How do you increase efficiency in head and neck procedures?

Precisely.

If you already use HARMONIC™ devices for thyroidectomies, then you’re familiar with the efficiency and precision ultrasonic technology offers. But HARMONIC™ technology advantages apply to other head and neck procedures.

The same qualities that allow HARMONIC™ technology to shorten thyroidectomy times by 30 minutes* without compromising safety can yield important advantages in other head and neck procedures:

• In parotidectomies, reduce intraoperative blood loss and duration of drainage.*

• In parathyroidectomies, improve efficiency while minimizing thermal tissue injury.

• In all procedures, reduce instrument exchanges by enabling you to dissect, cut and coagulate with the same device.

*Save 30 minutes in thyroidectomies vs. clamp, cut and tie. Data on file at Ethicon Endo-Surgery.


For further information please email

ukfocus@its.jnj.com

ENT MASTERCLASS® COURSES

CALENDER 2012-13

• 8TH ANNUAL NATIONAL ENT MASTERCLASS®
  27th-29th Jan 2012  Venue: Royal College of Surgeons, London

• 1ST NATIONAL ADVANCED ENT EMERGENCIES’ MASTERCLASS®
  22nd June 2012  Venue: Doncaster Royal Infirmary, England

• 5TH NATIONAL THYROID AND SALIVARY GLAND MASTERCLASS®
  23rd June 2012  Venue: Doncaster Royal Infirmary, England

• 3RD NATIONAL ENT RADIOLOGY MASTERCLASS®
  24th June 2012  Venue: Doncaster Royal Infirmary, England

• 5TH NATIONAL TRACHEOSTOMY MASTERCLASS®
  29th Sep 2012  Venue: Doncaster Royal Infirmary, England

• 6TH NATIONAL ENT NURSING MASTERCLASS®
  30th Sep 2012  Venue: Doncaster Royal Infirmary, England

• 9TH ANNUAL NATIONAL ENT MASTERCLASS®
  25th-27th Jan 2013  Venue: Doncaster Royal Infirmary, England

FOR COURSE DETAILS, REGISTRATION FORMS AND AUTHOR GUIDELINES VISIT

WWW.ENTMASTERCLASS.COM
JOURNAL OF ENT MASTERCLASS®
Volume 4 Issue 1 December 2011

Contents

Chairman’s Comment and Editorial Board: 3

A Review of Tinnitus Treatments (Part 2) 4
Claudia Nogueira, T Meehan, Neil Fergie,

Ototoxicity: Evaluation and Management 11
Natalie Watson, David Selvadurai

Principles of Mastoid Surgery 16
Dhar V, Bowdler, Aymat A

Non-Neoplastic Lesions of the Temporal Bone 20

Otitis Media with Effusion 27
Mathew Rollin, Antony A Narula

Management of Children with Permanent Childhood Hearing Impairment (PCHI) 33
Adrian Davis OBE, Gwen Carr and Margaret Martin

Evaluation and Management of Benign Paroxysmal Positional Vertigo 38
Charlotte Agrup, Linda Luxon

Allergic Fungal Sinusitis 45
David A. Gudis, Robert T. Adelson, James N. Palmer

Paediatric Rhinosinusitis- Management and Indications for Surgery 52
Lisha McClelland, Nick Jones,

Frontal Sinus Mucocoeles 56
L. McClelland, A. Rokade, A. Sama

The Reliability of Patient Outcome Scores in Rhinology 61
Claire Hopkins

Common Genetic Syndromes in Otolaryngology 66
Mr V.Visvanathan, H Kabba

Assessment and Management of Congenital Atresia of the Ear 72
Christopher Loh, Ray Clarke

Paediatric Obstructive Sleep Apnoea 76
Premjit S Randhawa, Antony A Narula

Surgical Management of Primary Hyperparathyroidism 82
Chee Yean Eng, M.Shahed Quraishi

Management of Cervical Chyle Leaks 90
<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder Dysfunction after Neck Dissection</td>
<td>95</td>
</tr>
<tr>
<td>Nilesh Vasan, Jesus E. Medina</td>
<td></td>
</tr>
<tr>
<td>Evidence based Management of Glottic Laryngeal Dysplasia</td>
<td>99</td>
</tr>
<tr>
<td>Paul Nankivell, Hisham Mehanna</td>
<td></td>
</tr>
<tr>
<td>The Current Role of Chemotherapy/ Biotherapy in the Primary</td>
<td>104</td>
</tr>
<tr>
<td>Management of Advanced Squamous Cell Carcinoma of the Head and Neck</td>
<td></td>
</tr>
<tr>
<td>Pol Specenier, Jan B Vermorken</td>
<td></td>
</tr>
<tr>
<td>Globus – a Diagnosis still Shrouded in Mystery in 2011</td>
<td>111</td>
</tr>
<tr>
<td>Paul M. Weinberger, Gregory N. Postma</td>
<td></td>
</tr>
<tr>
<td>Exercise Induced Laryngeal Obstruction (EILO): Diagnosis and Management</td>
<td>117</td>
</tr>
<tr>
<td>John-Helge Heimdal, Thomas Halvorsen, Robert Christiaan Maat,</td>
<td></td>
</tr>
<tr>
<td>Ola D. Roksund MSc. and Jan Olofsson</td>
<td></td>
</tr>
<tr>
<td>ENT Manifestations of HIV in Clinical Practice</td>
<td>123</td>
</tr>
<tr>
<td>Oskar Edkins, Tashneem Harris, Johannes J. Fagan</td>
<td></td>
</tr>
<tr>
<td>Management of Metastatic Cutaneous Squamous Cell Carcinoma of the Head Neck; State of the Art Review</td>
<td>128</td>
</tr>
<tr>
<td>Faruque Riffat, Michael J. Veness, Carsten E Palme</td>
<td></td>
</tr>
<tr>
<td>Presentation, Diagnosis and Treatment Options for TMJ Dysfunction</td>
<td>133</td>
</tr>
<tr>
<td>Andrew Sidebottom</td>
<td></td>
</tr>
</tbody>
</table>

Disclaimer: The individual authors have responsibility for the integrity of the content of the manuscripts.
Welcome to Volume 4 Issue 1 of Journal of ENT Masterclass 2011

The ENT Masterclass has continued to thrive during the calendar year 2011 and is providing a wide spectrum of postgraduate activities for surgical residents, nurses and others related to the practice of Oto-Rhino-Laryngology, Head and Neck Surgery (ORL-HNS) in the United Kingdom and abroad.

During the year, activity included the 7th Annual National ENT, 4th Tracheostomy, 4th Thyroid and Salivary gland, 2nd Radiology and the 5th National ENT Nursing Masterclass. The delegate feedback has been very encouraging and all the courses were oversubscribed. Next year, the 8th Annual National Masterclass is being held at the Royal College of Surgeons, London. This venue has an increased capacity and has resulted in greater interest both by delegates and faculty! Inspite of the greatly increased expenses for the London venue, the course remains free. In 2012 another course has been added to the stable: the First National Advanced ENT Emergencies' Masterclass in June.

In January 2011, the ENT “Cyber Textbook on Operative Surgery” was launched with more than 150 videos of all aspects of ENT Surgery – Head and Neck, Otology and Rhinology, contributed from all over the world. This has increased hits to our website by 600% by surgeons from over 52 countries and is expanding everyday. The 6th and 7th National ENT Masterclasses were transmitted live as a free International WEBCAST and this shall continue in 2012 from the RCS, London. The archives of these Webcasts are available as an iplayer recording on our website.

The Journal of ENT Masterclass continues to expand and is now in its 4th year and includes some twenty-three articles from National and International Experts across the surgical and non-surgical topics. Our thanks to all those who helped contribute to make this Journal of ENT Masterclass a free Annual Publication. The Journal has now obtained an ISSN number and is registered with the British Library.

During the 7th Annual National ENT Masterclass, the first ENT Masterclass Registrars’ Gold Medal was awarded to Mr Nick Gibbins, SpR from London, for his paper on “Lingual Carcinoma Metastases” – congratulations! The abstracts of the finalists are included in this Masterclass Journal.

The ENT Masterclass Registrars’ Gold Medal will continue with all finalist’s abstracts published.

Our Editorial Board remains unchanged and continues to work as a team, making suggestions for topics and possible authors, who’s expertise will enhance the quality and depth of this Annual Journal of ENT Masterclass.

The Masterclass platform continues to seek your comments. On the website, www.ENTMASTERCLASS.com there is a guest page where comments can be registered and through your feedback we strive to satisfy your needs! In this modern era, silence or not commenting cannot be assumed to signify approval for what the Editorial Board continues to provide!

Adding my personal note, I continue to be amazed at the dedication, activity and enthusiasm of Shahed Quraishi, long may he enjoy good health and continue his magnanimous dedication to ENT training and teaching!

Professor Patrick J Bradley, MBA, FRCS
Chairman of the Editorial Board
Journal of ENT Masterclass, Nottingham.
E-mail: pjbradley@zoo.co.uk

November 2011.
A Review of Tinnitus Treatments (Part 2)

Miss Claudia Nogueira MRCS, PhD. Dept of Otolaryngology
Dr T Meehan, FRCS, MSc Aud Med., Dept of Audiovestibular Medicine
Mr Neil Fergie, FRCS (ORL-HNS), Dept of Otolaryngology
Nottingham University Hospitals, Queen’s Medical Centre Campus
Derby Rd, Nottingham. NG7 2UH, UK

Abbreviations
FDA - Food and drug administration
MHRA - UK Medicines and Healthcare products Regulatory Agency
NIHL - Noise-induced hearing loss
RCT - Randomised controlled trials
TCA - Tricyclic antidepressant
THI - Tinnitus Handicap Inventory
SSRIs - Selective serotonin re-uptake inhibitors

Abstract
Tinnitus is a common condition affecting 10% of the adult UK population, which in a minority can be severely debilitating. This review introduces to a number of pharmacological therapeutic agents which have been assessed for their utility in the management of tinnitus. The conclusion is that many agents have been successful in the management of tinnitus. However there is a need for further randomised clinical trials required for specific subgroups of tinnitus patients and analysis reporting using standardised outcome measurements.

Key Words
Tinnitus, Pharmacologic agents, Treatment, Effectiveness

Introduction
Tinnitus is a common condition affecting 10% of the adult UK population, which in a minority can be severely debilitating. This review introduces to a number of pharmacological therapeutic agents which have been assessed for their utility in the management of tinnitus. The conclusion is that many agents have been successful in the management of tinnitus. However there is a need for further randomised clinical trials required for specific subgroups of tinnitus patients and analysis reporting using standardised outcome measurements.

Table I: Pharmacological medications groups investigated for the treatment of tinnitus

<table>
<thead>
<tr>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-arrhythmics</td>
</tr>
<tr>
<td>Glutamate receptor antagonists</td>
</tr>
<tr>
<td>GABA receptor agonists</td>
</tr>
<tr>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Beclofen</td>
</tr>
<tr>
<td>Antiepileptics</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>Selective serotonin re-uptake inhibitors</td>
</tr>
<tr>
<td>Prostaglandin analogues</td>
</tr>
<tr>
<td>Ca 2++ antagonists</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Agent</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Lidocaine</td>
</tr>
<tr>
<td>Tocaine</td>
</tr>
<tr>
<td>Acamprosate</td>
</tr>
<tr>
<td>Memantine</td>
</tr>
<tr>
<td>Alprazolam</td>
</tr>
<tr>
<td>Baclofen</td>
</tr>
<tr>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Gabapentin</td>
</tr>
<tr>
<td>Tripramine</td>
</tr>
<tr>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Sertraline</td>
</tr>
<tr>
<td>Paroxetine</td>
</tr>
<tr>
<td>Misoprolol</td>
</tr>
<tr>
<td>Melatonin</td>
</tr>
</tbody>
</table>
methodology, lack of long term follow-up, absence of reliable objective tinnitus assessment and limitations of animal models.

**Local anaesthetic agents**
The administration of local anaesthetics in the treatment of tinnitus was reported by Barany\(^4\) in 1935, Lewy\(^5\) performed the first study on their usage for the relief of tinnitus. Several clinical trials reported that lidocaine can reduce tinnitus in 20% - 60% of subjects\(^6-9\). The only randomised control study was conducted by Duckert and Rees\(^8\), and reported that although 40% of the lidocaine group reported a decrease in tinnitus, 30% of the same group reported an increased tinnitus.

The mechanism of action of lidocaine in the relief of tinnitus remains unclear, however current research indicates that lidocaine given intravenously affects central auditory pathways as well as the cochlea\(^10-12\). These effects produce short-term relief (up to a few hours) but cardiac side-effects have also been reported and are worrisome to patients\(^13\). There have been several attempts to minimise the side effects and extend the half-life by using oral analogues such as tocainide\(^14\), mexiletine\(^15\) and flecainide\(^16\). However, these drugs are less effective, and almost all of them exhibit severe side-effects.

**Glutamate receptor antagonists**
Glutamate is the principal excitatory neurotransmitter in the peripheral and central auditory system\(^17\). Excessive release of glutamate results in over-activity of synaptic receptors \(\alpha\)-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) and N-methyl-D-aspartate (NMDA) which can result in neuronal cell death, contributing to the clinical symptoms of hearing loss and tinnitus\(^18\).

Caroverine which is a quinoxaline-derivative has been shown to act as a reversible antagonist of NMDA and AMPA receptors in the cochlear afferents\(^19\). Denk et al\(^20\) reported that 63.3% of the patients with tinnitus responded positively to caroverine and in the placebo group none showed a significant response. However, most glutamate receptor antagonists have severe psychotic side-effects and thus cannot be administered systemically\(^21\). Chen et al\(^22\) suggested local administration of caroverine topically to the round window membrane as a more effective method of administration, to avoid systemic side effects.

