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Paediatric lung transplant outcomes vary with *Mycobacterium abscessus* complex species

To the Editor:

Mycobacterium abscessus complex species are rapid-growing non-tuberculous mycobacteria (NTM) with multiple drug resistance profiles [1]. Increasing prevalence in cystic fibrosis (CF) subjects [1] may reflect several factors, including improved detection and increased CF survival. Persistent NTM infection post-transplantation is associated with poorer outcome [2], and the risk is highest with *M. abscessus* [3]. However, recent small case series have suggested improved short-term post-transplantation outcomes may be achievable despite pre-transplantation *M. abscessus* infection [3]. The current approach to listing varies markedly across transplant centres and refusal to consider transplantation in those with active infection is common. Recent data have suggested a stratified approach to transplant listing for CF subjects with *Burkholderia cepacia* complex may be appropriate, as poor outcomes were attributable to genomovar III (*B. cenocepacia*) alone [4].

Recently, *M. abscessus* has been recognised to be a complex of three closely related species: *M. abscessus* (*sensu stricto*), hereafter referred to as *M. abscessus*, *M. massiliense* and *M. bolletii*, which are collectively termed *M. abscessus* complex [5]. The transplantation literature to date has not examined the impact of *M. abscessus* species type on outcome. In this case series we describe experience at a single paediatric lung transplant centre (Great Ormond Street Hospital, London, UK) with subjects infected with *M. abscessus* complex pre-transplantation and provide pilot data suggesting post-transplantation outcome may be influenced by the particular *M. abscessus* complex species encountered.

Five subjects have been transplanted since 2003 with active *M. abscessus* complex infection at the time of listing, as defined by American Thoracic Society guidelines. Isolates, originally identified at the national reference laboratory, were retrospectively examined in-house to *M. abscessus* complex species level using *hsp65* and *rpoB* gene sequencing methods, as previously published [6]. The intended management protocol was the same for all cases. Pre-transplantation, subjects received optimised multiple *M. abscessus* complex targeted therapy prior to listing (directed by sensitivity testing) to reduce NTM load for at least 6 months; at the time of transplantation, complete mediastinal and hilar lymphadenectomy, bilateral pleural cavity irrigatation with Amikacin solution (1 g diluted in 5 L of 0.9% saline) and change of surgical gloves prior to donor organ implantation; and post transplantation, individually tailored *i.v.* multiple anti-infective drug regimens, continued for at least 4 weeks, before switching to long term prophylactic therapy (typically nebulised amikacin, oral ciprofloxacin and clarithromycin), continued indefinitely, as tolerated. Induction therapy with basiliximab was used at the time of transplant followed by a lifelong triple immunosuppressant regimen (tacrolimus, mycophenolate mofetil and prednisolone). Pre-transplant features and post-transplant course of these five cases are summarised (in chronological order) in table 1.

Acceptable survival (four of five children, 80%) by the end of current follow-up (range 2.5–7.5 years) was achieved using this targeted management protocol, comparable with survival in non-NTM subjects at our institution (unpublished data). Furthermore, identification to species level suggested improved outcomes, with no re-isolation, in subjects with non-*M. abscessus* species of *M. abscessus* complex pre-transplantation (*i.e. M. massiliense* and *M. bolletii*). In comparison, mortality and morbidity was encountered in two of the three subjects infected with *M. abscessus (M. abscessus sensu stricto)*. Direct attribution of mortality to *M. abscessus* for case four is difficult but *post mortem* examination documented the cause of death as ''overwhelming sepsis secondary to organisms including *M. abscessus*'' (others isolated were *Pseudomonas aeruginosa* and candida). Histology did not show granuloma in the graft but *M. abscessus* was grown from trachea, bronchus, pleura and lungs *post mortem*. This pattern of risk has never been described before in transplant subjects.

