REVIEW

Treatment of non-tuberculous mycobacterial cervicofacial lymphadenitis in children: critical appraisal of the literature

Timmerman, M.K.,* Morley, A.D.† & Buwalda, J.*

*Department of Otorhinolaryngology, University Medical Center Utrecht, Utrecht, The Netherlands, and
†Department of Otolaryngology, Guys and St Thomas' Hospitals, London, UK

Accepted for publication 12 August 2008
Clin. Otolaryngol. 2008, **33**, 546–552

Background: Surgical excision has historically been the treatment of choice for non-tuberculous mycobacterial cervicofacial lymphadenitis. Emerging data suggests antibiotic treatment alone could be an attractive alternative to surgery. We questioned (1) what treatment offers best cure rates in children with this condition and (2) the evidence for antibiotic treatment alone.
Type of review: Structured literature search according to the Evidence Based Medicine guidelines.
Search strategy/methods: A structured search was conducted in PubMed, Embase and the Cochrane Library from 1966 up to November 2007. Relevant papers were critically appraised.
Results: Six papers were included, one of which was a randomised controlled clinical trial (RCT). In general, treatment sequencing was not consistent. Surgery and medical treatment were often used in combination, resulting in high overall cure rates. In the RCT surgery and antibiotic treatment were compared as single modalities. The outcome of surgery was far superior (96% *versus* 66% cure rate, respectively). Other studies indicated that substantial cure rates (up to 67%) were achieved with medical management alone, but failed to identify factors predicting response.
Conclusion: Surgical excision still is the backbone in the management of cervicofacial non-tuberculous mycobacterial lymphadenitis, although a considerable number of children can be cured with antibiotics alone or combined modality treatment. To date it is unclear which subset of patients can benefit from antibiotic treatment only.

Nowadays, up to 95% of the cases of mycobacterial cervicofacial lymphadenitis are caused by non-tuberculous mycobacterial (NTM).[1,2] The distribution of various NTM forms is not uniform and appears to be geographically or environmentally dependent.[3] The incidence in The Netherlands is estimated to be two to three cases per 100 000 children aged 0–4 years.[4] Infected children are most often 1–5 years of age and immunocompetent.[5]

The pathogenicity of NTM in humans ranges from asymptomatic colonization to visceral dissemination. The latter occurs especially in patients with impaired cell-mediated immunity.[6,7]

Non-tuberculous mycobacterial cervicofacial infections generally appear as slowly enlarging, painless neck masses. The clinical course varies from spontaneous cure to progression of the neck mass. If there is progression, the infected lymph nodes can surface to the skin, resulting in eruption and fistula or sinus formation. This often takes place over several months.[1]

Surgical excision through complete resection of the involved node(s) and diseased surrounding tissues/skin with or without adjuvant antimycobacterial agents is the treatment of choice. To date, the role of medical treatment alone is unclear but some authors report substantial cure rates.[8–11] Advantages of medical treatment are that general anesthesia, surgical sequelae and/or complications (scar formation, wound infection and cranial nerve deficits) can be avoided.

It is thus unclear which treatment, medical, surgical or a combination of both, gives the highest cure rate in children with NTM cervicofacial lymphadenitis. Important issues such as the efficacy of antibiotics alone and the proper sequence of combined modality treatment still exists. A literature search was performed to gain the best available evidence for the treatment of this condition.

Correspondence: M.K. Timmerman, MD, Department of Otorhinolaryngology, University Medical Center Utrecht, G 05.127, P.O. Box 85500, 3508 GA Utrecht, The Netherlands. Tel.: +31 30 250 6646; fax: +31 30 254 1922; e-mail: m.k.timmerman@erasmusmc.nl

Methods

Search strategy

A literature search was performed using PubMed, Embase and The Cochrane Library from 1966 to November 2007. A MeSH search within titles and abstracts, using the standard Boolean system linking the categories domains and determinants, was performed for the text words: mycobacterial lymphadenitis, medical and surgical treatment (Table S1). We primarily searched for both tuberculous and non-tuberculous mycobacterial lymphadenitis to avoid missing relevant papers.

Two researchers screened for relevance, and included papers for critical appraisal when medical therapy, surgical therapy and NTM lymphadenitis were mentioned. Other inclusion criteria were full text availability, English or Dutch language, and original or review papers. Papers focusing on adults, or tuberculosis and/or immunocompromised patients were excluded.

