Multimodality Treatment of Pediatric Lymphatic Malformations of the Head and Neck Using Surgery and Sclerotherapy

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Objectives: To describe a multimodality approach to the management of pediatric head and neck lymphatic malformations using surgery, sclerotherapy, or both and to review the outcomes of these approaches.

Design: Retrospective case series.

Setting: A single pediatric tertiary care referral center.

Patients: Ninety-seven pediatric patients (aged 1 month to 16 years) diagnosed as having lymphatic malformations of the head and neck during a 7-year period. Follow-up ranged from 3 months to 7 years.

Interventions: All of the patients underwent clinical and radiologic (magnetic resonance imaging) assessment. Treatment modality was selected according to disease location, cyst size, and parental preference. Treatments included surgery (open excision, tongue reduction, electrocautery, and laser treatment), sclerotherapy with OK-432 (Picibanil) or a fibrosing agent (Ethibloc), and a combination of modalities.

Main Outcome Measures: Clinically determined responses to treatment, complications, and number of treatments required.

Results: All isolated neck disease had complete or near-complete responses, with no nerve palsies sustained. Although most patients achieved complete or near-complete responses, disease with parotid, laryngopharyngeal, or oral components had poorer outcomes and frequently required multiple treatments. Significant long-term neural injury was sustained in 3 of 6 surgical patients for mediastinal disease and in only 4% (n=4) of other surgical procedures.

Conclusions: Surgery retains an important role in the treatment of pediatric head and neck lymphatic malformations despite the advent of sclerotherapy. Isolated neck disease has an excellent outcome with either modality. Treatment decisions were made via a problem-based approach and were individualized according to anatomical location and disease classification.


Lymphatic malformations have traditionally been treated by surgical excision. Sclerotherapy is not a new treatment, but OK-432 (Picibanil, Chugai Pharmaceuticals; Tokyo, Japan) has become increasingly used during the past decade. Both treatments have their merits, and we report a multimodality approach to lymphatic malformations of the head and neck in children using both treatments selectively based on clinical features, anatomical location, and cyst size.

Lymphatic malformations are benign congenital abnormalities of the lymphatic system composed of varying-sized lymphatic spaces and channels. More than half of all lesions are found in the head and neck. Lymphatic malformations have been categorized according to histologic appearance, cyst size, anatomical position relative to the hyoid, and unilateral or bilateral extent. Although the exact pathogenesis remains uncertain, they are thought to arise from disordered embryologic development of the lymphatic system. Abnormal or absent communications between central venous sacs and the peripheral lymphatic system give rise to lymphatic accumulation and cyst formation.

Lymphatic malformations are seen at birth in 50% of patients and usually manifest as an asymptomatic mass. Ninety percent of lymphatic malformations are diagnosed before age 2 years. They have a variable clinical course, and cysts may fluctuate in size, particularly after trauma or inflammation, with mass-related effects on surrounding structures (including those in the mediastinum, where tracheal obstruction may pose life-threatening...
reduction can be performed,\textsuperscript{16} and microcystic mucosal disease may be ablated via topical laser, electrocautery, or coblation therapy.\textsuperscript{17} Sclerosants, including bleomycin, a fibrosing agent (Ethibloc; Ethicon GmbH, Norderstedt, Germany) (composed of the corn protein zein in alcohol solution), and pure ethanol, have undergone clinical trials; however, these agents may cause significant localized reactions and cicatricial contraction with fistula formation, scarring, and potential for damage to adjacent structures. Subsequent surgery is also made technically difficult.\textsuperscript{18} Attention has thus turned to OK-432 (Picibanil), a sclerosant developed in Japan from a low-virulence strain of group A \textit{Streptococcus pyogenes} and first used in children in 1987.\textsuperscript{18,19} Cyst aspiration followed by OK-432 injection gives rise to an intracystic acute inflammatory event with cytotoxic effects, subsequent fibrosis,\textsuperscript{20} and resolution. Successful results have been published in several series for macrocystic disease.\textsuperscript{6,21,22} Sclerotherapy outcomes for children with microcystic disease are unfavorable because each cyst must be individually injected to exert an effect.

Lymphatic malformation is an uncommon condition, reported as accounting for only 5\% of all benign pediatric lesions.\textsuperscript{23} Most pediatric surgical departments see only occasional cases, with most previous articles reporting results of relatively small case series. This is a large case series with the ongoing involvement of a single surgeon (B.E.J.H.) in the management of all cases. We report our experience in the treatment of lymphatic malformations of the head and neck in pediatric patients at a pediatric tertiary referral center during a 7.5-year period (January 1, 2001, to June 30, 2008). The principles guiding treatment decisions at Great Ormond Street Hospital for Children (GOSH), London, England, are discussed. The importance of availability of multimodality therapy using surgery, sclerotherapy, or a combination of both in the child’s treatment is emphasized to achieve favorable outcomes for these patients.