Further research has attempted to circumvent these side-effects by using more recently developed NMDA receptor antagonists. Acamprosate is a non-selective NMDA receptor antagonist. In a double blind RCT study, conducted in Brazil\(^23\) with 50 participants with subjective tinnitus, 87% of the subjects in the acamprosate group showed some improvement, including three subjects in which tinnitus disappeared, compared with only 44% in the placebo group. A larger trial to test the efficacy of acamprosate in reducing tinnitus is currently underway in Portland, Oregon\(^24\). If this trial confirms the preliminary results, acamprosate may prove to be a major breakthrough in the treatment of tinnitus.

A randomised, double-blind crossover study was performed to assess the efficacy of memantine, a non-selective NMDA antagonist to suppress tinnitus. Figueiredo et al.\(^25\) concluded that there was no significant improvement in the scores of the tinnitus handicap inventory (THI) after memantine treatment compared with placebo. The efficacy of the memantine analogue neramexane, which blocks NMDA is currently being examined in a large clinical study. Neramexane has entered phase III clinical trials and is one of the first drugs developed specifically for tinnitus treatment. Initial findings from this clinical study are expected in late 2011\(^26\). The therapeutic benefits of intratympanic delivery of AM-101, a non-competitive antagonist of NMDA, is also currently being investigated in a phase III double-blind, randomised, placebo-controlled, multiple dose study\(^27\).

**GABA receptor agonists**
In the auditory system, inhibition of the efferent system is mostly mediated by GABA (gamma-aminobutyric acid). A down-regulation of GABA, resulting from noise induced damage in the auditory periphery, has been suspected to be an important etiological factor in the production of tinnitus\(^28\). Using single-photon emission computed tomography (SPECT), Shulman et al\(^29\) have demonstrated reduced chemical binding in GABA receptors, in patients with severe tinnitus. This finding has prompted research into GABAergic modulators in the treatment of tinnitus\(^30\).

**Benzodiazepines**
Benzodiazepines are GABA\(_A\) receptor agonists and have anxiolytic, hypnotic and anticonvulsant properties. In a double-blind, placebo-controlled study\(^31\), 77% of patients treated with alprazolam reported a reduction in tinnitus severity, compared with 5% in the placebo group. In a small randomised, single blind clinical trial a clonazepam was also found to significantly reduce tinnitus loudness\(^32\). Although these results indicate benefit, benzodiazepines are known to lead to dependence and post- withdrawal enhancement of tinnitus\(^33\), therefore great care should be taken when prescribing them.

**Baclofen**
The antispasmodic agent baclofen is a GABA\(_B\) receptor agonist. Based on the observation that L-Baclofen has
been shown in animals to have inhibitory effects within the cochlear nucleus, Szczepaniak and Moller suggested that Baclofen could represent a potential treatment for hyperactive auditory disorders such as tinnitus. Westerberg reported no significant difference in the subjective improvement in tinnitus between the baclofen treated group (9.7%) and placebo group (3.4%). Furthermore, withdrawal from the baclofen arm of the study occurred in 26% of participants due to side effects such as confusion, dizziness and gastrointestinal upset.

**Antiepileptics**

Trials in animals with induced tinnitus, have shown that carbamazepine significantly suppresses the behavioral manifestations of salicylate-induced tinnitus in rats. However in humans carbamazepine failed to show benefit when compared with placebo in four RCTs. Only a small sub-population of patients with intermittent tinnitus, that sounds like a typewriter, popping corn or ear clicking, have been shown to gain significant relief from carbamazepine.

Simpson *et al.* published a double-blind, placebo controlled, cross-over clinical trial on 33 patients and showed no statistically significant difference in tinnitus relief between lamotrigine and placebo groups, although the study used only a modest treatment dose.

Sodium Valproate (SV) is also commonly prescribed as an antiepileptic and mood stabiliser and has been investigated as a possible tinnitus suppressant. However, the true value of this drug in the management of tinnitus remains unknown, it’s effects are only substantiated by case reports and uncontrolled trials.

Gabapentin, a GABA analogue is the most commonly studied antiepileptic drug for the treatment of tinnitus, however the results are inconsistent. In a case report by Zapp *et al.* a patient treated with gabapentin for chronic pain reported subjective improvement in tinnitus. In a placebo-controlled single blind trial, Bauer *et al.* reported that Gabapentin is effective in reducing subjective and objective aspects of tinnitus in some individuals with tinnitus secondary to acoustic trauma. However, in a randomised, placebo-controlled, double-blind trial Witsell *et al.* reported that gabapentin is no more effective than placebo in the treatment of tinnitus.

**Antidepressants**

The use of antidepressants in the management of tinnitus stems from the observation of the high comorbity between depressive disorders and tinnitus. However, a review which investigated the results of five clinical trials involving 525 patients, found no conclusive proof that SSRIs or TCAs improved tinnitus. The tricyclic antidepressants; trimipramine, amitriptyline and nortriptyline were investigated for the treatment of tinnitus in RCTs. Although some TCAs seem to cause tinnitus as a side-effect; in some patients, these medications result in some improvement in tinnitus symptoms. The first TCA study was performed by Mihail who reported no significant outcome difference between trimipramine and placebo. Podoshin reported that 27.5% of patients reported subjective improvement in tinnitus at rest when treated with amitriptyline, versus 5% with placebo, although only 15.8% of the amitriptyline patients reported improvement during activity. In a single blind study, Bayar reported that amitriptyline decreased tinnitus severity in 95% in the treatment group after 6 weeks, compared with 12% in the placebo group. Sullivan *et al.* reported that Nortriptyline was found to reduce tinnitus loudness and severity, but this effect was most apparent in those who were depressed. Some TCA side-effects reported in these studies included dry mouth, worsening of tinnitus, mild sedation, blurred vision and constipation.

Selective serotonin re-uptake inhibitors (SSRIs) are an alternative option to TCAs in the management of tinnitus. Zoger *et al.* compared sertraline with placebo and after 16 weeks of treatment, they reported a significant improvement in tinnitus severity over placebo, however no benefit was found for tinnitus annoyance. Other SSRIs such as paroxetine provided no significant improvement and some drugs such as fluoxetine exacerbated tinnitus. As SSRIs are better tolerated, these antidepressants should be used as first line treatment.

**Prostaglandin analogues**

Prostaglandins act as neuromodulators of the afferent pathway in the cochlea and are involved in the hormonal control of cochlear microcirculation. Based on the observation, that a decrease in cochlear prostaglandins may play a role in the production of tinnitus, Briner performed a study to evaluate the effect of Misoprostol (synthetic prostaglandin E1) on the treatment of tinnitus. One third of patients reported improvement during the active drug phase, together with improvement in sleep and concentration. In a double-blind placebo controlled RCT, Yilmaz found a significant difference in improvement in subjective tinnitus loudness between misoprostol and placebo. In addition, they noted that misoprostol was most effective in patients who had sudden-onset tinnitus. Overall, there is little data on the effectiveness of misoprostol for tinnitus reduction but the few studies which are available on this subject show encouraging results.
Calcium channel antagonists
Calcium (intra and extracellular) plays a major role in the fast transduction process in hair cells. Nimodipine, an L-calcium channel antagonist was reported by Jastreboff to abolish quinine and aspirin induced tinnitus in rats. Davies found only a 16% improvement in the subject rating of tinnitus after an 8-week trial with nimodipine. Further studies are needed to assess benefit or otherwise of this group of drugs.

Melatonin
Melatonin is a neurotransmitter secreted by the pineal gland and not only is it a key regulator of the circadian rhythm but it also plays a role as a blood pressure modulator and as an antioxidant.

In a randomized, prospective, double-blind, placebo-controlled crossover trial, Rosenberg reported that the difference in the THI scores between melatonin and placebo treatment were not statistically significant. However, there was a significant improvement in insomnia due to tinnitus when compared with placebo. Rosenberg therefore concluded that patients with difficulty sleeping are the most likely to benefit from treatment with melatonin.

Alcohol
The relationship between alcohol and tinnitus is contradictory. Pugh et al. distributed a self-report questionnaire over a four-month period to 100 chronic tinnitus sufferers. The results showed that 62% of the sample reported that alcohol had no effect on their tinnitus, 22% of the sample reporting that drinking worsened tinnitus and 16% reporting that alcohol improved tinnitus.

Zinc
It has been suggested that a low serum zinc level is one of the risk factors in the production of tinnitus. Gersdorff et al. reported an association between tinnitus and a low serum level of zinc: 68.7% of 115 patients with tinnitus had hypozincemia.

In a small randomised, placebo-controlled study, Arda et al. reported that zinc did not significantly reduce objective tinnitus loudness. However, it significantly decreased the severity of subjective reported tinnitus, regardless of the patients’ serum zinc level being normal or low.

Vitamin B12
Shemesh et al. reported that vitamin B12 deficiency is common in people exposed to loud noise who developed tinnitus and noise-induced hearing loss. In 12 patients with low vitamin B12 levels who received vitamin B12 replacement therapy, some improvement was observed in tinnitus and associated complaints.

Cinnarizine
A small randomized, placebo-controlled trial conducted by Podoshin et al. found cinnarizine to be ineffective in the treatment of tinnitus.

Betahistine hydrochloride
Novotny and Kostrica investigated the effects of betahistine hydrochloride on tinnitus in patients suffering from Meniere’s disease and found tinnitus severity was reduced in these patients. A randomised control trial by Maqbool et al. showed no significant effect of betahistine hydrochloride compared to placebo in the treatment of tinnitus due to noise induced hearing loss.

Intratympanic Steroid Injection
Sakata et al. in 1996 treated 1214 patients (1466 ears) with tinnitus with intratympanic dexamethasone injections. These patients had a range of co-morbidities including chronic otitis media, labyrinthine syphilis, Ménière’s disease, vertigo, sudden deafness, genetic deafness, acoustic trauma, head injury or other otological disease. The authors reported an immediate improvement in symptoms in 71% of the ears treated. At 6 months post-treatment the improvement decreased to 68%. The patients with chronic otitis media, Ménière’s disease and labyrinthine syphilis had the best results. However a randomized prospective single-blind study by Araujo et al. concluded that there was no significant difference between intratympanic injections of dexamethasone and placebo in the treatment of tinnitus of cochlear origin. Topak et al. also concluded that intra-tympanic methylprednisolone had no benefit, compared with placebo, for the treatment of subjective tinnitus of cochlear origin.

Discussion
Currently, no pharmacological agent has been shown to cure or consistently alleviate tinnitus. However, some drugs have been shown to be effective in some groups of patients. Studies carried out in patients with intermittent tinnitus which sounds like a typewriter, popping corn or ear clicking suggest benefit from treatment with carbamazepine. Other drugs already shown to be effective in the specific treatment of tinnitus are gabapentin (in patients with acoustic trauma), melatonin (in patients with insomnia) and zinc (in zinc deficiency).

In recent years, drug therapies have primarily focused on drugs acting on brain neurotransmitters, like glutamate,
GABA and serotonin. GABA receptor agonists such as clonazepam and alprazolam have been shown to be effective in the treatment of tinnitus for patients with associated anxiety. With respect to SSRIs, it is interesting to note that sertraline significantly reduced tinnitus compared with paroxetine which provided no significant improvement and fluoxetine which exacerbated the tinnitus symptoms. Large clinical trials for promising new drugs such as neramexane, AM-101 and acomprasate are currently underway.

Our understanding of the mechanisms of tinnitus is incomplete and many unknown factors remain. Clinical research varies in methodological rigor and has been hampered by difficulties in the objective measurement of tinnitus. The subjective scales commonly used in clinical trials may have only modest accuracy. Like many other complex neurological conditions, tinnitus is a symptom that can result from several diverse pathophysiological mechanisms.

Summary;
One drug is unlikely to alleviate tinnitus in all patients; consequently therapies targeting specific subgroups are likely to be more beneficial. There is currently no one medication likely to benefit all tinnitus sufferers and drug therapy should be tailored to the specific needs of the individual. Consequently, the authors tend to reserve pharmacological treatment for a small minority of tinnitus patients who don’t benefit from non-pharmacological treatment.

References
Ototoxicity: Evaluation and Management

Natalie Watson MBBS BSc (Hons), Senior House Officer, St George’s Hospital, London,
David Selvadurai MD FRCS (ORL-HNS), Consultant Otolaryngologist, St George’s Hospital, London

Corresponding Author:
Mr David Selvadurai,
Address: St George’s Hospital, Tooting, London, SW17
Email: david.selvadurai@stgeorges.nhs.uk

Introduction

Ototoxicity is the umbrella term for functional impairment and cellular degeneration of the tissues of the inner ear caused by a chemical agent1. Exposure to ototoxic agents can cause a loss of hearing (cochleotoxicity) and/or vestibular function disruption (vestibulotoxicity)1. Cochleotoxicity typically manifests itself as a bilateral high frequency sensorineural hearing loss with or without tinnitus, which can be permanent or temporary depending on the offending agent. These symptoms may be apparent at the time of exposure or present months later. The symptoms commonly associated with vestibulotoxicity include nausea and vomiting, nystagmus leading to oscillopsia/ dizziness, equilibrium disturbance and light-headedness2.

Over 200 substances are known to be ototoxic and can be classified into 3 broad groups: occupational (e.g. paint solvents, fuels), recreational (e.g. spray adhesives), and medicinal (e.g. aminoglycosides, loop diuretics, platinum-based chemotherapeutic agents, quinine, organophosphates)3,4.

Risk factors for ototoxicity include renal impairment, age (under 5 and elderly patients), pre-existing hearing disorders, cumulative dosage, dosing schedule, duration of treatment and repeated courses of therapy5. Genetic predisposition also plays a role in ototoxicity. A number of genetic factors have been discovered, namely specific genotypes of glutathione S-transferase (the presence of both Val-GSTP1 alleles offers protection against cisplatin hearing loss6), single nucleotide polymorphisms of megalin may also affect susceptibility to cisplatin ototoxicity7, and mutations in the 12S rRNA gene (associated with aminoglycoside ototoxicity)8.