Critical appraisal

Appraisal by two researchers was performed according to criteria for studies described at http://www.cochrane.nl, i.e. study design, level of evidence and internal validity of the study. Criteria for measuring the internal validity of cohort studies were number of patients, description of characteristics of study groups, presence of selection bias, description of treatment, clear outcome definition, presence of blinded measuring of outcome, complete follow-up, presence of selective loss-to-follow-up and of confounding variables (Table 1a). For randomised controlled trials and reviews, criteria described by Offringa *et al.*[12] were used for internal validity (Table 1b,2).

Results

Fourteen articles fulfilled inclusion criteria for critical appraisal (Fig. 1). Three were not available full text (nor online, nor in paper version). Therefore, 11 articles were critical appraised.

Five papers were then excluded due to poor internal validity. These are described below and summarized also in Tables 1 and 2.

Shah *et al.* describe a small retrospective case series; three patients are treated with antibiotics before surgery.[13] This case series was excluded due to size and poor description of antibiotic dose and duration. Jervis *et al.* describe a retrospective cohort study, which was excluded on three counts: unclear allocation to a treatment arm, poor definition of patient characteristics of both groups and no clarity on antibiotic dose and children's immunocompetence.[14] Miedema *et al.* describe a small case series (three children).[15] One patient had an axillary swelling, and antibiotic dose/duration and outcome data were insufficient (Table 1). The papers of Loeffler[5] and Allbright *et al.*[1] are both reviews and were excluded due to the absence of an explicit question. Moreover, search

Table 1. Study design and internal validity (a) original papers and (b) randomised controlled trial

	Shah *et al.*[13]	Jervis *et al.*[14]	Miedema *et al.*[15]	Berger *et al.*[8]	Losurdo *et al.*[16]	Hazra *et al.*[9]	Mandell *et al.*[2]	Luong *et al.*[10]
(a)								
Study design	RC	RC	CS	PC	PC	RC	RC	RC
Level of evidence	3	3	3	3	3	2B	2B	2B
n	3	15	3	8	7	19	30	55
Definition of study groups*	n.a.	−	n.a.	+	n.a.	+	n.a.	+
Selection bias†	+	+	n.a.	+	+	+	−	+
Treatment‡	−	−	−	+	+	+	+	−
Outcome§	+	+	−	+	+	+	+	+
Blinded measuring outcome; if not, of influence¶	−	−	−	−	−	−	−	−
Follow-up**	+	+	+	+	+	+	+	+
Selective loss-to-follow-up††	−	−	−	−	−	−	−	−
Confounding‡‡	+	+	n.a.	+	−	−	−	+
Inclusion or exclusion	Excl.	Excl.	Excl.	Incl.	Incl.	Incl.	Incl.	Incl.

Table 1. (Continued)

	Lindeboom *et al.*[11]
(b)	
Study design	RCT
Level of evidence	1B
n	100
Randomisation§§	+
Randomisation concealment¶¶	+
Patients blinded***	−
Physicians blinded†††	−
Physicians who assess the effect of treatment blinded‡‡‡	−
Groups comparable§§§	+
Follow-up**	+
Selective loss-to-follow-up††	−
Intention to treat¶¶¶	+
All same treatment****	+
Inclusion or exclusion	Incl.

n.a., not applicable; PC, prospective cohort study; RC, retrospective cohort study; CS, consecutive case series; RCT, randomised controlled trial.

Level of evidence: 1B, a randomised controlled trial of good quality; 2B, a randomised controlled trial of less quality or a cohort- or patient-control study; 2C, outcome research; 3, case series or a cohort- or patient-control study of less quality; 4, opinion of expert. Number of patients (*n*).

*+, Characteristics of study groups are clearly described; −, characteristics of study groups are not clearly described.

†+, Selection bias can not sufficiently be excluded; in- and exclusion criteria of the study groups are not clearly described; −, selection bias can sufficiently be excluded; in- and exclusion criteria of the study groups are clearly described.

‡+, Treatment is clearly described and reproducible; −, treatment is not clearly described and not reproducible.

§+, Outcome and used criteria to determine outcome are clearly defined and reproducible; −, outcome and used criteria to determine outcome are not clearly defined and not reproducible.