A database of all pediatric patients with a head and neck lymphatic malformation seen in the Department of Paediatric Otolaryngology at GOSH between January 1, 2001, and June 30, 2008, was retrospectively reviewed. All cases were managed by the senior author (B.E.J.H.), with involvement by other members of a multidisciplinary team as indicated. The diagnosis was made via a combination of initial clinical examination, appearance on magnetic resonance imaging, and histologic confirmation in patients undergoing surgery. Patients with other forms of vascular malformation were excluded. Patient demographics, disease characteristics, treatments, and outcomes were examined. Details of sex, date of birth, treatment undertaken before presentation at GOSH, age at first treatment at GOSH, tracheostomy requirement, anatomical sites involved, and length of follow-up were recorded. Collected data were supplemented by review of the patients’ medical records. All children underwent magnetic resonance imaging to determine disease type and extent (Figure 1). Lymphatic malformations were then classified according to cyst appearance. Microcystic disease involved cysts 1 cm\textsuperscript{3} in diameter or larger; macrocystic disease, cysts less than 1 cm\textsuperscript{3} in diameter; and mixed disease, a range of cyst sizes.

Patients underwent surgery, sclerotherapy, a combination of treatment modalities, or observation. Patients were allocated to treatment modality according to anatomical location of their malformation. Cyst size was also considered because it is generally accepted that microcystic component disease responds poorly to sclerotherapy. Isolated macrocystic neck disease was treated with either surgery or sclerotherapy. Treatment decisions for these children were made taking parental preference into consideration, after a full discussion of both modalities (Table 1). Isolated microcystic disease was surgically resected. Mediastinal disease was treated via surgery if there was airway compromise present or if there was a risk of compromise developing. Mediastinal lesions were observed if the airway was not at risk. Laryngopharyngeal component disease...
was usually treated surgically via either open excision or potassium-titanyl-phosphate laser, particularly in patients without tracheostomy cover. Patients with oral involvement had their symptoms defined, and treatment was selected accordingly. Tongue protrusion was addressed via tongue reduction surgery, surface lesions using carbon dioxide laser or electrocautery, and floor of mouth cysts by surgery or sclerotherapy. Parotid disease was treated conservatively if possible, with active treatment reserved for severe or progressive symptoms. Superficial lobe disease was treated with either surgery or sclerotherapy if macrocystic or with superficial parotidectomy if microcystic. Deep lobe disease was considered for subtotal parotidectomy if symptomatic.

Surgical treatment included open excision with or without cardiothoracic involvement, with complete disease resection performed wherever possible. Incomplete resection was performed if complete excision had a high likelihood of neurologic injury or functional impairment. Tongue reduction, electrocautery, and laser (carbon dioxide and potassium-titanyl-phosphate) treatments were used as described.

Sclerotherapy injection was performed using general anesthesia with ultrasonographic guidance to accurately localize the cysts. Lyophilized OK-432 was prepared by dilution to 0.1 mg per 10 mL of 0.9% saline solution. The cysts were aspirated via a 22/23-gauge needle introduced under ultrasonographic guidance in sterile conditions. OK-432 was then injected into each cyst, with a maximum dose of 0.2 mg per session. Further injections were performed at 6 to 12 weekly intervals if clinically indicated, with a maximum of 4 doses per treatment. A fibrosing agent was used via the same technique, although patients received only a single dose of 1.0 to 1.5 mL.

The outcomes of each treatment modality were examined by reviewing responses to treatment, complications, and number of treatments required. Responses to treatment were clinically determined at follow-up reviews in the outpatient clinic. These were classified as complete (complete resolution with no abnormality evident), near complete (marked improvement with near-complete resolution of the pathologic abnormality), partial (some improvement but significant ongoing abnormality), and minimal (no or minimal change in the initial pathologic condition).

## RESULTS

The review identified 101 patients (47 girls and 54 boys) with lymphatic malformations of the head and neck treated at GOSH in a 7-year period. Four patients were excluded from further analysis: histologic examination after resection confirmed that 3 had another underlying pathologic abnormality (1 thymic cyst, 1 teratoma, and 1 cavernous hemangioma), and the remaining patient did not return for recommended treatment and was lost to follow-up. Patients who underwent active treatment were aged 1 month to 16 years at their first treatment (mean age, 44 months). Eighteen children received treatment before age 12 months. Eight patients were awaiting planned further treatment. Follow-up ranged from 3 months to 7 years (mean, 34 months), and only 4 patients in this series had 3 to 6 months of follow-up since their last treatment. Twenty-three patients had undergone previous treatment of their lymphatic malformations before their referral to GOSH. Macrocystic disease occurred most commonly (61 patients [63%]); only 10 patients (10%) had microcystic, and 26 (27%) demonstrated mixed disease. The proportions of macrocystic, microcystic, and mixed disease found in each anatomical location are shown in Figure 2.