Concomitant noise exposure with ototoxic chemicals can have a synergistically deleterious effect3. “Toxic noise” has been described as occupational e.g. industrial, manufacturing, construction and military, or recreational in the form of concerts, sports stadia, hunting and headphones, and can be due to either blast or chronic noise exposure5,8. One group we must protect are neonates in specialist units requiring aminoglycosides. These units are particularly noisy environments and so ototoxicity may take effect on this vulnerable group3.

Ototoxicity is a public health concern in developing countries, where protective equipment provision and education is poor and there is unregulated availability of medications such as aminoglycoside antibiotics. In children, loss of hearing may hamper the development of speech, cognitive abilities and social interactions9. It is important to detect these toxic effects early to prevent susceptible patients losing the most important frequencies of hearing for speech intelligibility10. Vestibulotoxicity alone also creates significant morbidity with an impact on the ability to engage in activities of daily living or work and may also lead to falls. It is therefore important to stress the significance of limiting the toxic effects of these drugs and chemicals at both individual and population levels.

We review the most recent advances in evaluation and management of ototoxic agents. We also briefly discuss the potential therapies of the future.

Groups of ototoxic agents

The two most commonly described ototoxic agents are aminoglycoside (AG) antibiotics and platinum-based chemotherapeutic agents. AGs are extensively used for a variety of bacterial infections, as monotherapy or in combination with other antimicrobials for urinary tract infections, severe gram-negative enterococcal or mycobacterial infections and systemic infections like bacterial endocarditis and pseudomonal infections5. AGs affect different parts of the inner ear. Streptomycin and gentamicin preferentially causes vestibulotoxicity, whereas amikacin, neomycin, tobramycin and kanamycin can lead to a more cochleotoxic effect5. The incidence of AG cochleotoxicity ranges from a few percent to 33% and AG vestibulotoxicity, 15%. These percentages are higher in developing countries due to the unregulated prescriptions and scarce monitoring1.
Platinum-based chemotherapeutic agents (cisplatin and carboplatin) are commonly used in many childhood cancers leading to an 80% cure rate\(^\text{12}\). Ototoxicity is dose-dependent with around 25-90% of children treated with these chemotherapeutic medications suffering some permanent hearing loss\(^\text{1,12,13}\). Treatment of neuroblastomas in particular can include cranial radiation therapy in addition to cisplatin, which can increase the susceptibility to ototoxicity.

Other medicinal ototoxic drugs of note are loop diuretics, salicylates and quinine. Around 6-7% of patients taking loop diuretics suffer with ototoxicity. Salicylates, are known to cause temporary tinnitus but have been shown in some clinical trials to be otoprotective. With conflicting evidence there is still much debate on their clinical role in ototoxicity\(^\text{14}\). Quinine therapy is known to sometimes cause a transient hearing loss due to temporary outer hair cell dysfunction\(^\text{15}\). Other current malarial treatment has not been shown to be ototoxic e.g. artemether/lumefantrine\(^\text{15}\).

Finally, occupational chemicals like organophosphates have also been investigated and been shown to degrade the vestibulocochlear system\(^\text{16}\). In a Brazilian study 89% of workers with pesticides had vestibular symptoms and 39% of workers had evidence of cochleotoxicity\(^\text{4}\). The current recommendation for detection and monitoring of chemotherapeutic ototoxic drugs is “testing” prior to therapy onset, before each successive dose and upon evidence of symptoms including hearing loss\(^\text{17}\). For people receiving AGs weekly testing for ototoxicity is recommended, particularly if they receive AGs for longer than 21 days\(^\text{10,18}\). Traditionally, evaluation has included air conduction, bone conduction, speech audiometry and tympanometry\(^\text{12}\). In infants or people unable to perform these simple tests, electrophysiological assessment may be necessary e.g. auditory brainstem response measurement\(^\text{12}\). Reavis et al. found that approximately a third of patients receiving ototoxic medications become unable to perform behavioural hearing tests such as audiograms due to progressing illness\(^\text{19}\). As a result of this and other recent data suggesting that extended high-frequency audimetry and distortion product otoacoustic emissions (DPOAEs) can reveal earlier changes in auditory function than conventional audiometry\(^\text{1,20,21}\). Standard clinical practice ideally should now include these tests in favour of routine audiometry.

**Grading system**

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) criteria grade hearing loss secondary to ototoxicity on a scale from 1 to 4 combining subjective hearing loss with objective PTA measurement shifts at 2 contiguous frequencies\(^\text{17}\). The CTCAE grading scale has come under criticism with claims that this scale under-reports ototoxicity, it is not sufficiently sensitive and grades do not reflect true clinical impact\(^\text{13,17}\). The Brock grading scale is another classification system for ototoxicity. Brock’s scale reflects the physiological sequelae of ototoxicity grading by specifically weighting loss of low-frequencies higher than high-frequency loss (Table 1). Chang et al. have developed a modified Brock grading scale, which is hoped to be more clinically consistent and robust (Table 1)\(^\text{17}\). The Chang scale describes the clinical severity of hearing loss and predicts the anticipated level of rehabilitation required\(^\text{17}\).

The American Speech-Language Hearing Association 1994 guideline (ASHA) is another method of assessing ototoxicity. This scale observes for a >20dB decrease at one frequency, a >10dB decrease at 2 consecutive test frequencies or loss of response at 3 consecutive test frequencies in which responses were previously obtained. This is a good measurement to detect an ototoxic effect but lacks information on the clinical impact and severity of ototoxicity\(^\text{17}\).

### Table 1: Brock and Chang classification of cisplatin-induced hearing loss (adapted from Chang and Chinosornvatana). HL, hearing level\(^\text{17}\).

<table>
<thead>
<tr>
<th>Brock Grade</th>
<th>Hearing Threshold (dB HL)</th>
<th>Chang Grade</th>
<th>Sensorineural Hearing threshold (dB HL)</th>
<th>Chang clinical application</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 &lt;40dB at all frequencies</td>
<td>0</td>
<td>≤ 20bD at 1, 2, and 4kHz</td>
<td>No clinical effect</td>
<td></td>
</tr>
<tr>
<td>1 ≥ 40dB at 8kHz</td>
<td>1a</td>
<td>≥ 40dB at any freq 6 to 12kHz</td>
<td>Measurable hearing loss for early detection of ototoxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>&gt;20 and &lt; 40 dB at 4kHz</td>
<td>Can be aided by FM system</td>
<td></td>
</tr>
<tr>
<td>2 ≥ 40dB at 4kHz and above</td>
<td>2a</td>
<td>≥ 40dB at 4kHz and above</td>
<td>FM system aids – clinically significant &lt;10 years old</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>&gt;20 and &lt; 40 dB at any freq below 4kHz</td>
<td>Requires hearing aids – clinically significant &gt;10 years old and adult population</td>
<td></td>
</tr>
<tr>
<td>3 ≥ 40dB at 2kHz and above</td>
<td>3</td>
<td>≥ 40dB at 2 or 3 kHz and above</td>
<td>Absolute indication for hearing aids</td>
<td></td>
</tr>
<tr>
<td>4 ≥ 40dB at 1kHz and above</td>
<td>4</td>
<td>≥ 40dB at 1 kHz and above</td>
<td>Less satisfactory correction with hearing aids</td>
<td></td>
</tr>
</tbody>
</table>
Finally, a percentage hearing loss calculation is used in medico-legal cases to detect moderate to severe ototoxicity using PTA-5123 method of calculating 0.5, 1, 2 and 3kHz into a percentage calculation. By definition this percentage scale cannot detect mild ototoxic effects, i.e. loss of high-frequency hearing.

Mitochondrial DNA analysis testing and or a family history looking specifically for mutations in the 12S rRNA gene can predict if aminoglycoside-induced ototoxicity will affect a particular individual. This may be currently an unrealistic option as this test takes 2 days for the results to process, and due to clinical urgency there is pressure on time to commence treatment. It is useful to keep in mind that if ototoxic agents are administered at high doses or for prolonged periods even individuals who do not have the predisposing mutations for ototoxicity can develop symptoms.

Evaluation of vestibulotoxicity is more complex. The gold standard is electronystagmography (ENG) with caloric irrigation, however these tests are technically difficult to perform and time consuming. The head impulse test (HIT) is a useful bedside examination to identify vestibular deficits and thus can detect vestibulotoxicity.

Management
There are 10 general management principles for ototoxicity:

1. It is important that patients, parents and healthcare professionals have an awareness of the potential side effects of ototoxic chemical agents.
2. Prompt appropriate referral to an otolaryngologist to minimize otology pathology e.g. chronic otitis media or externa, tympanic membrane abnormalities and cerumen impaction.
3. Amplification devices for patients with hearing loss (30-40% of survivors of childhood cancers are recommended to have hearing aids) and rarely cochlear implants.
4. Adaptive strategies, for example, FM systems, reduction of background noise, preferential seating and mechanisms to increase face-to-face contact.
5. Assessment and follow up by a speech and language therapist (particularly in children) to limit the impact of hearing loss on articulation and language development.
6. Avoid toxic noise by limited exposure or personal protection equipment. In particular limit exposure to the noise of power saws, vacuum cleaners, lawn mowers, trimmers, leaf blowers, hair dryers, stereo devices, loud amplifiers, and avoid activities such as shooting, hunting, waterskiing, power boating, motorcycling. The removal of these noise sources is optimally performed prior to the administration of ototoxic chemicals but exposure is also important to be minimized during the encounter of these chemicals and afterwards.
7. Avoid simultaneous use of 2 or more ototoxic agents e.g. aminoglycoside antibiotics and diuretics or select alternative medications for people particularly at risk (i.e. cystic fibrosis patients, family history).
8. Single daily dosing instead of multiple daily dosing, although it seems paradoxical that single daily dosing is less ototoxic, the inner ear AG toxicity is reliant on a saturation process, therefore saturating only once is better than multiple daily saturations.
9. Frequent monitoring of serum drug levels (particularly the AGs) and renal function.
10. Vestibular rehabilitation therapy is the mainstay of treatment for Vestibulotoxicity.

Future Management
Protection against ototoxicity is yet to be achieved. The mechanisms for this protection may come from manipulation of endogenous molecules, administration of exogenous molecules or by a combination of the two. A number of mechanisms and chemicals have been investigated in vitro and in animal studies to reduce the oxidative stress created by the offending ototoxic agents. Otoprotective agents must fulfill 3 criteria: it should be non-toxic, achieve high concentrations in the inner ear and not affect the therapeutic actions of the ototoxic compound in question. Local application of otoprotective compounds have also been tested in animals to help reduce any systemic side effects of these compounds in addition to creating a higher concentration of the drug protecting the target organ and reduce the interaction of the otoprotectant with the offending drug.

Some clinical trials of otoprotective compounds have been performed. Sodium thiosulfate is currently being tested by the Children’s Oncology Group and Société Internationale d’Oncologie Pédiatrique – Epithelial Liver Tumor Study Group in 2 intervention trials of paediatric patients treated with cisplatin. Results for these studies are yet to be published. There is conflicting evidence regarding the use of amifostine in patients treated with platinum-based chemotherapeutic agents. The current recommendation from the American Society of Clinical Oncology does not support the routine use of amifostine for the prevention of ototoxicity. One clinical trial in paediatric patients shows significant otoprotection with an intravenous bolus of amifostine immediately prior and 3 hours after cisplatin and cranial radiation therapy. In contrast, other studies using amifostine have shown no otoprotection clinically using a different administration protocol, on a different
population of subjects, and with different chemotherapeutic agents used. N-acetylcysteine (NAC) has been shown to prevent ototoxicity, associated with intraperitoneal amikacin and vancomycin in 60 patients with CAPD peritonitis and in another study with 40 haemodialysis patients receiving gentamicin. Currently, clinical trials are being performed for a number of other otoprotective agents e.g. alpha-lipoic acid, Ringer’s Lactate, for which we are awaiting the results (www.clinicaltrials.gov).

By contrast, a multitude of in vitro and animal studies, namely in rats, guinea pigs and hamsters have shown promising otoprotective effects when administered with the most common otoxic medications e.g. cisplatin and AGs. Ginkgo biloba (EGb 761) has been shown to protect cochlear hair cells against ototoxicity induced by gentamicin via reducing reactive oxygen species and nitric oxide-related apoptosis in vitro and in guinea pig studies. Other otoprotective chemicals tested on animals include flunarizine, pomegranate extract, Vitamin E and its derivative alpha-tocopherol, melatonin, D- and L-methionine, diethylthiocarbamate, sodium thiosulfate, 4-methylthiobenzoic acid and lipoic acid. Other AGs. Ginkgo biloba (EGb 761) has been shown to protect the vestibulocochlear system ultrastructural aspects of guinea pigs. By contrast, a multitude of in vitro and animal studies, namely in rats, guinea pigs and hamsters have shown promising otoprotective effects when administered with the most common otoxic medications e.g. cisplatin and AGs. Ginkgo biloba (EGb 761) has been shown to protect cochlear hair cells against ototoxicity induced by gentamicin via reducing reactive oxygen species and nitric oxide-related apoptosis in vitro and in guinea pig studies. Other otoprotective chemicals tested on animals include flunarizine, pomegranate extract, Vitamin E and its derivative alpha-tocopherol, melatonin, D- and L-methionine, diethylthiocarbamate, sodium thiosulfate, 4-methylthiobenzoic acid and lipoic acid. Other AGs. Ginkgo biloba (EGb 761) has been shown to protect the vestibulocochlear system ultrastructural aspects of guinea pigs.

Conclusions
Otototoxicity is a major social and economic problem. Much research is being performed to investigate the mechanisms behind the pathophysiology, evaluation and management of ototoxicity. The latest evaluation methods and general management have been discussed. There is a significant amount of work still to do to try and prevent ototoxicity and we eagerly await the results of the clinical studies.

