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.
Surgery in nontuberculous mycobacteria pulmonary disease

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.

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

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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 | Trough levels |
| | Auditory-vestibular toxicity (tinnitus, high-frequency hearing loss) | Serum levels |
| Amikacin (nebulisation)* | None described | |
| Azithromycin (oral)+ | Nausea, vomiting, diarrhoea | Symptoms |
| | Auditory-vestibular toxicity | Audiology |
| | Prolonged QTc | ECG |
| Bedaquiline (oral)* | Headaches, dizziness, joint aches | Symptoms |
| | Prolonged QTc | ECG |
| | Liver enzyme derangement | LFT |
| Cefoxitin (intravenous)* | Fever, rash | Symptoms |
| | Eosinophilia, anaemia, leukopenia, thrombocytopenia | |
| | Interference with serum creatinine measurement | |
| Clofazimine (oral)* | Discoloration of skin or sclera | Symptoms |
| | Enteropathy (can mimic pancreatic insufficiency), nausea and vomiting | |
| Ethambutol (oral)+ | Optic neuritis | Symptoms, colour vision and acuity |
| Imipenem (intravenous)* | Nausea, vomiting, diarrhoea | Symptoms |
| | Hepatitis | LFT |
| Linezolid (oral)* | Anaemia, leukopenia, thrombocytopenia | FBC |
| | Peripheral neuropathy, optic neuritis | Symptoms/clinical |
| Minocycline (oral)* | Photosensitivity, skin discoloration | Symptoms |
| | Nausea, vomiting, diarrhoea | |
| | Vertigo | |
| Moxifloxacin (oral)* | Nausea, vomiting, diarrhoea | Symptoms |
| | Insomnia, agitation, anxiety | ECG |
| | Tendonitis | |
| | Photosensitivity | |
| | Prolonged QTc | |
| Rifabutin (oral)+ | Leukopenia, anterior uveitis (when combined with clarithromycin), flu-like symptoms (polyarthralgia or myalgia) | Symptoms |
| | | FBC |
| Rifampicin (oral)+ | Orange discoloration of bodily fluids, fever, chills, nausea, vomiting, diarrhoea | Symptoms |
| | Hepatitis | LFT |
| | Thrombocytopenia | FBC |
| | Renal failure | EUC |
| Streptomycin (intravenous, intramuscular)* | Nephrotoxicity | Trough levels, serum creatinine |
| Tigecycline (intravenous)* | Nausea, vomiting, diarrhoea | Symptoms |
| | Pancreatitis | Serum amylase, lipase |
| | Hypoproteinaemia, bilirubinaemia | 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.
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; I² 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 posterol- 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 | 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. kansasi 54% | Lung cavities 77% |
|                      |                         |          |                          |           | M. intracellulare 42% | |
|                      |                         |          |                          |           | Rapid grower 2% | |
| Pomerantz [36]      | 1983–1990 Colorado, USA | 38       | 50 (33–39)               | 68%       | MAC 87% | Previous lobectomy 18% |
|                      |                         |          |                          |           | M. kansi 3% | Previous TB 8% |
|                      |                         |          |                          |           | M. chelone 3% | Bronchopleural fistula 8% |
|                      |                         |          |                          |           | M. xenopi 3% | 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%  | Multiple cavities 55% |
|                      |                         |          |                          |           | M. abscessus 9% | |
|                      |                         |          |                          |           | Destroyed lung 46% | |
|                      |                         |          |                          |           | Bilateral disease 36% | |
|                      |                         |          |                          |           | No immunocompromised | |
| Watanabe [39]       | 1990–2005 Tokyo, Japan | 22       | 54 (30–77)               | 68%       | MAC 100%  | Bronchiectasis predominant 64% |
|                      |                         |          |                          |           | Cavity predominant 36% | |
|                      |                         |          |                          |           | No immunocompromised | |
| Mitchell [43]       | 1983–2006 Colorado, USA | 236      | 54 (23–77)               | 83%       | MAC 80%  | Focal bronchiectasis 55% |
|                      |                         |          |                          |           | M. abscessus 14% | |
|                      |                         |          |                          |           | Cavitary lung disease 29% | |
|                      |                         |          |                          |           | Mixed pattern 9% | |
|                      |                         |          |                          |           | Prior thoracic surgery 20% | |
| Koh [40]            | 2002–2007 Seoul, Korea | 23       | 45 (24–66)               | 70%       | MAC 43%  | Cavities 70% |
|                      |                         |          |                          |           | M. abscessus 52% | |
|                      |                         |          |                          |           | M. xenopi 4% | |
| van Ingen [19]      | 2000–2009 Holland       | 8        | 52 (41–59)               | 25%       | MAC 88%  | Cavitary disease 62% |
|                      |                         |          |                          |           | Mixed pattern 25% | |
|                      |                         |          |                          |           | Bronchiectasis 13% | |
|                      |                         |          |                          |           | No immunocompromised | |
| Yu [30]             | 2004–2009 Colorado, USA | 128      | 59 (34–81)               | 96%       | MAC 88%  | Bronchiectasis 95% |
|                      |                         |          |                          |           | M. abscessus 10% | |
|                      |                         |          |                          |           | 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% | |
|                      |                         |          |                          |           | Cavitory disease 37% | |
|                      |                         |          |                          |           | Previous smokers 23% | |
|                      |                         |          |                          |           | Previous TB 8.3% | |
Most studies followed patients for 6–8 years, but 21% and was mostly due to respiratory failure. Mortality summarises the outcomes following surgical intervention. Table 4 describes the most common procedures performed. Table 4 summarises the outcomes following surgical treatment of pulmonary NTM disease declined from 7% in the 1980s to <1% today [43].

### Airway toilet

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 surgical treatment of pulmonary NTM disease declined from 7% in the 1980s to <1% today [43].
## 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\(^{2}\) | 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%\(^{6}\) 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% |
### Table 3

| First author [ref.] | Patients n | Surgical indications | Type of surgery | Hospital stay | Complications |
|---------------------|------------|----------------------|-----------------|---------------|---------------|
| **JARAND [41]**     | 24         | Localised bronchiectasis 86% Cavitary disease 37% Haemoptysis 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% Cavitae; 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 | NTM species | Pre-surgery antibiotics | Post-surgery antibiotics | Follow up duration* † | Sputum conversion immediately post-surgery | Relapse | Mortality early and total |
|---------------------|----------|-------------|--------------------------|--------------------------|-----------------------|------------------------------------------|---------|---------------------------|
| **Studies without clarithromycin** |          |             |                          |                          |                       |                                          |         |                           |
| Elkadi [23]          | 48       | *M. kansasi* 54%  
*M. intracellular* 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. kansasi* 2.6%  
*M. chelona* 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
| First author [ref.] | Patients | 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) | 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% | Not reported | None and None |
| Yu [30]             | 128      | MAC 88% M. abscessus or cheknae 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 |
| 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% | Uncertain or relapsed 35% |
| 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. kansasii 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% |

†: 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.
alone, while Coree [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.

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Surgery in NTM pulmonary disease

Suggested answers

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