TABLE 1 Pre- and post-transplantation course, microbiology and anti-non-tuberculous mycobacteria treatment

	Case 1	Case 2	Case 3	Case 4	Case 5
Pre-transplantation course					
Age at transplant years	10.6	14.5	16.2	15.1	14.1
Sex	Female	Female	Female	Female	Female
Chronically infected with	*S. aureus* *A. fumigatus* *Candida*	*S. aureus* *A. fumigatus* *S. maltophilia*	*S. aureus* *A. fumigatus*	*S. maltophilia* *P. aeruginosa*	*P. aeruginosa* *S. aureus* *A. fumigatus* Coliforms
1st NTM growth, time prior to transplant	~2 years	~3 years	~5 years	~4 years	~3 years
M. abscessus complex species	*M. bolletti*	*M. massiliense*	*M. abscessus* (*sensu stricto*)	*M. abscessus* (*sensu stricto*)	*M. abscessus* (*sensu stricto*)
Colony morphotype	Smooth	Rough	Rough	Rough	Smooth
Duration NTM treatment pre-transplant	>12 months *p.o.* Rifampicin *p.o.* Ethambutol *p.o.* Clarithromycin	7 months *p.o.* Rifampicin *p.o.* Isoniazid *p.o.* Clarithromycin Neb. Amikacin	>3 years Neb. Amikacin *p.o.* Clarithromycin *p.o.* Ciprofloxacin	>3 years Neb. Amikacin *p.o.* Clarithromycin *p.o.* Ciprofloxacin *p.o.* Septrin	15 months Neb. Amikacin *p.o.* Ciprofloxacin *p.o.* Clarithromycin
Smear positive at referral	Yes	No	Yes	Yes	Yes
Smear positive at transplant	Yes	No	No	Yes	No
Most recent sputum culture pre-transplant at GOSH	6 months prior; smear and culture positive	3 months prior; smear negative, culture positive	3 months prior; smear negative, culture positive	3 months prior; smear and culture positive	15 days prior; smear and culture negative
Post transplantation course					
Transplant type	HLT	BSSLT	BSSLT	BSSLT	BSSLT
CMV mismatch	Yes	Yes	Yes	Yes	No
Histological evidence of active NTM in explanted lung	Yes	Yes	Yes	No	
NTM re-isolation *M. abscessus complex* species	No	No	Yes *M. abscessus* (pleural fluid)	Yes *M. abscessus* (BAL, *post mortem* lung, trachea and pleura)	No
Perioperative Antibiotic treatment	Amikacin Clarithromycin Cefoxitin, Ceftazidime Teicoplanin	Amikacin Clarithromycin Ciprofloxacin Teicoplanin Co-trimoxazole	Amikacin Clarithromycin Ciprofloxacin Tigecycline Ceftazidime	Amikacin Clarithromycin Ciprofloxacin Tigecycline Imipenem Teicoplanin Co-trimoxazole	Amikacin Clarithromycin Ciprofloxacin Tigecycline Teicoplanin Colistin
i.v. antibiotics duration	4 weeks	4 weeks	Amikacin 10 weeks tigecycline 17 months		Tigecycline and amikacin 14 weeks
ICU stay days	5	7	11	21	11
Day of extubation	2	2	1	N/A	1
Inpatient stay days	29	43	68	N/A	Day 18 transfer to local hospital
Acute issues	Prolonged pleural effusions	ARF GORD (Nissens) Mild rejection at 1 month	Prolonged pleural effusions ARF PRES Paraspinal fungal abscess	ARDS DIC Severe pulmonary haemorrhage	Recurrent seizures GORD Hiatus hernia Unexplained transient limb weakness
BOS	No	No[#]	No[#]	N/A	No
Long term anti-NTM antibiotic treatment	*p.o.* clarithromycin *p.o.* ciprofloxacin Neb. amikacin	*p.o.* clarithromycin *p.o.* ciprofloxacin Neb. amikacin	*p.o.* clarithromycin *p.o.* ciprofloxacin Neb. amikacin *p.o.* linezolid	N/A	*p.o.* clarithromycin *p.o.* ciprofloxacin Neb. amikacin
Side effects of NTM treatment	Bilateral SNHL Amikacin ceased	Bilateral SNHL Amikacin weaned	Bilateral SNHL CRF	N/A	None
Survival	7.5 years	28 months[#] (7 years to date)	39 months[#] (4.3 years to date)	21 days	30 months