References


34. Yang TH, Young YH, Liu SH. EGB 761 (Ginkgo biloba) protects cochlear hair cells against ototoxicity induced by gentamicin via reducing reactive oxygen species and nitric oxide-related apoptosis. J Nutr Biochem 2011; 22(9):886-94


49. Zheng JL, Gao WQ. Differential damage to auditory neurons and hair cells by ototoxins and neuroprotection by specific neurotrophins in rat cochlear organotypic cultures. Eur J Neurosci 1996;8:1897-1905
Principles of Mastoid Surgery

V Dhar MRCS, DA Bowdler FRCS, A Aymat FRCS(ORL-HNS)
Department of Otolaryngology, University hospital Lewisham, Lewisham High Street, Lewisham, London SE13 6LH, United Kingdom

Correspondence:
Mr Vikram Dhar
email: vdhair100@hotmail.com

Abstract:
Mastoid disease usually requires a surgical solution. A full understanding of middle ear anatomy and proficiency in a wide array of operative techniques allows the surgeon to tailor mastoid surgery to each individual patient, taking into account the anatomy, disease, hearing, social circumstance and co-morbidities.

Keywords
Combined approach tympanoplasty, Mastoid surgery, cholesteatoma. Chronic Suppurative Otitis Media

Introduction:
Mastoid disease is potentially life threatening, therefore historically the management was focused on creating a safe, and if possible dry, ear. Today our aims are higher, with a greater emphasis on function. To achieve this we have three tools that potentiate our success:1. Better knowledge of the anatomy2. Greater clarity and choice of operative technique3. Improving range and quality of equipment.

The trainee otologist is confronted with intricate anatomy, which may be distorted by destructive pathology and with which they are not necessarily familiar; for this reason a full understanding of the principles of mastoid surgery is essential. Having a clear, fairly standardised approach to the surgery with a step by step algorithm aids the surgeon.

However an accomplished otologist will develop his or her own techniques, which will respond to anatomical and pathological variation.

Indications:

Anatomical areas of focus:

Facial nerve
The facial nerve is located by orientating it against other identifiable structures. The short process of the incus lies just posterior to the horizontal facial canal and lateral to the second genu and vertical portion of the facial nerve. The lateral semi circular canal lies posteriorly to the second genu. The stapes helps identifying the horizontal portion of the facial nerve. Dehiscence, most commonly in its horizontal course, has been reported at 33%1. In the authors practice this figure is approximately 10%. Risk is reduced by using large burrs if possible and commencing drilling antero-superiorly to identify landmarks.

Tegmen tympani
The tegmen tympani which separates the middle cranial fossa from the tympanic cavity is an important surgical landmark and should be located early in the procedure. A diamond burr should be used when approaching the tegmen to avoid breaching the dura. If a breach of the dura does occur a temporalis fascia graft usually controls the risk of CSF leak.

Facial recess and sinus tympani
Both spaces comprise the retrotympanum and are difficult to access so that they are common sites for both primary and residual cholesteatoma. The facial recess lies lateral to the facial nerve; with the fossa incudis superiorly and the chorda tympani lateral to it. The sinus tympani lies between the facial nerve and the medial wall of the mesotympanum.
Access is difficult because of the facial nerve. Creating a posterior tympanotomy and using an angled oto-endoscope is particularly helpful in accessing the retrotympanum.

**Diagnosis:**
Diagnosis is based on the history, examination, audiology, and radiology including CT scanning.

**Disease:**
Chronic suppurative otitis media is the main disease that necessitates mastoid surgery and can be classified into tubo-tympanic and attico-antral disease.

Tubo-tympanic disease is characterised by a perforation of the pars tensa without epithelial in-growth and has a low risk of developing intracranial complications, hence the term “safe” disease. This has been challenged by Browning who reported cases of intracranial abscesses in active tubo-tympanic disease, nevertheless complications remain uncommon.

Attico-antral disease involves the posterior-superior part of the pars tensa or the pars flaccida, characterised by retraction pockets that accumulate keratin and may develop into a cholesteatoma, with the potential for complications, hence the use of the term “unsafe” for this type of disease. Cholesteatoma erodes bone and can lead to facial nerve dehiscence, lateral semi circular canal dehiscence, and cerebral complications. The symptoms of CSOM are aural discharge and hearing loss but can present with vertigo, facial palsy or rarely cerebral infection. Examination focuses on the presence of perforation, retraction pockets and frank cholesteatoma.

Pars flaccida retraction pockets can be graded using the Tos classification system and the pars tensa retraction pockets graded using the Sade system. Pockets should be cleaned of keratin if possible to assess the extent and nature of disease.

**Investigations:**
Pure tone audiogram; bone and air conduction with full masking are a prerequisite before mastoid surgery both as a clinical and medico-legal baseline. There is ongoing debate amongst otologists about the value of CT scanning prior to mastoid surgery. We feel that CT scanning is indicated as it provides a guide to the approach though probably not influencing the decision to operate. It may reveal the extent of disease and helps to identify lateral semi circular canal dehiscence, the level of the tegmen tympani, ossicular erosion and the presence of an anterior sigmoid sinus, thus forewarning of complications. CT can determine the extent of cholesteatoma by revealing the combination of a soft tissue mass and bone erosion with 80% specificity. However, cholesteatoma, granulation tissue, mucosal oedema and effusion are indistinguishable on CT. In addition it may identify secondary conditions such as acoustic neuromas.

**Objectives:**
Goals will be affected by pathology and social circumstances. Surgery is the only effective method of dealing with cholesteatoma and achieving a dry, safe ear. The type of approach and the extent of effort in improving auditory function will vary according to socioeconomic factors that prevail in different countries. Restoration or at least maintenance of hearing should be an aim, and ossiculoplasty at a primary or a staged procedure in our experience can achieve excellent closure of the air-bone gap.

Each case should be treated individually according to the extent and location of disease, however the objectives outlined should be adhered to and fundamental surgical steps followed.

**Surgical options:**
Mastoid surgery can be open or closed cavity. If open, the three broad options are; small cavity, modified radical or radical with or without obliteration. Closed cavity, otherwise known as “Canal wall up” procedures can also occasionally be obliterated.

**Canal wall down mastoidectomy**
Canal wall down procedures include atticotomy, attico antrostomy, small cavity mastoidectomy, modified radical and radical mastoidectomy with or without obliteration.

We believe that once the surgeon has become proficient in canal wall up surgery there are few circumstances where the surgeon must resort to a canal wall down surgery, though it remains a preferred choice for many surgeons. One such circumstance is where one can’t access the epitympanum in a sclerotic mastoid.

![Canal wall down mastoid cavity](Image)
The procedure involves exteriorising the mastoid into the external ear canal by taking the posterior canal wall down. In a modified radical mastoidectomy the middle ear space is preserved and the incus is removed as well as the head of the malleus. In a radical procedure the middle ear space is eliminated and the eustachian tube orifice is obliterated.

The advantages of an open approach are said to be that one can inspect the cavity easily and readily identify residual disease. In canal wall down mastoidectomy it is rare (2.1%) to have a recurrence of cholesteatoma as the facial recess is exteriorised.

However, the disadvantages are that the cavity will need a lifetime of aural toilet and often requires revision because of mucosal breakdown. The healing time is longer and water precautions are necessary.

In canal wall down mastoid surgery a decision needs to be made on whether to perform a front to back or back to front approach.

With the front to back approach, one starts by drilling and finding the disease in the attic and following backwards to its limit whether it be the attic alone (atticotomy) or all the way back to the sigmoid sinus. The residual cavity is limited to the extent of the disease and no more. The principle of wide exposure allowing easy manipulation of instruments is vital. One should be wary of the middle fossa dura that can catch out the novice if low lying. By keeping the cavity as small as possible, operative time is kept to a minimum and the cavity may be self cleaning and easy to manage. However this technique does run the risk of leaving hidden disease.

In the back to front approach, a cortical mastoidectomy is performed, followed by taking down the posterior ear canal wall down to the facial nerve, leaving a bony ridge (facial ridge). The cholesteatoma sac is approached from behind, so plenty of uninvolved mastoid bone has to be drilled away before the sac is encountered, increasing operative time and leaving a large, potentially high maintenance cavity.

**Intact canal wall (ICW)**

The technique of canal wall preservation is increasingly popular and is commonly called a combined approach tympanoplasty (CAT) when combined with a posterior tympanotomy. In the majority of cases we feel a posterior tympanotomy (ie a true CAT) should be performed to improve access and reduce the chance of leaving behind disease. Usually a further procedure (or more) at 6-12 months is needed to check for residual disease and to consider ossicular reconstruction. Brackmann in 1993 published his series of ICW mastoidectomies in children and adults, with only a three percent incidence of recurrent cholesteatoma; suggesting that the intact canal wall technique is preferable when circumstances allow. However, other authors report a higher, though acceptable rate of recurrent and residual disease.

The procedure has advantages over the aforementioned canal wall down procedure, in that healing time is rapid, they are far easier to manage in the long term care, hearing aids are easy to fit and no water precautions are needed. However, it is a technically more difficult procedure and the need for a second look staged procedure to ensure no residual disease is present is a drawback. Diffusion weighted MRI may eventually obviate the need for second look procedures and is discussed later.

**Mastoid Obliteration**

Mastoid obliteration is a technique used to reduce the size of the mastoid cavity in a canal wall down approach, with
the aim of achieving a dry care free cavity. Various materials have been used, including autogenous bone and cartilage, free or vascularised soft tissue, and bioactive or biocompatible alloplastic materials including hydroxyapatite granules. There is a risk of leaving disease behind in an obliterated cavity and re-exploration can be troublesome. Also obliteration can be used in ICW surgery when there is recurrence.

**Hearing outcomes**

Hearing outcomes are not significantly different between canal wall down and intact canal wall mastoid surgery, with the proportion of patients maintaining an air bone gap of less than 20 db; 58.6 % vs. 68.4 % respectively\(^\text{10}\).  

**Conclusion:**

The authors are strong advocates of CAT as it provides a dry safe ear requiring minimal clinic care; although we do follow up these patients for 10 years. The CAT procedure gives ample opportunity to reconstruct the hearing. Minimally invasive staged procedures can be performed with the aid of an otoendoscope via a stab incision into the cavity, giving an excellent view limiting further potentially unnecessary dissection whilst ensuring that disease is identified\(^\text{11}\). We advocate the use of the laser to areas where there is residual cholesteatoma as evidence points to significant reduction in residual rates\(^\text{12}\).

The major limitation of CAT is the need for staged procedures. Non-echo planar diffusion weighted MRI is promising in the detection of residual disease thus negating the need for second look procedures. Sensitivity, specificity, positive predictive value, and negative predictive values of 97%\(^\text{13}\) have been published, however at the present time in the vast majority of institutions MRI quality, know how and reporting skills is not at a level that enables it to be relied upon as a replacement for second look procedures, though it is an exciting prospect for the future.

Mastoid surgery and ultimately patient outcome can be improved by focusing on the three aforementioned principles, namely the anatomy, the surgical choices and the available equipment.

**References**

Non-Neoplastic Lesions of the Temporal Bone

Judith S. Kempfle MD
Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, MA

Daniel J. Lee MD
Department of Otolaryngology and Laryngology, Harvard Medical School, Boston, MA

Joseph B. Nadol, Jr. MD
Eaton Peabody Laboratory, Massachusetts Eye and Ear Infirmary, Boston, MA

Corresponding author:
Joseph B. Nadol, Jr., M.D.
Department of Otolaryngology, Massachusetts Eye and Ear Infirmary
243 Charles St., Boston, MA 02114
Phone: 617-573-3652 Email: joseph_nadol@meei.harvard.edu

Abstract
Non-neoplastic lesions of the temporal bone represent a highly heterogeneous group of disease entities that involve every region of the temporal bone. Patients can present with a variety of symptoms that include otorrhea, otalgia, aural fullness, hearing loss, tinnitus, and dizziness. Causes range from genetic defects or trauma to neurologic, vascular and autoimmune disease. In some cases, the pathology can extend beyond the temporal bone or is associated with an underlying systemic disorder. A comprehensive multidisciplinary approach involving otolaryngology, audiology, radiology, neurology, infectious disease or rheumatology is often necessary for these complex patients. Advances in molecular diagnostics, radiology and therapeutic regimens have led to significant progress in our knowledge of these conditions. The aim of this article is to provide an update on the evaluation and management of selected non-neoplastic lesions of the temporal bone, with a particular emphasis on cellular and molecular mechanisms and novel therapeutics.

Keywords
benign; temporal bone; lesion

INFECTIONS

Lyme disease
Lyme disease is a zoonosis caused by Borrelia burgdorferi (carried by Ixodes ricinus) and is endemic in certain areas in the United States and Europe. The nervous system, including cranial nerves are affected in 15% of the patients and otolaryngological manifestations with hearing loss, otalgia and dizziness, have been described in up to 75% of the patients. The hearing loss is sensorineural and can be unilateral or bilateral and involves low and high frequencies equally. Diagnostics for Lyme disease include MRI and serological testing for Borrelia antibodies in blood and CSF (IgG and IgM). However, serology is often falsely negative, and some patients with neuroborreliosis have no measurable CSF antibody titer. In addition, no significant difference in characteristics of hearing loss or in recovery has been found in seropositive versus seronegative patients. Some studies report complete recovery, others no recovery of hearing loss in treated seropositive patients. Therefore, it is still difficult to demonstrate a causal relationship between sudden sensorineural deafness and Lyme disease. Nevertheless, two recent case reports describe isolated unilateral or symmetric bilateral hearing loss as the only neurologic symptom of neuroborreliosis.