¶+, Outcome is measured without knowing the kind of treatment the patients received or outcome is measured with knowing the kind of treatment the patients received, but is not of influence; −, outcome is measured with knowing the kind of treatment the patients received and is of influence.

**+, Follow-up is long enough; the outcome can be measured in that time of period; −, follow-up is not long enough; the outcome can not be measured in that time of period.

††+, Selective loss-to-follow-up; −, no selective loss-to-follow-up.

‡‡+, Confounding; −, no confounding.

§§+, Assignment of treatment is randomised; −, assignment of treatment is not randomised.

¶¶+, Person who includes patients, does not know the randomisation concealment; −, person who includes patients, does know the randomisation concealment.

***+, Patients did not know what treatment they received; −, patients did know what treatment they received.

†††+, Physicians did not know what treatment the patients received; −, physicians did know what treatment the patients received.

‡‡‡+, Physicians who assess the effect of treatment did not know what treatment the patients received; −, physicians who assess the effect of treatment did know what treatment the patients received.

§§§+, Groups comparable at beginning of trial; −, groups not comparable at beginning of trial.

¶¶¶+, Intention to treat; −, no intention to treat.

****+, Apart from the intervention, patients were treated the same in both groups; −, apart from the intervention, patients were not treated the same in both groups.

Incl., inclusion of article; Excl., exclusion of article.

terms, sources and selection procedure were not mentioned in both reviews (Table 2).

The six remaining papers were included and are described below and in Table 1.

Berger *et al.* prospectively studied five children with culture-proven NTM lymphadenitis with sinus formation after incomplete surgical excision and three children with suspected NTM lymphadenitis whose parents or surgeons refused surgery fearing its sequelae.[8] In the group of five patients, oral treatment with clarithromycin plus rifabutin resulted in resolution within 2 months in all cases. In the group of three patients, two were cured with antibiotic

Table 2. Study design and internal validity (reviews)

	Loeffler[5]	Albright *et al.*[1]
Study design	SR	R
Question*	−	−
Search strategy†	−	−
Selection‡	−	−
Quality assessment§	−	−
Data extraction and presentation¶	+	−
Combining results**	+	−
Diversity of results††	+	−
Results‡‡	+	+
Conclusion§§	+	+
Inclusion or exclusion¶¶	Exclusion	Exclusion

+, meets all criteria; ±, meets some criteria; −, meets none of the criteria or not described in the article, R, review; SR, systematic review.
*Explicit question.
†Mentioning used search terms and sources.
‡Selection procedure described.
§Inclusion and exclusion criteria, explicit and reproducible.
¶Univocal presentation, presentation of confidence interval from every study.
**Pooling of the results when they are clinically and statistically uniform, subgroup analyses.
††If present, described and adequately resolved.
‡‡Result relevant for clinical question.
§§Conclusion supported by results.
¶¶Inclusion or exclusion of article.

treatment alone within 2 months. One patient initially treated with antibiotics eventually underwent surgery to achieve resolution.

Losurdo *et al.* monitored seven children after administering systemic antibiotic therapy for 6 months as treatment for cervical lymphadenitis due to NTM (mean follow-up 2.5 years, range 6 months–4 years).[16] Six of these seven children had undergone partial surgery prior to antibiotic therapy. All patients achieved resolution after therapy.

Hazra *et al.* reviewed 19 cases of NTM cervicofacial lymphadenitis.[9] Nine patients underwent initial surgical excision. Of these nine patients, three were cured with resection only, four received adjuvant antibiotic therapy and two required a second surgical procedure. Ten children were initially treated with macrolide-containing antibiotic regimes. Five of these ten patients achieved resolution without surgical excision. The other five patients required subsequent surgical excision.

Mandell *et al.* retrospectively studied the primary treatment for 34 foci of NTM cervical lymphadenitis in 30 children.[2] The treatment consisted of excisional biopsy ($n = 8$), incision and drainage procedures ($n = 14$), fine-needle aspiration biopsy ($n = 7$), observation only ($n = 4$) and antimycobacterial chemotherapy ($n = 1$). With an average follow-up of 32 months, disease resolution was confirmed in 29 of the 30 patients. One patient, with a persistent fluctuant mass after incision and drainage, was lost to follow-up after 6 months.