Almost half the patients (43 of 97) underwent surgical treatments only, and most of these (32 patients) required just a single procedure. Sclerotherapy was used as the only modality in 21 patients, with all but 1 patient requiring a single procedure. Combination therapy (surgery and sclerotherapy) was undertaken in 16 patients. The overall number of procedures performed for each modality was also recorded (Table 2). Seventeen patients with mild symptoms underwent a period of observation due to other medical circumstances or parental preference. Thirteen patients had spontaneous complete or near-complete resolution of their disease, all with macrocystic disease.

The neck was the most commonly involved location (84 cases). Most of these children had unilateral disease (67 cases), leaving 17 patients with bilateral neck involvement. Disease commonly extended into adjacent sites (64% of those with neck disease [54 patients]). Thirty patients (36%) had isolated neck involvement, which was predominantly macrocystic disease (28 of 30 patients). The most common treatment approach for isolated neck disease was surgical excision (15 patients); 6 patients received sclerotherapy alone, and just 2 patients required combined treatment with sclerotherapy and surgery. Seven patients were observed. Only 2 patients had a microcystic component to their disease, and both underwent sur-

### Table 1. Advantages and Disadvantages of Surgery and Sclerotherapy for Consideration in Treatment Choice

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery Complete permanent excision possible</td>
<td>Surgery Scar</td>
</tr>
<tr>
<td>Short treatment duration</td>
<td>Potential for nerve injury site dependent</td>
</tr>
<tr>
<td>Histopathologic diagnosis</td>
<td>Possible complications</td>
</tr>
<tr>
<td>Sclerotherapy</td>
<td>Marked increase in size after therapy</td>
</tr>
<tr>
<td>Usually avoids scar</td>
<td>Slow reduction in size across 3 mo</td>
</tr>
<tr>
<td>Less invasive</td>
<td>Recurrence possible</td>
</tr>
<tr>
<td>Avoids risk of nerve injury</td>
<td>No histopathologic diagnosis</td>
</tr>
<tr>
<td>Shorter hospital admission</td>
<td>Long-term toxic effects remain unknown</td>
</tr>
</tbody>
</table>

![Figure 2](https://example.com/fig2.png)
gery. Isolated neck disease fared well with either sclero-
therapy or surgery, with every child achieving either com-
plete (22 patients) or near-complete (8 patients) re-
sponses. In the surgical group, there were no major com-
plications, and just 3 of 16 patients (19%) developed a mi-
nor complication (1 hematoma, 1 seroma, and 1 temporary
marginal mandibular nerve weakness). Isolated neck dis-
ease rarely required more than 1 treatment (2 of 29 pa-
tients [7%]) compared with disease extending from the
neck into adjacent anatomical structures, which required
multiple treatments in 33% of cases (18 of 54 patients).

Twelve patients had mediastinal involvement, and half of
these involved the neck and mediastinum only. Surgi-
cal excision and observation were common treatment
choices for this group of children. Six patients required
surgical resection to address the thoracic component, 2
others had surgery to address the neck disease but did not
require excision of the mediastinal component, 3 re-
cieved sclerotherapy for neck disease, and 1 had sponta-
naneous resolution while awaiting surgery. Most patients
(92%) with mediastinal malformations achieved com-
plete or near-complete responses. Four of 6 patients who
underwent thoracic procedures, however, developed com-
plications, and 3 of these involved ongoing neural injury
(Table 3).

Twenty-eight patients had a component of parotid dis-
ease. Seventeen patients (61%) had extensive disease, with
pathologic abnormalities extending beyond the parotid
and neck to multiple sites. Many of these patients (16 of
28 [57%]) had a microcystic component of disease, with
4 microcystic and 12 mixed cases. Eight patients had sur-
gery, 7 received sclerotherapy, and 8 required com-
bined treatment. Five patients with macrocystic disease
were observed.