TRAUMA

Noise induced hearing loss (NIHL)
NIHL is caused by either a one-time exposure to very loud noise or chronic exposure to loud sounds. Increased
production of a superoxide radical anion and nitric oxide (NO) in combination with deficient antioxidant defense may play a role in NIHL. Animal studies have shown progressive hearing loss following a single exposure to noise (independent of age-related effects), with both loss of hair cells and degeneration of primary neurons. More recent studies have demonstrated that hair cells are not damaged in temporary NIHL with full threshold recovery, but neurons are severely affected. Synapses between hair cells and neurons are permanently lost within the first 24 hours of noise exposure, and neuronal cell bodies subsequently degenerate over the course of months to years (Fig. 1). This indicates that even apparently reversible noise damage has long-term consequences on hearing, and might contribute to hearing difficulties in noisy environments, tinnitus and hyperacusis. Several drugs are currently being tested, mainly in animal models, to determine their protective or therapeutic effects on NIHL. Alpha-tocopherol, idebenone, co-enzyme Q10, N-acetylcystein (NAC) and ferulic acid have shown benefit as antioxidants in preventing cell death after noise exposure. Current human clinical trials are currently under way for NAC treatment after NIHL but have not yet yielded consistent results.

**VASCULAR DISORDERS**

**Susac’s syndrome (SS)**

Susac’s syndrome was first described in 1979 as “microangiopathy of the brain and the retina” and presents with hearing loss, encephalopathy and branch retinal artery occlusion (BRAO). Diagnosis can be delayed, as sometimes not all symptoms are present at the same time. The pathology suggests an autoimmune process that affects the endothelium and leads to microischemia and infarction. Its immunopathogenesis is similar to that of dermatomyositis and is seen more often in women than men. The onset and progression of hearing loss is variable. It usually presents as a high frequency sensorineural hearing loss with poor word recognition, and the onset can be abrupt. In addition, it can affect both ears and is frequently associated with tinnitus and vertigo. In diagnosing SS, MRI is the most helpful tool, showing central involvement similar to multiple sclerosis, affecting the corpus callosum and sometimes deep gray matter and leptomeninges, in addition to enhancement of cranial nerves. Retinal artery occlusion can occur in one eye or both and is usually diagnosed by fundus examination or fluorescein...
angioarchitecture. To date, no controlled studies or clinical trials are available for SS treatment and therapy is empirical. Immunosuppressive management similar to that for dermatomyositis has shown promising results. Nearly all patients treated received corticosteroids and reported improvement. In some cases, cyclophosphamide, plasmapheresis or mycophenolate mofetil were used, but varied in their success. Newer alternatives include intravenous immunoglobulins, which demonstrated hearing improvement in many patients, or treatment with rituximab (monoclonal antibody to CD20+ B-cells) and infliximab (monoclonal antibody to tumor necrosis factor (TNF) alpha). However, to date, the number of case studies is very low.

**DISORDERS OF THE IMMUNE SYSTEM**

**Autoimmune inner ear disease (AIED)**

AIED is an uncommon condition of the inner ear that is characterized by unilateral or bilateral fluctuating or progressive hearing loss. AIED is often limited to the cochlea but can be seen as a manifestation in a variety of other autoimmune diseases such as ankylosing spondylitis, Cogan’s disease, ulcerative colitis, Wegener’s granulomatosis, systemic lupus erythematosus (SLE), Sjögren’s syndrome, or rheumatoid arthritis. Possible theories on the pathogenesis of AIED include the action of cytokines in the cochlea or cross reaction with common antigens leading to T-cell response and inner ear damage.

Diagnosis can be made based on clinical presentation and audiometry. Screening for the 68 kD cochlear antigen is no longer considered useful due to its low sensitivity and specificity. ABR testing and/or MRI with contrast should be performed to exclude retrocochlear pathology. AIED is generally responsive to systemic steroids. Intratympanic steroids can be used for those patients who cannot tolerate oral steroids, but is not a viable long-term treatment option. Cyclophosphamide and Etaenercept (tumor necrosis factor (TNF) inhibitor) are two reasonable approaches for long-term immunosuppression.

Methotrexate has not been associated with favorable outcomes. AIED patients who develop profound hearing loss may benefit from cochlear implants.

**UNKEN**

**Superior canal dehiscence syndrome**

Superior canal dehiscence syndrome (SCDS) was first described in 1998 and is due to absence of bone over the superior semicircular canal (Fig. 2). Symptoms include an apparent conductive hearing loss, vertigo induced by sound or pressure, aural fullness and autophony. The etiology of SCDS is unknown, but it has been hypothesized that a second event (e.g. straining, exercise or head trauma) results in the disruption of developmentally thin or absent bone (first event) overlying the arcuate eminence. Many cases have a low-lying and dehiscent tegmen found intraoperatively. Middle fossa craniotomy with superior canal plugging is the most common approach used in patients with intractable dizziness and auditory symptoms. Alternatively, a new study from our institution has described a series of adult and pediatric patients with bony defects in the postero-medial limb of the superior canal in association with the superior petrosal sinus (SPS). A transmastoid approach may be a reasonable option for these SPS-associated SCDS patients given the location of the defect, and our study was the first to report a pediatric case of SCD repair in a 15 year old patient with chronic dizziness.

**NEURAL DISORDERS**

**Auditory Neuropathy**

Auditory neuropathy (AN) may be defined as dysfunction of the cochlear nerve with normal outer hair cell activity. Patients often present with speech perception scores that are much poorer than would be predicted by threshold audiometry. The hearing loss can vary widely, with no predominant pattern. The otoacoustic emissions (OAE) and cochlear microphonics (CM) are present (indicating normal cochlear function) but auditory brainstem responses (ABR) are abnormal or absent (as are the acoustic reflexes). Imaging is essential to rule out a retrocochlear lesion or inner ear malformation. The site of the lesion in AN may be the synapse between the inner hair cell and dendrite and/or within the spiral ganglion cells. Ototoxic drugs, prematurity, perinatal asphyxia, family history and consanguinity are known risk factors for AN. Recent studies have associated AN with mutations in the AN gene. AN is seen in hereditary neuropathies such as Friedreich ataxia, Charcot-Marie-Tooth syndrome or Refsum disease, and can also be found in Waardenburg syndrome, or Harding and Gaucher disease. Initial management includes amplification and speech therapy, and in some carefully selected AN patients with poor word recognition scores, cochlear implant surgery can be considered. Some benefit after CI has been demonstrated in these patients, although less than in other CI patients.

**INTOXICATION**

**Aminoglycosides**

Aminoglycosides (e.g. gentamycin, kanamycin and streptomycin) are bactericidal antibiotics that have been in use since the 1940s. Incidence of ototoxicity in patients after aminoglycoside administration is dose-dependent and ranges from 2-45% after aminoglycoside
intake for 4 consecutive days. Patients generally present with bilateral high frequency hearing loss, that can be accompanied by peripheral vestibular hypofunction. Susceptibility to aminoglycosides is increased by certain mitochondrial mutations (e.g. DNA 1555A>D). Recent studies investigated the molecular mechanisms involved in aminoglycoside toxicity and showed that production of free radicals activates c-jun N-terminal kinase (JNK) inducing apoptosis. Heat-shock proteins (Hsp) may play a protective role in aminoglycoside toxicity. New animal models will help to better understand the molecular mechanisms of aminoglycoside induced hearing loss.

Cisplatin

Hearing loss is a known side effect of chemotherapy with cisplatin. The hearing loss is usually bilateral, permanent, and dose dependent; at high doses (200-400mg/m2), 50-100% of the patients show a variable degree of hearing loss. High frequencies are affected first, followed by middle frequencies, and the hearing loss can occur and progress even months after cessation of cisplatin administration. Risk factors for hearing loss include young age, high number of cycles and/or cumulative dose, and concomitant radiotherapy. Cisplatin activates NADPH oxidase (NOX) 3 and transient receptor potential vanilloid (TRPV)1 in hair cells, which leads to production of free oxygen radicals and activation of apoptosis. Studies have shown otoprotective effect using N-acetyl-cystein (NAC) or brain-derived neurotrophic factor (BDNF) in animal models exposed to cisplatin. Aside from small studies using intratympanic steroids in mice, no protective agent for clinical use has been described.
BONE

Otosclerosis

Otosclerosis is a progressive disease of the otic capsule characterized by abnormal bone remodeling. Common sites for otosclerosis are the areas anterior to the oval window, the round window niche, as well as the medial and apical cochlear walls. Cochlear otosclerosis, located within the otic capsule and leads to sensorineural hearing loss (SNHL). Studies have shown evidence for autosomal-dominant inheritance with incomplete penetrance in about 40%, and to date, 10 loci (OTSC 1-10) have been described. The variable phenotype of otosclerosis also suggests environmental influence, and otosclerosis has been linked to measles, endocrine factors such as estrogen, connective tissue disorders and disorders of the immune system. New research has revealed altered expression of osteoprotegerin (OPG) and bone morphogenetic protein receptors (BMPRs), both of which may play a role in otic capsule remodeling.

High resolution CT imaging can help assess the size and extent of otosclerotic foci in selected cases. Recent radiologic classifications may be useful in preoperative decision making. Therapeutic options include amplification or surgical intervention (stapedectomy/stapedotomy). Bisphosphonates have been proposed for treatment of otosclerosis, but while some cases report success, several other case reports have shown additional hearing loss associated with bisphosphonates. In addition, cochlear implants have been used with good results for sensorineural hearing loss in cochlear otosclerosis. The most recent development of semi-implantable and fully implantable middle ear implants provide another alternative in patients where hearing aids are not tolerated, or where previous ossiculoplasty surgery has been unsuccessful.

References


57. Guthrie ONW. Aminoglycoside induced ototoxicity. Toxicology 2008; 249:91-96.


Otitis Media with Effusion

Matthew Rollin FRCS (ORL-H&N)
Professor A. A. Narula MA, FRCS
Department of Otolaryngology/Head & Neck Surgery
St Mary’s Hospital, London

Otitis media with effusion (OME) is chronic inflammation of the middle-ear mucosa, associated with accumulation of mucus in the middle-ear space and (potentially) mastoid cells, without signs of infection. OME usually presents with hearing loss, typically following a preceding upper respiratory illness with or without otalgia. The usual definition of “chronic” in this context is twelve weeks.

The common term is “glue ear”, and several outdated medical terms (including secretory otitis media, serous otitis media and chronic nonpurulent otitis media) have fallen from use owing to ambiguity over their precise meanings. Recovered middle-ear fluid shows a full spectrum of viscosity, from serous to mucoid, dependent on mucin content.

Aetiology

The nasal cavity and Eustachian tube are lined by respiratory-type ciliated mucus-producing epithelium, which gives way in the anterior middle-ear cavity to the flat cuboidal mucosa lining the remainder of the middle-ear and mastoid cavities. Chronic mucosal inflammation leads to disorganised de-differentiation into thickened pseudostratified epithelium, and the inefficiency of this de-ciliated disorganised type, plus submucosal inflammation, results in the retention of secretions in the middle-ear space.

In the standard theory of pathogenesis, initial mucosal damage comes from a viral upper respiratory tract infection. Bacteria may then secondarily-infect stagnant secretions, leading to acute otitis media.

The incidence of pathogens isolated from middle-ear fluid is greater in younger children, and in those suffering from frequent infections. S.pneumoniae and B.catarrhalis are the two most commonly-isolated organisms; but a negative culture is much more common still, and no study has ever reported isolating pathogens from an effusion present for six months or more.

Other proposed theories of pathogenesis, including allergy and cigarette-smoke irritation, have not been convincingly shown to be important. Centres differ in their reported incidence of allergy in OME patients, but it has been independently shown not to be a risk factor either in younger (less than two years) or older children.

Pharyngeal acid reflux been widely demonstrated radiographically in children, and pepsin has been discovered in up to 80% of middle-ear effusions, but causation is debated.

Epidemiology

There is a bimodal age-distribution, with peak prevalence (approximately 20%) at two years of age, and a secondary peak (approximately 16%) at roughly five years of age. It is worth noting that the first is approximately the age when most children first attend nursery, and the second approximates to the age when most children start primary school; although one other study has placed the first peak of incidence nearer one year of age.

These peaks of prevalence, and their association with bursts of new social interaction, lend credence to the theory that viral infection is the initial factor causing damage to the upper respiratory mucosa. Furthermore, in temperate climes, there is a strong association between prevalence of childhood OME and seasons, with approximately twice as many diagnoses in winter as compared to summer.
Risk factors

Identification of risk factors has been complicated by the lack of a standardised diagnostic test; however, in multivariate analyses, risk factors for development of OME in children under three years of age were\textsuperscript{21}:

\begin{tabular}{|l|l|}
\hline
Factor & Odds ratio \\
\hline
History of acute otitis media & 1.7 \\
Age & 1.0 per month \\
Number of older siblings & 1.6 per sibling \\
Family history of OME & 1.4 \\
\hline
\end{tabular}

Other multivariate analyses have suggested a doubling of risk from nursery or day-care attendance with four or more other children under 3.5 years of age\textsuperscript{8,22}. A twin study\textsuperscript{23} showed significantly greater concordance in episodes of OME during the first two years of life for monozygotic over dizygotic twins.

Race and sex have not been shown to be significant risk factors. Studies disagree on whether or not cigarette smoke is a significant risk factor for development of OME, but maternal smoking has been shown to be a risk factor for persistence of existing childhood OME\textsuperscript{22,24}.

Duration and resolution of OME

One large study found a skewed distribution of duration of OME episodes in young children, with the median at 3 months, but the 95th centile at 12 months\textsuperscript{25}. In this cohort, half the affected ears had resolved after three months, but half of these suffered a further episode of OME. A further study reported that those young children suffering most with OME do so in the form of a series of short episodes, rather than fewer long episodes\textsuperscript{26}.

A similar pattern is seen in older children, with a small but significant percentage of episodes proving persistent. One study in children between five and eight reported 91% resolution at 12 months\textsuperscript{27}. Another study of 7-year-old children reported 88% resolution at 6 months. In this study, episodes of OME diagnosed in autumn/winter (September to February) lasted longer than those diagnosed in spring/summer (March to August).

Three studies looking at risk factors for persistence of OME episodes\textsuperscript{10,12,13} collectively identified:

- presence of URTI
- significant hearing loss
- maternal smoking
- autumn/winter diagnosis.

Diagnosis

Although there is no formally-standardised diagnostic test, secondary-care diagnosis will typically involve otoscopy, pneumatic otoscopy, tympanometry and pure-tone audiometry.