Luong *et al.* retrospectively reviewed 55 paediatric patients with NTM cervicofacial lymphadenitis.[10] Of the 55 children, 45 (82%) were initially treated with a macrolide alone or in combination with another antibiotic agent. Of these 45, 30 (67%) children were cured with medical treatment only. Adjuvant surgical resection was needed in the remaining 15 (33%) children. Ten of the 55 children (13%) underwent initial surgical excision. In five of the ten children complete resolution was achieved. The other five children needed adjuvant antibiotic treatment.

Lindeboom *et al.* prospectively studied 100 children with microbiologically proven NTM cervicofacial lymphadenitis.[11] The children were randomly assigned to undergo surgical excision ($n = 50$) (consisting of a modified neck dissection technique with excision of skin island where skin was involved) or to receive antibiotic therapy ($n = 50$) (with clarithromycin and rifabutin for at least 12 weeks). Forty-eight of 50 children (96%) who underwent surgery were cured compared to 33 of 50 patients (66%) who received antibiotic therapy. Adjuvant medical treatment was required in two (4%) patients who initially underwent surgery. Adjuvant surgical excision was required in 15 (30%) patients who initially received medical treatment. Two (4%) children had to cease antibiotic therapy as a result of severe adverse effects.

Discussion

Literature

Critical appraisal of the literature up to November 2007 resulted in six papers of sufficient quality addressing the treatment of non-tuberculous cervicofacial lymphadenitis. Different levels of evidence were encountered. One of the studies was a well designed randomised clinical trial (RCT) (Level IB).[11] Three were retrospective cohort studies (Level 2B).[2,9,10] Two studies were prospective in nature but were conducted in small populations (Level 3).[8,16]

Management

In most studies, combined modality treatment was applied. Overall, the cure rate of children with non-tuberculous cervicofacial lymphadenitis was high. There was no general agreement upon allocation to either