NTM: non-tuberculous mycobacterium; GOSH: Great Ormond Street Hospital; CMV: cytomegalovirus; ICU: intensive care unit; BOS: bronchiolitis obliterans syndrome; *p.o.*: by mouth; Neb.: nebuliser; HLT: heart lung transplant; BSSLT: bilateral sequential single lung transplant; BAL: bronchoalveolar lavage; ARF: Acute renal failure; ARDS: acute respiratory distress syndrome; GORD: gastro-oesophageal reflux disease; DIC: disseminated intravascular coagulation; PRES: posterior reversible encephalopathy syndrome; SNHL: sensorineural hearing loss; CRF: chronic renal failure. [#]: at transition to adult services.

Other factors contributing to recurrence risk include mycobacterial load, viability and colony morphotype at the time of transplant, and the ability to surgically remove all infected foci. While eradication of infection pre-transplantation is unlikely, reduction of viable organisms may be achievable. Failure to achieve sputum smear negativity in the one patient with *M. abscessus* who did not survive the initial post-operative period (case four) suggests a higher NTM load at the time of transplantation. A ''rough'' colony morphotype, associated with increased virulence [7], was persistently seen pre-transplantation

in both cases with recurrence following (cases three and four). The surgical aim, to remove all infected foci using widespread lymph node excision, was not feasible in the two cases with recurrence (cases three and four), due to excessive bleeding, leaving mediastinal and hilar lymph nodes *in situ*. Granulomatous inflammation in excisable lymph nodes was not seen in either subject histologically, but these were not sent for culture so infection was not excluded. Contamination of the pleural space during explantation or by direct contiguous infection is a further risk factor and retrospective examination of computed tomography changes did not predict the degree of explantation difficulty in either case. Amikacin chest cavity wash out was employed as this antibiotic could be applied in high concentration with good prolonged effect (it binds to the cell wall and is active after free concentration is reduced). No efficacy studies are available on this treatment, but it was not used in the fatal case with persistent infection (case four).

In general oral or nebulised prophylactic NTM combinations were well tolerated, although side-effects of long-term *i.v.*, oral and nebulised antibiotics were encountered, including bilateral hearing loss and chronic renal impairment. No clear recommendations about anti-NTM treatment duration exist in this setting. Clarithromycin-based regimens may suppress disease, and combination therapy is recommended [1]. Due to lifelong immunosuppression, we continued prophylactic treatment if tolerated. Choice of anti-NTM antibiotics was limited by *in vitro* sensitivity data suggesting resistance to most agents tested in all isolates, although there were variable results with different isolates over time (data not shown). Agents with evidence of activity were usually clarithromycin, tigecycline and amikacin. Synergy testing had not been performed.

In summary, acceptable post-transplant outcomes in subjects infected with *M. abscessus* complex can be achieved with four out of five, or 80%, survival to date, in this the longest follow up study to date in the literature, comparable with non-NTM subjects at our institution. These findings have important implications for CF subjects referred for lung tranpslant with active *M. abscessus* complex infections, as we believe that active infection should not be seen as a contraindication for transplantation. Risk stratification may be warranted in *M. abscessus* complex, as was recently described for *Burkholderia cepacia* complex [4], with greater risk in those colonised with *M. abscessus (sensu stricto)* and lower risk with other species. These pilot data do not directly test this hypothesis and direct testing with multicentre retrospective data is challenging given the low rate of transplantation listing of these subjects; of 5200 screened transplant cases, only two out of 17 with post-transplantation infection had isolated pre-transplant [8]. Our hypothesis is supported, however, by improved treatment response with *M. massiliense* in immunocompetent hosts, attributed to a lack of inducible clarithromycin resistance [9]. Inducible clarithromycin resistance varies between strains of *M. abscessus* [10] and although the clinical significance is not confirmed, it warrants study as a potential prognostic factor. The role of morphology and NTM load at transplantation also requires further study. Multicentre efforts to identify *M. abscessus* complex isolates to this degree, increased consideration of these subjects for transplantation, and pooling of both future and retrospective data will be required in the future to formally test this hypothesis.

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