In primary care, diagnostic options are more limited. Parental report of a child’s hearing ability has been shown to be a surprisingly poor discriminator\textsuperscript{28,29}; however, parental report of hearing loss in association with frequent URTI, snoring and mouth-breathing does make a diagnosis of OME more likely\textsuperscript{16}. Primary-care diagnosis, therefore, rests on history and otoscopy, plus additional modalities where available. It must be tirelessly stressed that all children in whom there is a suspicion of hearing loss should undergo formalised evaluation, in order to exclude sensorineural loss.

Common-sense would suggest that a schoolteacher, who has the ability to compare many children of a similar age, would be a more effective judge of an individual’s hearing ability; however, this has not been formally examined.

Natural outcomes of OME in childhood

The MRC-funded multi-centre TARGET study (Trial of Alternative Regimens in Glue Ear Treatment) examined 3831 children aged between three and seven years. The diagnostic standard was set at 20dB hearing loss bilaterally, in the presence of bilateral effusions, and 34% of GP referrals met these criteria.

These symptoms persisted beyond an initial twelve-week wait in 51% of cases, and these children were then randomised to various treatment pathways. Half of those assigned to further waiting (“non-specific medical management” in the study) had effusions which persisted beyond another twelve weeks. This equates to approximately 25% of those diagnosed with OME, or alternatively to 8.5% of all GP referrals with concern over hearing loss\textsuperscript{10,12,13}.

The key question is therefore not whether or not effusions will ultimately resolve in the majority of cases, but rather what harm may be caused by the child’s hearing loss in the meantime.

Hearing loss

Levels of hearing loss in bilateral OME vary between effusions and children. One study of 385 children aged 2-11 years showed mean thresholds in the better-hearing ear of 21dB (standard deviation 10), and in the poorer-hearing ear, 31dB (sd 13)\textsuperscript{30}. Another investigation found that viscosity of recovered middle-ear fluid bore no correlation to severity of hearing loss\textsuperscript{31}.
However, pure-tone audiograms are by definition performed under ideal conditions. They provide accurate measurements of the thresholds of hearing, but are only useful as far as they can predict “real-world” hearing disability.

The MRC’s Reported Hearing Disability questionnaire contains nine questions answerable by adults in close contact with a child, four of which have been shown to predict hearing disability:

<table>
<thead>
<tr>
<th>Question</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>How would you describe your child’s hearing?</td>
<td>normal, slightly below normal, poor, very poor, not sure</td>
</tr>
<tr>
<td>Has he/she misheard words when not looking at you?</td>
<td>no, rarely, often, always, not sure</td>
</tr>
<tr>
<td>Has he/she had difficulty hearing when with a group of people?</td>
<td>no, rarely, often, always, not sure</td>
</tr>
<tr>
<td>Has he/she asked for things to be repeated?</td>
<td>no, rarely, often, always, not sure</td>
</tr>
</tbody>
</table>

Evidence exists that there are long-term sequelae from effusions - or possibly from the infections and inflammatory response that precipitate them. In one cohort followed-up until the age of 18, those suffering recurrent otitis media (without differentiation between AOM and OME) had a mean air-conduction hearing deficit of 4dB, and a mean bone-conduction deficit of 2dB, compared to unaffected individuals.

Language and intellectual development

Language-development is complex and incompletely-understood, and therefore standard assessments use comparison against standardised milestones within acceptable time-frames. On this basis, prospective studies and meta-analyses have suggested that:

• OME does have a deleterious impact on language development
• there is a correlation between number of days in early childhood spent with bilateral effusions, and adverse impact on speech production and language development
• such children have largely caught up with their unaffected peer-group in terms of spoken language, by the age of eight years.

It has not been determined how much this “catch-up” effect relies on extra effort from parents and input from specialist therapeutic services, or whether it is a spontaneous phenomenon. In contrast to the above, however, the subtler effects of this mild delay in development appear to be much more persistent.

The effect of OME on cognition and intellectual development is clearly harder to determine and quantify, and most investigations have studied early development. Cohort studies have suggested that the effects of OME are concentrated during a child’s early intellectual development – typically, three to four years of age – and that mitigation occurs by the age of eight, when observation ceased.

However, evidence exists from a long-term birth-cohort study suggesting that OME-related deficit in IQ testing scores remains significant as far as 13 years of age, and that OME-related deficit in reading ability remains significant as far as 18 years, with cases of persistent bilateral OME in childhood showing a two-year delay in mean reading scores, compared to unaffected peers. Further evidence from this cohort suggests that diagnosis and treatment at five years of age comes too late to prevent such effects on language development and reading ability.

Two questionnaires are commonly used to quantify a child’s behaviour: the MRC Behaviour Questionnaire and the Rutter score. In one study, 55% of three-year-olds with bilateral persistent OME had abnormal Rutter scores, compared to 10-15% of unaffected three-year-olds. In another study, children aged 3-7 years with persistent OME and a bilateral hearing loss of 20dB showed significantly poorer behaviour scores than their unaffected peer-group.

Children with OME suffer significantly more clumsiness and balance problems than the general child population, both on parental report and formalised assessment. It is possible that this phenomenon represents an effect of inflammation surrounding middle-ear structures, but no formal investigation has been made.

Management of OME

1. Hearing tactics can be used for less-severely-affected children:

<table>
<thead>
<tr>
<th>Hearing tactics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Get the child’s attention before starting to talk</td>
</tr>
<tr>
<td>Reduce background noise as much as possible</td>
</tr>
<tr>
<td>Face the child directly, so that they can see you speaking</td>
</tr>
<tr>
<td>Speak in a normal voice, as close to the child as possible</td>
</tr>
<tr>
<td>Avoid unusual volume, speed or emphasis</td>
</tr>
</tbody>
</table>
These tactics may be of great benefit in mild hearing loss, but how successful they would be when the affected child is the youngest of three – or indeed, in a class of twenty – is less clear.

2. No medical therapy has been adequately shown to be beneficial, including local steroids, systemic steroids, mucolytics, antibiotics and decongestants. Most of these investigations followed their subjects up for one or two weeks, before drawing conclusions.

3. Autoinflation of the middle-ear can be helpful, but the procedure is not simple to perform, relies heavily on compliance, and is not really practical in young children.

4. In surgical management, myringotomy and aspiration without placement of a ventilation tube (VT) was shown to be ineffective in a 1992 systematic review of three trials. VTs designed for long-term placement are associated with higher complication rates, therefore short-term designs are recommended for use in children. Several studies have investigated the natural history of VTs. Typical findings are that at six-month follow-up, 55% of short-term VTs are functioning, and 30 to 55% have extruded. Analyses of surgical techniques have brought the recommendation that VTs are placed in the antero-inferior tympanic membrane, via a radial or circumferential incision.

**Outcomes of interventions for OME**

Children undergoing VT placement (without adenoectomy) spend on average 32% less time with effusions in the year following the procedure. A point study, using otoscopy nine months after VT insertion, reported 46% less OME in treated children than controls.

VTs have been shown to improve hearing thresholds by approximately 10dB at six-month follow-up, after which the benefit over untreated children diminishes, possibly as the effusions in untreated children resolve, and VTs extrude. In the TARGET trial, VTs conferred an improvement in hearing thresholds over non-surgically-managed cases, of 12dB on average. Thresholds in the “non-surgically-treated” group improved over time – however about half of parents in this group opted into surgical management after randomisation. Differences between the two groups were negligible after 12 months’ follow-up, fitting with the consensus of several studies and meta-analyses.

Although this benefit (as measured by pure-tones) may seem modest, the effects are certainly measurable. In one study of children with bilateral OME, 25dB hearing loss and “disruptions to speech, language, learning or behaviour”, participants were randomised, aged 3, to immediate or delayed surgical intervention. At 9-month follow-up, the non-surgical cohort were on average 3.2 months behind in their objective speech and language development.

TARGET compared VTs against VTs plus adjuvant adenoectomy. This further procedure conferred no additional benefit after 3 or 6 months of follow-up; however after both 12 and 24 months of follow-up, when the benefit of VTs alone had diminished, adenoectomy provided an additional 4.2dB of hearing benefit, and significantly reduced the requirement for revision surgery.

TARGET also included the MRC Reported Hearing Disability questionnaire. On this measure, the difference between VTs and non-surgical management was “large, even when adjusted for the expectation effect of surgery”. Over a two-year monitoring period, the reduction in hearing disability was “modest”. This latter finding is expected, as the efficacy of VT placement is naturally skewed towards the early post-operative period. Parental report of children’s hearing ability showed continued benefit of VTs into the second year of observation, even when there was no further benefit as measured by pure-tone thresholds.

These findings are of interest: even though the absolute improvement in hearing thresholds is modest by the standards of adult audiology, it appears sufficient to produce a major improvement in hearing disability scores. Possibly this dichotomy is a function of pure-tone audiometry not representing a particularly “real-world” measure of a child’s hearing ability and language development; or possibly a 10-12dB hearing improvement has a more significant impact at this age than a similar improvement would do at 18 years of age, when patterns of language reception and production are firmly established.

It is an accepted principle that children with early language delay are at risk for later low intelligence scores, poor reading attainment and behavioural difficulties. The available evidence suggests that children suffering with OME in early childhood are disadvantaged in development, and that the disadvantages arising from under-treated OME linger well into the teens, secondary education, and the threshold of working life.
References


59. Haggard MP et al on behalf of the MRC Multicentre Otitis Media Study Group. A randomised controlled trial in otitis media with effusion [TARGET]. Effect of treatments with ventilation tubes and adenoidectomy on measured and reported hearing through 2 years. Clin Otol 2011 (pending)
Management of Children with Permanent Childhood Hearing Impairment (PCHI)

Professor Adrian Davis OBE FFPH FSS, Gwen Carr and Margaret Martin
NHS Newborn Hearing Screening Programme
Royal Free Hampstead NHS Trust & Ear Institute, UCLP

Dr Katrina Davis MB BChir MRCPsych
South London and Maudsley NHS Foundation Trust

Introduction

In the UK there are substantial problems with hearing and deafness from birth in about 800 children per year, about 1 in 1000 births. This figure increases to about 1 in every 330 babies who have spent more than 48 hours in intensive care. There are another 1 per 1000 who may have unilateral deafness and others who have more mild problems but which are nevertheless a compromise to health development. The majority of these babies are born into families with no experience or history of hearing loss. The impact of permanent childhood hearing impairment (PCHI) for these children and their families is much wider than that figure would suggest. The effects on language development, communication, family functioning, literacy, academic achievement, social and emotional well-being can be extreme.

Identification and intervention before 6 months of age can dramatically reduce these effects. Before the introduction of the NHS Newborn Hearing Screening Programme (NHSP) in 2006, services would have missed about 400 of these children by 1½ years of age, and about 200 of these children by 3½ years of age. Hearing impaired children identified late are at risk of substantial delay in their acquisition of language and communication skills, with consequent longer-term risk to educational achievement, mental health and quality of life.

The impact of hearing and communication problems for children with hearing problems or deafness depends substantially on the severity of the problem, when it occurs, the cause(s) of the problem, any comorbidities and the extent to which support is successful in dealing with the problems. The severity of hearing impairment is usually categorized by average hearing threshold (over 0.5, 1, 2 & 4kHz) in each ear. There are several ways of categorising this average and it is suggested to use as a guide 20-34dB HL as mild, 35-49 dB HL as moderate, 50-64 as moderately severe, 65-79 as severe, and 80+ dB HL as profound.

Where children experience temporary hearing impairment such as otitis media with effusion (OME or ‘glue ear’), the individual consequences are not as severe as permanent childhood hearing impairment (PCHI). Greater numbers of children with OME means that it impacts on the capacity needed in paediatric hearing services. For the rest of this chapter we concentrate on PCHI.

Epidemiology

Prevalence of PCHI

One of the largest studies aiming at a calculation of prevalence of PCHI across the UK was carried out by Fortnum and colleagues in 1998 (prior to the Newborn Hearing Screening Programme). Observed prevalence of PCHI increased with age until reaching a plateau at age 9, and that this was present at all studied severities: moderate, severe and profound. The adjusted prevalence of PCHI of moderate and greater severity at age 3 was around 1.1 per 1,000, rising to 2.1 per 1,000 at aged 9-16 – a rise of 92%. The reasons for the increased prevalence at older ages are multiple, including acquired injury, post-natal presentation, delayed confirmation of impairment.

Results from universal newborn hearing screening (UNHS) studies, pilots and programmes around the world provide a ‘yield’ of hearing impairment detected per 1,000 babies screened. We have reviewed 95 sets of published data, of which we were able to extract 83 unique sets of results, including 13.6 million screening episodes and about 17,700 cases of hearing impairment (as defined by individual studies). This gives a very rough yield of 1.3 cases of PCHI per 1,000 babies screened.

Results from the 21 pilot sites for the NHSP in England showed a rate of 1.00 (95% confidence interval 0.78-1.22) per 1,000 babies screened having a congenital hearing impairment, and another 0.69 per 1,000 had a unilateral
imPAIRMENT. THIS ADDS UP TO A YIELD OF 1.69 CASES WITH PCHI PER 1,000 SCREENED.