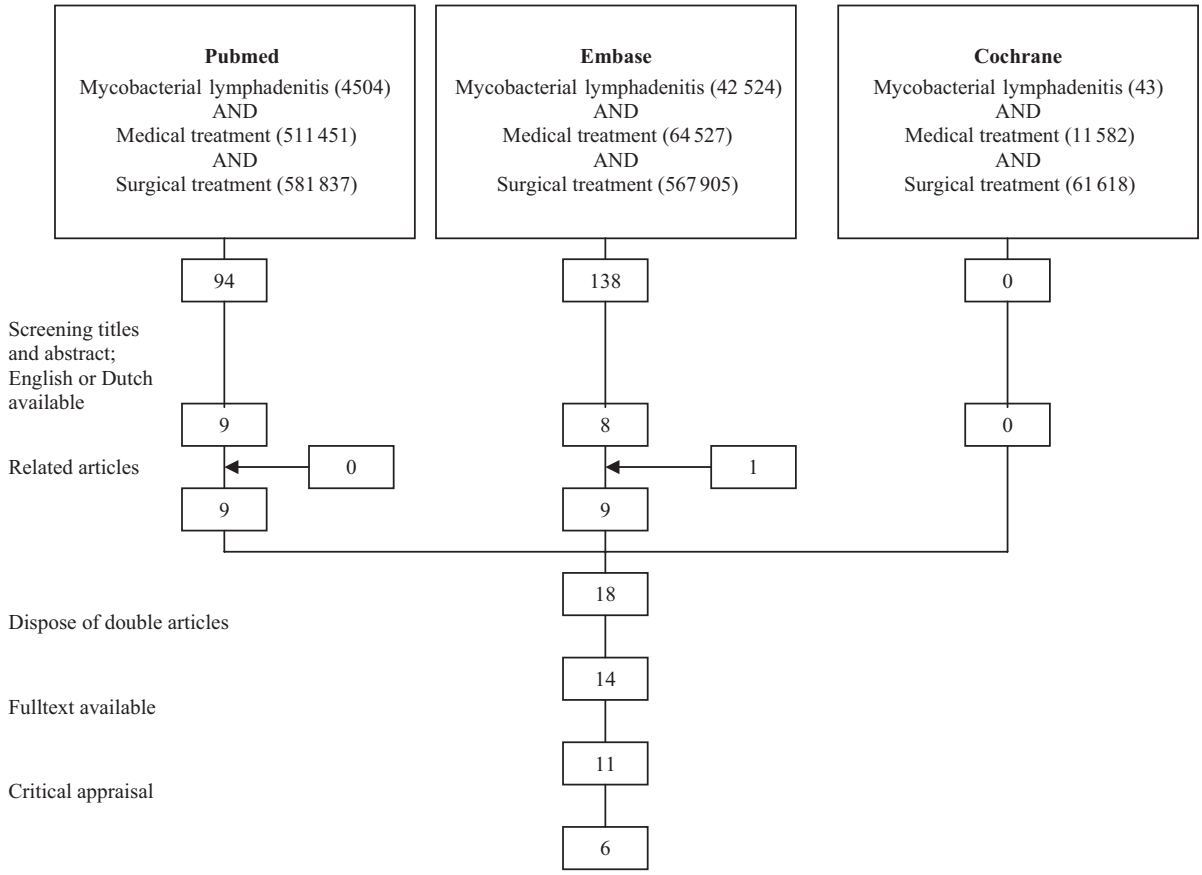

Fig. 1. Flowchart search strategy.

surgical or antibiotic treatment, or both. Furthermore, surgical procedures varied from incision and drainage procedures to partial resection and selective neck dissection and/or parotidectomy. In medical management, differences existed regarding (the combination of) agents, dose and duration. Most often antibiotic regimens contained a macrolide (azithromycin or clarithromycin) and an antituberculous drug (rifabutine or ethambutol).

Outcome

The RCT by Lindeboom *et al.* clearly showed that surgery (96% success rate) was superior to antibiotic treatment (66% success rate) as a single modality (Level IB).[11] Moreover, the results of surgery in this paper compared favourably to other studies.[9,10] This may be the result of designated surgeon applying uniform head and neck surgical procedures. In this large study, the mean surgical duration was 88.8 (±38.5) min and hospital stay 1.9 (±0.6) days. Obvious disadvantages of surgery are general anaesthesia, scar formation and possible complications such as wound infections and damage to the facial nerve branches at certain sites (parotid and submandibular region). These complications, although occurring infrequently can have serious consequences, especially in children.

The two papers with the largest study population also revealed that a considerable proportion (66–67%) of patients were cured with antibiotic treatment alone (Level IB, 2B).[10,11] Also in most studies adjuvant antibiotic treatment was required after surgery for some patients (Level 2B, 3).[8–10,16] Apparently there is a role for antibiotic treatment for a subgroup of patients. None of the studies, however, succeeded to identify patient characteristics predicting the response to antibiotic treatment. Possible factors such as age, size and site of the lesion, time elapsed since onset of the disease, type of mycobacterium and drug resistance did not differ between the patients in both surgical and medical treatment arms in the study by Lindeboom *et al.*[11] To date, studies analysing the predictive value of the abovementioned factors within the responding group, are lacking.

Recommendations

Until the role of antibiotic treatment for a subgroup of patients is further clarified, head and neck surgical

procedures offer the best chance of cure for children with NTM cervicofacial lymphadenitis. What with adverse effects from antibiotic therapy seen in up to 74% of patients, surgery gives superior outcomes. A trial of multi-agent antibiotic therapy could be considered if the infection is located at sites with a high risk of facial nerve damage or cosmetically disturbing scar formation, or if there is considerable resistance to surgical management.

Keypoints

- Surgical excision has historically been the treatment of choice for non-tuberculous mycobacterial cervicofacial lymphadenitis in children. Emerging data suggest antibiotic treatment alone could be effective. Advantages of medical treatment are that general anesthesia, surgical sequelae and/or complications can be avoided.
- A literature search according to the evidence based medicine guidelines addressing the treatment of this condition resulted in six papers which were critically appraised: 1 RCT (level IB), three retrospective cohort studies (level 2B) and two small prospective studies (level 3).
- A high overall cure rate was achieved with combined modality treatment. Allocation to surgical or antibiotic treatment or both was not consistent. Surgical procedures and medical treatment protocols (agents, dose and duration) differed within and between studies.
- In the RCT surgery and antibiotic treatment were compared as single modalities. The outcome of surgery was far superior (96% *versus* 66% cure rate, respectively).
- Other studies showed that a considerable proportion of patients (up to 67%) were cured with antibiotic treatment alone. Possible factors predicting response to medical treatment such as age, size and site of the lesion, time elapsed since onset of the disease, type of mycobacterium and drug resistance could not be identified.
- With the present evidence, surgical excision is the treatment of choice in the management of cervicofacial non-tuberculous mycobacterial lymphadenitis. If the infection is located at sites with a high risk of facial nerve damage or cosmetically disturbing scar formation, or if there is considerable resistance to surgical management, medical treatment could be considered.