Twenty-seven patients had oral disease involving the
anterior tongue, the floor of the mouth, or the oral mu-
cosa, and 23 of them (85%) had extensive disease in-
volving multiple sites beyond the neck. Seventy percent
of oral disease had a microcystic component, with mac-
rocystic malformations being predominantly found in the
floor of the mouth. Thirteen patients underwent sur-

Table 2. Procedures Performed for Each Treatment Modality and Associated Complications

<table>
<thead>
<tr>
<th>Modality and Procedure</th>
<th>Patients, No. (%)</th>
<th>Procedures Performed</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sclerotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OK-432 (Picibanil; Chugai Pharmaceuticals, Tokyo, Japan)</td>
<td>37</td>
<td>4 (11)</td>
<td></td>
</tr>
<tr>
<td>Ethibloc (Ethicon GmbH, Norderstedt, Germany)</td>
<td>4</td>
<td>4 (100)</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open surgical excision</td>
<td>54</td>
<td>21 (39)</td>
<td></td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>6</td>
<td>4 (67)</td>
<td></td>
</tr>
<tr>
<td>Tongue reduction</td>
<td>5</td>
<td>1 (20)</td>
<td></td>
</tr>
<tr>
<td>Laser or electrocautery</td>
<td>20</td>
<td>3 (15)</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>

a Excludes cases involving cardiothoracic surgery.

Table 3. Complications Categorized According to Severity and Type of Surgery Performed

<table>
<thead>
<tr>
<th>Surgical Procedure and Complication</th>
<th>Patients, No.</th>
<th>Head and Neck</th>
<th>Thoracic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor/temporary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroma</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hematoma</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intraoral swelling</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abscess</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Horner syndrome</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Marginal mandibular nerve weakness, temporary</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vocal cord palsy, temporary</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Major/ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marginal mandibular nerve weakness, ongoing</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vocal cord palsy, ongoing</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>XI nerve palsy, ongoing</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Phrenic nerve division</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Chest infection/respiratory arrest</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

a Some patients developed several complications during a single procedure.

b Intraoral swelling that required prolonged hospital admission or that resulted in significant functional effects, for example, aspiration and speech problems.

c Pain and swelling of substantially greater magnitude than that typically seen after sclerotherapy.
Airway obstruction occurred relatively uncommonly in this series of patients. Fifteen percent of all children reviewed (15 patients) required a tracheostomy tube, and all were placed to address airway compromise. Nine of these patients had been successfully decannulated after treatment. Two patients were undergoing downsizing or gradual decannulation protocols, and 4 had persisting disease and were undergoing review for further surgery.

Complications were predominantly minor and temporary in surgical procedures without a thoracic component, with only 3 ongoing neural injuries (2 marginal mandibular nerve weakness and 1 XI nerve palsy) in 79 patients (4%). Minor complications occurred in 19 of these 79 patients (24%) (Table 3). Eight of the 41 sclerotherapy procedures (20%) had complications. Of these, none of the OK-432 cases developed serious problems, with 4 developing temporary pain and swelling greater than that routinely expected. All 4 patients treated with a fibrosing agent developed significant local sequelae. Patients with macrocystic disease developed complications much less commonly (13% of patients) than did children with microcystic (50%) or mixed (67%) disease.

There is wide variation in the extent and nature of head and neck lymphatic malformations, and treatment decisions should be individualized based on clinical features and radiologic appearance. Complete surgical resection was usually possible for macrocystic disease. Microcystic disease was diffuse and infiltrative, with loss of tissue planes, making surgery technically demanding. Surgery remains the best treatment option for these cases, however, because the underlying microcystic pathologic disorder is not conducive to sclerotherapy. Multiple treatments were frequently required to achieve favorable outcomes in microcystic component disease, particularly in the oral cavity.

Complete surgical excision gives optimal outcomes with a reduced potential for recurrence and subsequent histologic confirmation of the diagnosis, but it is possible in only 18% to 50% of patients.21,25,26 We concur with the general consensus that complete resection of this benign disease should not be performed at the cost of incurring significant complications, such as cranial nerve injury, with potentially lifelong sequela. In this series, partial removal with associated “reshaping” gave good cosmetic outcomes. Remaining cysts were opened to facilitate fibrosis and scarring, and although there was a potential for progression,7 this has not been our experience to date. Ongoing neural damage occurred in 7% of surgical procedures in this series (predominantly thoracic procedures), which compares favorably to previously reported rates of up to 33%.24

Disease location had a major influence on prognosis, with isolated neck disease having the highest likelihood of complete resolution regardless of treatment modality. Outcomes were not so favorable for children with parotid, laryngopharyngeal, or oral disease. Disease in these locations was frequently extensive and often demonstrated microcystic component malformations (Figure 2). Multiple treatments were required in approximately a third of the patients undergoing active treatment, regardless of initial treatment modality. Combination therapy was used where appropriate to achieve favorable outcomes in patients who required further treatment after an initial procedure. Photographs of 2 patients are included to demonstrate their clinical appearance before and at the completion of treatment (Figure 4 and Figure 5).