WATKIN AND COLLEAGUES IN THE EAST LONDON BOROUGH OF WALTHAM FOREST FOLLOWED A COHORT THAT HAD BEEN SCREENED BETWEEN 1992 AND 2000. NEWBORN SCREENING IDENTIFIED 1.58 CHILDREN WITH BILATERAL PCHI PER 1,000 LIVE BIRTHS; A FURTHER 0.24 PRIOR TO 12 MONTHS OF AGE; 1.30 BETWEEN AGE 1 AND 5 YEARS OLD; AND 0.34 BY THE SCHOOL-ENTRY SCREEN. THIS GIVES A COMBINED TOTAL PREVALENCE OF 3.47 PER 1,000 CHILDREN BY PRIMARY SCHOOL AGE IDENTIFIED AS HAVING PCHI, OF WHICH 1.89 (54%) WAS NOT DETECTED AT BIRTH. THIS INCREASE CAME PARTLY FROM PEOPLE MOVING INTO THE AREA, BUT ALSO FROM CHILDREN WHO HADN’T BEEN OFFERED, DECLINED OR FAILED TO COMPLETE THE SCREENING PROCESS; AND 10% HAD A HISTORY OF MENINGITIS. THEY CALCULATE THAT THE SENSITIVITY OF THE UNIVERSAL NEWBORN HEARING PROGRAMME (TAKING INTO ACCOUNT COVERAGE, FOLLOW-UP AND FALSE NEGATIVES) WAS 83% FOR MODERATE AND GREATER BILATERAL HEARING IMPAIRMENT, 69% FOR UNILATERAL AND 46% FOR MILD BILATERAL HEARING IMPAIRMENT.

CHILDREN WITH PCHI DIFFER FROM THE HEARING POPULATION IN THE UK BY BEING SIGNIFICANTLY MORE LIKELY TO HAVE A VISUAL IMPAIRMENT, PROBLEMS WITH GROSS AND FINE MOTOR SKILLS AND LEARNING DISABILITY, 17% HAVING ONE OTHER DISABILITY, AND A FURTHER 18% HAVING MORE. THOSE WITH ANOTHER DISABILITY TEND TO HAVE WORSE OUTCOMES ON A WIDE RANGE OF INDICES. NINETY PERCENT OF HEARING IMPAIRED CHILDREN HAVE PARENTS WHO DO NOT HAVE HEARING IMPAIRMENTS THEMSELVES, AND THESE ARE MORE LIKELY TO RECEIVE A COCHLEAR IMPLANT.

AETIOLOGY

THE AETIOLOGY OF PCHI IS DIVIDED INTO CONGENITAL AND POSTNATAL. THE SPLIT BETWEEN THESE PRESENTATIONS IS PROBABLY ABOUT 90:10 BY SCHOOL AGE IN THE UK, BUT THE PROPORTION ACQUIRED POSTNATALLY APPEARS TO RISE IN DEVELOPING COUNTRIES. IN MODERN PRACTICE, IT IS STILL FAIRLY COMMON TO NOT FIND AN OBVIOUS AETIOLOGY FOR PCHI. IN THE WALTHAM FOREST 1992-2000 COHORT, 34% HAD NO OBVIOUS CAUSE.

CONGENITAL

THE IDENTIFICATION OF SOME RISK FACTORS HAVE COME FROM UNDERSTANDING THE AETIOLOGY OF PCHI; CONVERSELY THE AETIOLOGY HAS SOMETIMES BEEN WORKED OUT AFTER OBSERVATIONAL STUDIES SHOWED SOMETHING AS A RISK FACTOR. E.G. JOINT COMMITTEE ON INFANT HEARING. THESE INCLUDE FAMILY HISTORY, IN UTERO INFECTIONS, SUCH AS CMV, HERPES, RUBELLA, SYphilIS, AND TOXOPLASMOSIS, NICU FACTORS, CRANIOFACIAL ANOMALIES AND ABNORMALITIES AND SYNDROMIC PRESENTATION.

GENETIC

IT IS THOUGHT THAT AT LEAST HALF OF ALL CASES OF PCHI HAVE A GENETIC CAUSE. DESPITE SIGNIFICANT ADVANCES IN THE UNDERSTANDING OF THE MOLECULAR BASIS OF HEARING LOSS, IDENTIFYING THE PRECISE GENETIC CAUSE IN AN INDIVIDUAL REMAINS DIFFICULT.

PRE-NATAL

THE DELICATE NEURAL ELEMENTS OF THE INNER EAR DEVELOP AROUND 6 TO 7 WEEKS POST-CONCEPTION, SO THAT ANY DISRUPTION IN THIS PERIOD HAS INCREASED POTENTIAL TO CAUSE ACQUIRED SENSORINEURAL HEARING LOSS. THIS IS THOUGHT TO OCCUR MOST OFTEN THROUGH A TORCH INFECTION. CONGENITAL RUBELLA SYNDROME (CRS), THE SINGLE MOST COMMON REPORTED CAUSE OF PCHI IN EUROPE IN THE 1970S AND 80S, IS NOW VIRTUALLY ABOLISHED IN DEVELOPED COUNTRIES. CONGENITAL CYTOMEGALOVIRUS (CMV) DOES SEEM TO BE A CAUSE PCHI, BUT THE ONSET AND SEVERITY OF THE IMPAIRMENT IS SO VARIABLE THAT THE BURDEN OF DISEASE IS NOT KNOWN.

PERINATAL

THE PILOT UK NEWBORN HEARING SCREENING DATA SHOWED THAT AROUND 40% OF CHILDREN DIAGNOSED WITH PCHI HAD A HISTORY OF ADMISSION TO A NEONATAL INTENSIVE CARE UNIT (NICU) FOR MORE THAN 48 HOURS. GIVEN THAT AROUND 5% OF BABIES HAD BEEN SCREENED IN THE NICU, THIS SUGGESTS A PREVALENCE OF AROUND 8 PER 1,000, WHICH IS MANY TIMES HIGHER THAN THOSE WHO DID NOT REQUIRE NICU.

POST NATAL

IT IS POSSIBLE FOR THE CAUSE OF ACQUIRED PCHI TO BE GENETIC, BUT MOST ACQUIRED CASES ARE PROBABLY CAUSED POST-NATALLY BY ILLNESS (PRIMARILY INFECTION), OTOTOXIC AGENTS OR TRAUMA.

BACTERIAL MENINGITIS IS THE MOST COMMON CAUSE OF ACQUIRED HEARING IMPAIRMENT AMONGST CHILDREN. LOSS RESULTS FROM DIRECT DAMAGE TO THE COCHLEA BY THE INFECTION, BUT IT MAY BE EXACERBATED BY ADDITIONAL COCHLEAR DAMAGE RESULTING FROM ANY OTOTOXIC DRUGS USED TO TREAT THE DISEASE.

CHILDREN MAY BE GIVEN A NUMBER OF OTOTOXIC TREATMENTS, INCLUDING AMINOGlycosIDE ANtiBiOTICS. THEY CAUSE DOSE-RELATED RENAL TOXICITY AND OTOTOXICITY IN ALMOST EVERYONE WHO RECEIVES A SUITABLY HIGH DOSE, BUT SOME PEOPLE HAVE AN INHERITED PREDISPOSITION THAT MEANS THAT EVEN A SINGLE DOSE COULD RESULT IN PERMANENT HEARING LOSS.

VARIATION

THE AETIOLOGY OF PCHI HAS BEEN CHANGING IN THE DEVELOPED WORLD OVER THE LAST FEW DECADES, WITH FEWER PRENATAL AND POSTNATAL INFECTIOUS CAUSES, AND AN INCREASING PROPORTION ATTRIBUTED TO PERINATAL PROBLEMS AND GENETIC CAUSES.

A RECENT STUDY BY KORVER AND COLLEAGUES HAS CHALLENGED THE VIEW THAT “THE CAUSES OF PERMANENT CHILDHOOD HEARING IMPAIRMENT (PCHI) ARE OFTEN QUOTED AS BEING...”
hereditary in 50%, acquired in 25%, and unknown in 25% of cases.” In the study-population (n = 185) a hereditary cause was found in 38.9%, acquired cause in 29.7%, miscellaneous cause in 7.1%, and the cause remained unknown in 24.3%. The systematic review of the literature (n = 9 articles) resulted in a weighted mean of 30.4% hereditary, 19.2% acquired, and 48.3% unknown causes of PCHI15.

There needs to be a greater emphasis on collecting routine data on the prevalence and aetiology of PCHI; data from newborn hearing screening provides a unique opportunity to better inform public health policy for hearing screening.

The NHS Newborn Hearing Screening Programme

The first step in quality, safe and sustainable service is early access to those services. This is ensured in England by NHSP and by later case finding within that programme stemming from parental and professional concern. Current statistics for NHSP16 show that for babies born up to March 2011:

- 4,259,705 baby records are recorded on the screening management system (eSP) since the programme started its country wide roll out (2006)
- 4,254,922 screens have been offered (99.9% of babies born)
- 12,786,342 screening tests have been carried out
- 7,069 (1.6%) babies have been identified through the programme with a permanent childhood hearing impairment (PCHI) of at least 40 dB HL.

Evidence base for the NHSP

The evidence base and rationale for the NHSP is described in detail in the Health Technology Assessment (HTA) review “A critical review of the role of newborn hearing screening in the detection of congenital hearing impairment17.

Several more recent studies have shown that early identification of children with PCHI have improved language development18,19. A study by Korver and colleagues confirmed that newborn hearing screening improved the quality of life in children aged 3-5 years of age among children with PCHI20. A systematic review by Wolff and colleagues found that “screening versus no screening showed an improvement of speech development of children in the screening group compared with the group without screening. Early treatment was associated with better language development in comparison to children with later treatment21.” There is a need for high-quality studies evaluating the value of screening and support.

NHSP Care Pathways

Post identification, getting the right children in the right pathway at the right time, is critical. The NHS Newborn Hearing Screening Programme has helped develop three standard care pathways as well as the screening pathways22:
- Newborn hearing screening pathway
- Early audiological assessment
- Cochlear implant (paediatric)

PCHI involves complex health and family support issues, multiple human interaction variables for staff, children, parents and multi-agency services. The NHSP pathways set out the multi-disciplinary “route” for each condition, from initial assessment to interventions such as hearing aids and cochlear implants. These are available via the Map of Medicine23 a visual representation of evidence-based, practice-informed care pathways for common and important conditions.

NHSP Quality standards and assurance

The NHSP has a comprehensive quality assurance framework for both the screening and the follow-up by multi-disciplinary services which covers the whole care pathway, including commissioning, governance, family friendly practice and quality improvement culture.

The 28 NHSP Quality Standards24 are actively monitored25 and peer reviewed which has highlighted the need for quality improvement and in particular around the need to strengthen multi disciplinary working and paediatric audiological assessments.

Major influences on outcomes of children with PCHI

The major support for children with permanent childhood hearing impairment comes firstly through their families and others who have major contact time with the children. Hearing healthcare, habilitation, education, social and other, e.g. volunteer family to family support, might be considered as the second major influence on children’s outcomes.

Early identification alone will not necessarily lead to better outcomes for these children and their families, better support for parents and families, enabling them to
make the choices that they have to make for their children. As Young and colleagues point out: “the effectiveness of early intervention depends to a very great extent on its reception by families (not its provision)26.”

The importance of multidisciplinary team working

For this to happen there has to be a clear specification of the multi-disciplinary services to be provided from a wide range of professions and agencies.

Collaboration with ENT is critical in the management of PCHI. An otologist should be a core part of the MDT and work with other medical colleagues to ensure that the appropriate assessments and interpretation are available to the team, especially at key stages in decision making for families. This is particularly true where cochlear implantation may be an option. A common occurrence for deaf children with sensorineural loss is that they are more prone to get unrecognised glue ear (OME), which can depress their hearing even further. When Teachers of the Deaf (ToDs) and parents report potential glue ear complications there needs to be a prioritisation or fast-track access to ENT for assessment and agreement of a management plan for the child and family.

Within the NHSP programme, a key catalyst for embedding these messages in practice about the importance of multidisciplinary working is the Children's Hearing Services Working Group (CHSWG). CHSWGs cover all services involved in supporting deaf children and their families. The membership is multidisciplinary27. Parents need to be regarded as full and equal partners in the team.

Focus on outcomes which matter to children and their parents

Parents, children and professionals have different views of what a quality service looks like and what leads to good outcomes. Young and colleagues write that “universal newborn hearing screening has been a considerable catalyst for focusing attention on philosophy, style, and approach in working with families.... the overarching point [is] that attention has been paid to quality of intervention in terms of how it is delivered as a marker of quality, not just what it might contain28.”

The focus on outcomes important to children and parents is central. We still need to know more about key value chain areas such as the impact of PCHI on children and families’ quality of life and the extent to which interventions add value. The emphasis in the NHSP Programme on family friendly services and on empowering parents to make informed choices throughout the whole hearing care pathway should help ensure that it is this real picture which is the driver for obtaining all the best service outcomes.

References

5. Stacey et al opus cit.


22. NHSP pathways http://hearing.screening.nhs.uk/carepathways

23. Map of Medicine NHSP Care Pathways Links at http://hearing.screening.nhs.uk/carepathways


25. NHSP Quality Assurance http://hearing.screening.nhs.uk/qualityassurance


27. For example, the Swindon CHSWG (http://www.swindonparentsandcarers.org.uk/services/chswgbout.htm Is made up of Health, Audiologist, Integrated Service Operational Manager / Professional Lead for Health Visiting, Coordinator for Newborn Hearing Screening Programme, Speech and Language Therapist: Specialist in Deafness, Consultant ENT Surgeon, Children and Families, Advisory Teachers of the Deaf, Representatives from Special Resource Provisions (Schools), Disabled Children's Team Representative (Social Services, Parent Partnership Officer, Parent representatives from across all ages 0-19, Voluntary Sector - NDCS representative, local and regional.

Evaluation and Management of Benign Paroxysmal Positional Vertigo

Charlotte Agrup MD, MSc, PhD
Department of Neuroimmunology, UCL Institute of Neurology, Queen Square, London WC1N 3BG, U.K.

Linda M. Luxon CBE BSc FRCP
Department of Neuro-otology, The National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, U.K.

Abstract
Benign paroxysmal positional vertigo (BPPV) is by far the most common peripheral vestibular pathology in the adult population. BPPV typically presents with sudden onset of brief episodes of severe vertigo, lasting for a few seconds to a minute, triggered by specific change in head position such as lying down/turning in bed, bending forward and extending the neck to look up. The diagnosis of BPPV is easily made using positional tests, such as the Dix-Hallpike manoeuvre, which induces the vertigo, accompanied by a burst of nystagmus with characteristic directional features that often allow localisation of the affected side and the semicircular canal involved. The treatment is quick and in most patients highly successful and consists of a particle repositioning-procedure. Delays in proper diagnosis and treatment are still common and lead to unnecessary prolonged suffering for the patient with additional limitations of function and often unnecessary healthcare costs (e.g. medical treatments and inappropriate referrals).