References

1 Albright J.T. & Pransky S.M. (2003) Nontuberculous mycobacterial infections of the head and neck. *Pediatr. Clin. North Am.* **50,** 503–514

2 Mandell D.L., Wald E.R., Michaels M.G. *et al.* (2003) Management of nontuberculous mycobacterial cervical lymphadenitis. *Arch. Otolaryngol. Head Neck Surg.* **129,** 341–344

3 O'Brien D.P., Currie B.J.. & Krause V.L. (2000) Nontuberculous mycobacterial disease in northern Australia: a case series and review of the literature. *Clin. Infect. Dis.* **31,** 958–967

4 Haverkamp M.H., Arend S.M., Lindeboom J.A. *et al.* (2004) Nontuberculous mycobacterial infection in children: a 2-year prospective surveillance study in the Netherlands. *Clin. Infect. Dis.* **39,** 450–456

5 Loeffler A.M. (2004) Treatment options for nontuberculous mycobacterial adenitis in children. *Pediatr. Infect. Dis. J.* **23,** 957–958

6 Ottenhoff T.H., Verreck F.A., Lichtenauer-Kaligis E.G. *et al.* (2002) Genetics, cytokines and human infectious disease: lessons from weakly pathogenic mycobacteria and salmonellae. *Nat. Genet.* **32,** 97–105

7 Wolinsky E. (1979) Nontuberculous mycobacteria and associated diseases. *Am. Rev. Respir. Dis.* **119,** 107–159

8 Berger C., Pfyffer G.E.. & Nadal D. (1996) Treatment of nontuberculous mycobacterial lymphadenitis with clarithromycin plus rifabutin. *J. Pediatr.* **128,** 383–386

9 Hazra R., Robson C.D., Perez-Atayde A.R. *et al.* (1999) Lymphadenitis due to nontuberculous mycobacteria in children: presentation and response to therapy. *Clin. Infect. Dis.* **28,** 123–129

10 Luong A., McClay J.E., Jafri H.S. *et al.* (2005) Antibiotic therapy for nontuberculous mycobacterial cervicofacial lymphadenitis. *Laryngoscope* **115,** 1746–1751

11 Lindeboom J.A., Kuijper E.J., Bruijnesteijn van Coppenraet E.S. *et al.* (2007) Surgical excision versus antibiotic treatment for nontuberculous mycobacterial cervicofacial lymphadenitis in children: a multicenter, randomized, controlled trial. *Clin. Infect. Dis.* **44,** 1057–1064

12 Offringa M., Assendelft W.J.J.. & Scholten R.J.P.M.. (2003) Inleiding in evidence-based medicine. Klinisch handelen gebaseerd op bewijsmateriaal. Bohn Stafleu Van Loghum, Houten, The Netherlands

13 Shah M.B.. & Haddad J. Jr (2004) Nontuberculous mycobacteria-induced parotid lymphadenitis successfully limited with clarithromycin and rifabutin. *Laryngoscope* **114,** 1435–1437

14 Jervis P.N., Lee J.A.. & Bull P.D. (2001) Management of nontuberculous mycobacterial peri-sialadenitis in children: the Sheffield otolaryngology experience. *Clin. Otolaryngol. Allied Sci.* **26,** 243–248

15 Miedema C.J., Geelen S.P.M., De Langen Z.J. *et al.* (1999) Lymphadenitis door niet-tuberculeuze mycobacteriën, chirurgische of antibiotische behandeling? *Tijdschr Kindergeneeskd.* **67,** 140–143

16 Losurdo G., Castagnola E., Cristina E. *et al.* (1998) Cervical lymphadenitis caused by nontuberculous mycobacteria in immunocompetent children: clinical and therapeutic experience. *Head Neck* **20,** 245–249

Supporting information

Additional supporting information may be found in the online version of this article.

Table S1. Search terms in Embase, Pubmed and Cochrane.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