These data show that isolated macrocystic neck disease occurred commonly and did well with either sur-
gery or sclerotherapy. Parotid disease was typically extensive, with 57% having a microcystic component. Complete resection gives the best outcomes but has an inherent risk of facial nerve injury, particularly if there has been previous sclerotherapy. Further surgical procedures are technically difficult due to scarring adjacent to the facial nerve, so residual disease is best treated with sclerotherapy if possible. Oral involvement posed a management challenge and responded poorly to sclerotherapy; thus, it was usually treated surgically. However, complete excision is not possible functionally, so multiple procedures were often required. The mediastinal component of disease was treated via surgery, often in the first 12 months of life if compromised. This treatment has significant risk of complication, and the pros and cons of such surgery must be carefully considered in each child. Patients with laryngopharyngeal disease had extensive pathologic disease, with most undergoing surgical treatment. Sclerotherapy is not offered for lesions where reactive enlargement of the cysts after sclerosant would give rise to airway obstruction. Because the microcystic component of disease made up a large proportion of this group, it was not surprising that multiple treatments were often necessary.

Previous ultrasonographic-guided intracystic sclerotherapy performed at GOSH did not make subsequent surgery more challenging, as has been previously reported. In contrast, blind extracystic injection of cysts is likely to affect subsequent surgery. It is, therefore, important to have sclerotherapy performed by a physician experienced in these techniques. Complications from OK-432 were infrequent, mild, and temporary. A fibrosing agent was used for a short period (6 months) 5 years ago, when GOSH encountered difficulties obtaining OK-432. It produced significant local sequelae, with chronic inflammation and often scarring, and is no longer used at GOSH.

Active treatment can be postponed provided that the child is stable. Spontaneous regression has been previously reported and occurred in 13% of this series. It is thought to occur after infection or localized hemorrhage gives fibrosis and scarring. Although spontaneous resolution occurs more frequently in macrocystic lesions with fewer than 5 septae, this improvement is often unpredictable, with an ongoing potential for recurrence. Most parents, after an informed discussion, prefer definitive treatment to prolonged observation.

The complex nature of this disease requires treatment selection to be tailored to the individual patient according to the disease characteristics and the functional consequences. Supportive interventions, including tracheostomy, nasogastric or gastrostomy placement, and multidisciplinary input, are essential components of the overall management plan. Long periods of dependency on extraoral feeding due to aspiration often result in a very slow period of rehabilitation before oral feeding can be safely recommenced. We reintroduce oral feeding as soon as it is safely possible, particularly in younger children. The speech and language team may be consulted to assess swallowing and articulation issues. Others involved in patient care may include the cardiothoracic surgeon, plastic surgeon, maxillofacial surgeon, dentist, and clinical psychologist.

In conclusion, lymphatic malformations of the head and neck manifest with a range of clinical features. Each child requires individual assessment, and a problem-based approach to management should be adopted to achieve optimal outcomes. There is an important role for surgery and sclerotherapy in treating these lesions. Multimodality therapy should be available because neither surgery nor sclerotherapy in isolation can provide opti-
mal treatment for every lymphatic malformation. A proportion of these children will require multiple treatments to appropriately address the underlying disease process and its cosmetic and functional effects. Isolated neck masses are the most common lesions and have the best prognosis with either surgery or sclerotherapy. Both treatment options should be offered and discussed to facilitate an informed treatment decision. Laryngopharyngeal and tongue lesions are frequently microcystic, and surgical treatment is preferred. Children with extensive malformations require multiple interventions across a prolonged period. Mediastinal malformations have the highest rate of surgical complications, and surgery is restricted to those with airway compromise or risk of airway compromise. Parotid and facial swellings are treated with surgery or sclerotherapy depending on the potential risk to facial nerves. Spontaneous improvement was documented in some children in this series, and patients may be observed provided that there is no significant associated compromise.

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Author Contributions: Drs Boardman, Cochrane, Roeback, and Hartley had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Boardman, Cochrane, Roeback, and Hartley. Acquisition of data: Boardman, Cochrane, Roeback, Elliott, and Hartley. Analysis and interpretation of data: Boardman, Cochrane, Roeback, and Hartley. Drafting of the manuscript: Boardman, Roeback, Elliott, and Hartley. Critical revision of the manuscript for important intellectual content: Boardman, Cochrane, Roeback, and Hartley. Statistical analysis: Boardman. Administrative, technical, and material support: Cochrane and Hartley. Study supervision: Cochrane, Elliott, and Hartley.

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