacteria in cystic fibrosis. *Respir Res* 2014; 15: 41.
12. Griffith DE, Aksamit T, Brown-Elliott BA, *et al*. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; 175: 367–416.
13. Field SK, Cowie RL. Treatment of *Mycobacterium avium–intracellulare* complex lung disease with a macrolide, ethambutol, and clofazimine. *Chest* 2003; 124: 1482–1486.
14. Tanaka E, Kimoto T, Tsuyuguchi K, *et al*. Effect of clarithromycin regimen for *Mycobacterium avium* complex pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 866–872.
15. Wallace RJ, Brown BA, Griffith DE, *et al*. Clarithromycin regimens for pulmonary *Mycobacterium avium* complex. The first 50 patients. *Am J Respir Crit Care Med* 1996; 153: 1766–1772.
16. Kobashi Y, Matsushima T. The microbiological and clinical effects of combined therapy according to guidelines on the treatment of pulmonary *Mycobacterium avium* complex disease in Japan – including a follow-up study. *Respiration* 2007; 74: 394–400.

17. Griffith DE, Brown BA, Cegielski P, *et al.* Early results (at 6 months) with intermittent clarithromycin-including regimens for lung disease due to *Mycobacterium avium* complex. *Clin Infect Dis* 2000; 30: 288–292.
18. Dautzenberg B. Clarithromycin Study Group of France. Clarithromycin in the treatment of *Mycobacterium avium* patients without AIDS. *Chest* 1995; 107: 1035–1040.
19. van Ingen J, Verhagen AF, Dekhuijzen PN, *et al.* Surgical treatment of non-tuberculous mycobacterial lung disease: strike in time. *Int J Tuberc Lung Dis* 2010; 14: 99–105.
20. Ballarino GJ, Olivier KN, Claypool RJ, *et al.* Pulmonary nontuberculous mycobacterial infections: antibiotic treatment and associated costs. *Respir Med* 2009; 103: 1448–1455.
21. Thomson RM, Yew WW. When and how to treat pulmonary non-tuberculous mycobacterial diseases. *Respirology* 2009; 14: 12–26.
22. Fox GJ, Mitnick CD, Benedetti A, *et al.* Surgery as an adjunctive treatment for multidrug-resistant tuberculosis: an individual patient data meta analysis. *Clin Infect Dis* 2016; 62: 887–895.
23. Elkadi A, Salas R, Almond C. Surgical treatment of atypical pulmonary tuberculosis. *J Thorac Cardiovasc Surg* 1976; 72: 435–440.
24. Corpe RF. Clinical aspects, medical and surgical, in the management of Battey-type pulmonary disease. *Dis Chest* 1964; 45: 380–382.
25. Hattler B. Surgical management of pulmonary tuberculosis due to atypical mycobacteria. *J Thorac Cardiovasc Surg* 1970; 59: 366–371.
26. Zvetina JR, Neville WE, Maben HC, *et al.* Surgical treatment of pulmonary disease due to *Mycobacterium kansasii*. *Ann Thorac Surg* 1971; 11: 551–556.
27. Shields TW, Fox RT, Lees WM. Changing role of surgery in the treatment of pulmonary tuberculosis. *Arch Surg* 1970; 100: 363–366.
28. Shiraishi Y, Nakajima Y, Takasuna K, *et al.* Surgery for *Mycobacterium avium* complex lung disease in the clarithromycin era. *Eur J Cardiothorac Surg* 2002; 21: 314–318.
29. Shiraishi Y, Nakajima Y, Katsuragi N, *et al.* Pneumonectomy for nontuberculous mycobacterial infections. *Ann Thorac Surg* 2004; 78: 399–403.
30. Yu JA, Pomerantz M, Bishop A, *et al.* Lady Windermere revisited: treatment with thoracoscopic lobectomy/segmentectomy for right middle lobe and lingular bronchiectasis associated with non-tuberculous mycobacterial disease. *Eur J Cardiothorac Surg* 2011; 40: 671–675.
31. Shiraishi Y, Katsuragi N, Kita H, *et al.* Adjuvant surgical treatment of nontuberculous mycobacterial lung disease. *Ann Thorac Surg* 2013; 96: 287–291.
32. Griffith DE, Brown-Elliott BA, Langsjoen B, *et al.* Clinical and molecular analysis of macrolide resistance in *Mycobacterium avium* complex lung disease. *Am J Respir Crit Care Med* 2006; 174: 928–934.
33. Jeon K, Kwon OJ, Lee, NY, *et al.* Antibiotic treatment of *Mycobacterium abscessus* lung disease: a retrospective analysis of 65 patients. *Am J Respir Crit Care Med* 2009; 180: 896–902.
34. Shiraishi Y, Fukushima K, Komatsu H, *et al.* Early pulmonary resection for localized *Mycobacterium avium* complex disease. *Ann Thorac Surg* 1998; 66: 183–186.
35. Ono N, Satoh K, Yokomise H, *et al.* Surgical management of *Mycobacterium avium* complex disease. *Thorac Cardiovasc Surg* 1997; 45: 311–313.
36. Pomerantz M, Madsen L, Goble M, *et al.* Surgical management of resistant mycobacterial tuberculosis and other mycobacterial pulmonary infections. *Ann Thorac Surg* 1991; 52: 1108–1112.
37. Asakura T, Hayakawa N, Hasegawa N, *et al.* Long-term outcome of pulmonary resection for nontuberculous mycobacterial pulmonary disease. *Clin Infect Dis* 2017; 65: 244–251.
38. Nelson KG, Griffith DE, Brown BA, *et al.* Results of operation in *Mycobacterium avium–intracellulare* lung disease. *Ann Thorac Surg* 1998; 66: 325–329.
39. Watanabe M, Hasegawa N, Ishizaka A, *et al.* Early pulmonary resection for *Mycobacterium avium* complex lung disease treated with macrolides and quinolones. *Ann Thorac Surg* 2006; 81: 2026–2030.
40. Koh W-J, Kim YH, Kwon OJ, *et al.* Surgical treatment of pulmonary diseases due to nontuberculous mycobacteria. *J Korean Med Sci* 2008; 23: 397–401.
41. Jarand J, Levin A, Zhang L, *et al.* Clinical and microbiologic outcomes in patients receiving treatment for *Mycobacterium abscessus* pulmonary disease. *Clin Infect Dis* 2011; 52: 565–571.
42. Mitchell JD. Surgical approach to pulmonary nontuberculous mycobacterial infections. *Clin Chest Med* 2015; 36: 117–122.
43. Mitchell JD, Bishop A, Cafaro A, *et al.* Anatomic lung resection for nontuberculous mycobacterial disease. *Ann Thorac Surg* 2008; 85: 1887–1893.
44. Polk JW, Ponce L, Medina M. Surgical treatment in pulmonary infections due to atypical mycobacterium. *Am J Surg* 1967; 114: 739–743.
45. Gegia M, Kalandadze I, Kempker RR, *et al.* Adjunctive surgery improves treatment outcomes among patients with multidrug-resistant and extensively drug-resistant tuberculosis. *Int J Infect Dis* 2012; 16: e391–e396.
46. Floto RA, Olivier KN, Saiman L, *et al.* US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. *Thorax* 2016; 71: Suppl 1, i1–i22.

Suggested answers

1 c.
2 b.
3 c.
4 d.
5 d.