Keywords
Benign, central, positional, vertigo, nystagmus, particle repositioning procedures

Introduction
Benign paroxysmal positional vertigo (BPPV) is the most common peripheral vestibular pathology in the adult population with an incidence reported of 60 to 600 per 100,000. The incidence increase as age increases and by age 70 years, 30% of the elderly population have experienced BPPV1. It is more common in women 1.6:12 and uncommon in children, representing only around 3.6% of vertigo in the paediatric population. BPPV is in most cases idiopathic, but it is also frequently a sequel to other labyrinthine disorders, such as Menière’s disease and vestibular neuritis. BPPV is also a common complication of head injury with a reported incidence of around 60%3.

The pathophysiology of BPPV is thought to be due to debris from the otolith organs free-floating in the semicircular canal system. The high prevalence of BPPV in the elderly has been suggested to be related to release of otoconia due to “wear and tear” into the endolymph. A head trauma may, by the force of the impact, also cause release of otoconia into the endolymph, which may explain why more of these patients suffer from bilateral BPPV. BPPV can affect each of the three semicircular canals although posterior canal BPPV is the commonest (85.2%) followed by horizontal canal BPPV (13.6%) and anterior canal BPPV (1.2%)4.

The typical clinical presentation with BPPV is positional vertigo characterised by a sudden onset of brief episodes of severe vertigo, lasting for a few seconds to a minute consequent upon assuming a critical head position and, associated with a characteristic burst of nystagmus. The history and typical eye-movements for each canal appearing with positional testing are the gold standards for diagnosing BPPV.

Although BPPV is usually a self-limiting disorder, most cases resolve within six months, treatment with particle-repositioning manoeuvres (e.g the Semont and Epley manoeuvres) should always be considered5,6. BPPV affects
the quality of life, particularly in the elderly, and is associated with reduced activities of daily living, falls and depression. In an English retrospective study of 20 patients with BPPV, the average time from first referral to treatment was 93 weeks, with an average of 58 weeks within primary care and 40 weeks within hospital care. This review will discuss the typical clinical presentation of BPPV and how to make the correct diagnosis. In addition, different management techniques will be reviewed.

Pathoetiology
Two different pathophysiological mechanisms have been proposed to explain the development of BPPV, i.e. cupulolithiasis and canalolithiasis (Figure 1). It is generally thought that calcium carbonate crystals, otoconia, which are normally embedded within the gelatinous-membrane of the otolith organs, may become dislodged into the endolymph. In the canalolithiasis model, this debris is hypothesised to be free-floating in the semicircular canal. Due to the density of the debris relative to endolymph it moves in response to gravity, with the same effect as a plunger within the narrow semicircular canal, causing endolymph movement and thus movement of the ampulla of the affected canal. Stimulation of the ampulla will initiate a burst of nystagmic response beating in the plane of the affected canal. Canalolithiasis well explains the presentation of nystagmus and associated vertigo in the majority of cases of BPPV. Due to gravity, the otoconia will typically settle in the posterior canal. Once debris has entered the posterior canal, the cupula at the inferior end, blocks the exit of the debris which becomes trapped and can only exit through the upper part of the canal without the ampulla. In the cupulolithiasis model, otolithic debris is hypothesised to be attached to the cupula in the crista ampullaris making the cupula more inert but also causing a more powerful response to gravity, with stronger neuronal activity, when the threshold to initiate movement has been reached. Cupulolithiasis is uncommon in posterior canal BPPV but could well explain the clinical presentation with some subtypes of horizontal/anterior canal BPPV.

The rationale behind the particle-repositioning manoeuvres is based on the assumption that the manoeuvres clear debris, as a result of gravitational force, from the semicircular canals into the utricle. While in the utricle, the debris will no longer interfere with semicircular canal dynamics and it is thought that it will eventually dissolve.

Clinical presentation
BPPV typically presents with sudden onset of brief attacks of severe vertigo lasting seconds up to a minute, without associated auditory symptoms. The vertigo typically lasts for a few seconds up to 30 seconds, although, patients commonly overestimate the duration by several minutes. This may be related to the associated nausea and disequilibrium that often follow an attack. The majority of patients (80%) experience a rotatory vertigo but an experience of a floating sensation is also common (47%). The vertigo attacks tend to appear in clusters and patients will typically have several attacks in a week or during the course of one day. The symptoms are characteristically triggered by a specific change in head position such as lying down/turning in bed, bending forward and extending the neck looking up. The direction of movement that precipitates the attacks help to identify the affected ear in majority of cases (for example when rolling over in bed to the right specifically induces dizziness this indicates the right ear being the affected side).

Although named benign, the symptoms related to BPPV are commonly severe and patients often become extremely anxious. Some patients will go to great lengths to avoid the movements triggering symptoms and for this reason may not even realize that the condition has resolved spontaneously. Since BPPV has a very sudden onset and may cause drop attacks in which the patient falls to the ground and may vomit, the elderly patient often fears that the symptoms may represent a more sinister disorder, such as for example a stroke or brain tumour.

BPPV can be the primary cause of falls and a reduction in the number of falls after particle repositioning manoeuvres has been shown. Although BPPV does not have a progressive pattern, it often affects the quality of life and in a recent epidemiological study from Germany, the vertigo caused psychosocial limitations which interfered with daily activities and led to giving up driving (24%) or even leaving their homes (18%).

Figure 1 – Illustration of canalithiasis of the posterior canal and cupulolithiasis of the lateral canal. From: CMAJ 2003; 169(7): 681-693
The typical clinical sign of BPPV is positional nystagmus, which is characterized by a slow phase (eyes drifting in one direction) followed by a fast phase (rapid return to original position). The direction of the nystagmus is defined by the direction of the fast phase. The diagnosis of posterior canal BPPV is easily made using the Dix-Hallpike manoeuvre (Figure 2). The side that induces the nystagmus is the pathological side and the affected ear is the undermost ear. The associated provoked nystagmus with posterior canal BPPV is torsional geotropic (towards the ground; towards the undermost ear when this is the affected ear) with an additional smaller up-beating component. Typically there is delayed onset of the vertigo and nystagmus, which varies between a few seconds up to 20 seconds, and the patient should be kept in the position with the head over the edge of the couch for at least 30 seconds to make sure nystagmus is not missed. The characteristic latency of the nystagmus can be explained as a result of the time needed for motion of the otolith material within the semicircular canal to be initiated by the gravity. The nystagmus also typically adapts, fatigues and often temporarily disappears on repeated positional testing. Accordingly, it is important to make sure nystagmus can be appropriately observed during the first positional manoeuvre since it may not be present on a repeat manoeuvre. The vertigo with BPPV is violent and patients are often anxious and unkeen to have their symptoms provoked by a Dix-Hallpike manoeuvre. Therefore, patients should be told before starting this test what to expect (i.e. they may be severely dizzy but this will pass quickly) and should be asked to keep their eyes open, looking straight ahead fixating at one point on the examiner’s face (for example the tip/bridge of the nose). When the patient is returned to the upright position a nystagmus in the same plane, but in the opposite direction, rebound nystagmus, is sometimes seen and is probably due to the otolithic debris moving in the opposite direction.

The supine roll test is used to diagnose horizontal canal BPPV. The head is turned 90° to each side while supine. Typically a purely horizontal and geotropic nystagmus is seen which is present both when the head is turned towards and away from the affected ear. The direction of the head turn that creates the strongest response represents the affected ear. The horizontal canal slopes up and has its cupular barrier at the upper end and therefore free-floating debris tends to float back into the utricle as a result of natural head movements. This could explain why horizontal canal BPPV appears to resolve spontaneously much more quickly than posterior canal BPPV. An apogeotropic (in the opposite direction to gravity) nystagmus is occasionally seen with horizontal canal BPPV and the nystagmus is often more intense and less prone to fatigue. Turning away from the affected side will induce the strongest response with apogeotropic nystagmus. Cupulolithiasis is thought to play a greater role in horizontal canal BPPV than in the posterior canal BPPV and it has been suggested that apogeotropic direction changing nystagmus is associated with cupulolithiasis.

Anterior canal BPPV is rare and this is probably related to the fact that debris within the anterior canal should be self clearing due to the superior anatomical localisation of the anterior canal during most movements. The diagnosis is made using the Dix-Hallpike manoeuvre and with anterior canalolithiasis a predominantly down-beating nystagmus with an additional smaller torsional component is seen. The torsional component is mostly apogeotropic. In some patients, the nystagmus is triggered by both a right and left Dix-Hallpike test making it difficult to localize the affected ear. The safest way to determine the side of the lesion is to identify the direction of the torsional component which is toward the affected ear.

After successful treatment with positional manoeuvres some patients will continue to experience vestibular symptoms, such as a general imbalance and/or milder episodes of brief dizziness. These patients will benefit from additional vestibular testing (electronystagmography/ videonystagmography, caloric test and vestibular evoked myogenic potentials) to clarify peripheral vestibular function, particularly since BPPV is frequently a sequel to other vestibular disorders such as vestibular neuritis and Menière’s disease. In patients presenting with hearing problems or with suspected Menière’s disease, auditory tests should be arranged ( tympanometry, pure-tone audiogram and otoacoustic emissions).

Central positional vertigo
Not all positional vertigo has a peripheral origin and it is
crucial to identify the central positional vertigo caused by, for example, brainstem stroke, cerebellar pathology, multiple sclerosis and multisystem atrophy.

The diagnosis of horizontal canal BPPV, with an apogeotropic nystagmus, or anterior canal BPPV, with a weak torsional component, requires particularly careful consideration of the patient’s symptoms and the clinical characteristic of the nystagmus, since the clinical picture with both can be very similar to the clinical presentation with central positional nystagmus.

To identify central positional nystagmus, the Dix-Hallpike manoeuvre to right and left is performed, but in addition, the patient is brought straight back with the head in a central hanging position, as some central positional nystagmus may only be present in this position. A purely vertical nystagmus, up beating or down beating, should be considered to have a central origin. Typically, central nystagmus shows no fatigue, does not adapt, and there is often surprisingly little vertigo, given the magnitude of the induced nystagmus (Table 1). A purely downbeating nystagmus occurs particularly with posterior fossa lesions and is typical for cerebellar pathology but may also be seen with brain stem lesions. Central vestibular dysfunction is often associated with other neurological symptoms, but when vertigo is the only or main symptom, the differential diagnosis between central and peripheral disorders becomes difficult.

Migraine is a common cause of vertigo, which may be spontaneous or induced by head movements, including positional changes, or busy visual environments in both the adult and the paediatric population. The vertiginous episodes can occur during the headache, but most often they appear during a headache free interval. In 20 patients with migraine, we observed in 12 patients during an acute migraine and in 2 patients during a cluster headache. Interestingly, pathological positional nystagmus was present in eight patients (in five patients nystagmus was only present after positioning). In all patients, the induced positional nystagmus had central characteristics, showing no fatigue and accordingly persisted as long as the precipitating head position was maintained.

**Treatment**

Although BPPV is usually a self-limiting disorder, which generally resolves within six months, treatment with particle-repositioning manoeuvres are effective and safe therapy and should be offered to patients of all ages with BPPV. The **Epley manoeuvre** is designed to gradually, using gravity, move the debris into the utricle by moving the patient’s head through a series of positions (Figure 3). The first position of the corrective sequence is the Dix-Hallpike head hanging position; with the affected ear lowermost. Vibration applied to the mastoid process of the affected ear during the Epley manoeuvre has been advocated but there is no evidence that this improves the result of the repositioning manoeuvre. With the **Semont manoeuvre**, the patient is rapidly swung from laying on the affected ear to laying on the other side through a 180° motion with a duration less than 1.3 seconds. This manoeuvre uses acceleration of the head as well as gravity to move debris and the speed of movement during the Semont manoeuvre is critical to its clinical success. The Epley manoeuvre is probably the most commonly used procedure, but both the Semont and Epley manoeuvres are equally effective with documented recovery rates of 80-99% of patients with posterior canal BPPV. The Epley manoeuvre is also the most commonly used repositioning manoeuvre to treat anterior canal BPPV. With anterior canal BPPV a “reverse Epley manoeuvre” is performed; if

<table>
<thead>
<tr>
<th>Positional nystagmus</th>
<th>BPPV</th>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latent period</td>
<td>2-20secs</td>
<td>None</td>
</tr>
<tr>
<td>Adaptation</td>
<td>Yes</td>
<td>No, persistent</td>
</tr>
<tr>
<td>Fatigability</td>
<td>Disappears on repetition</td>
<td>No, persistent</td>
</tr>
<tr>
<td>Visual fixation</td>
<td>Inhibited</td>
<td>Usually little effect</td>
</tr>
<tr>
<td>Sensation of vertigo</td>
<td>Always present</td>
<td>Typically absent</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Combined torsional/horizontal geotropic</td>
<td>Variable but often pure vertical, horizontal or torsional. May change direction</td>
</tr>
</tbody>
</table>

Table 1: Typical characteristics of positional nystagmus seen with BPPV and central positional nystagmus.

![Figure 3: The Epley manoeuvre. Diagram to illustrate particle repositioning manoeuvre for canalithiasis of left posterior semicircular canal, as described by Epley (1992). S = sitting. 1-5 = stages of the manoeuvre. Semicircular canals: Ant = anterior, Post = posterior, Lat = lateral. From: Otoalryngol Head Neck Surg 1992; 107: 399-404](image-url)
the right ear has been identified as the effected ear, a left Epley manoeuvre is performed. If properly instructed, self-administered Epley and Semont manoeuvres are effective. However, the Semont manoeuvre is less commonly used which is probably due to the force and speed required for this manoeuvre and the fact that majority of patients with BPPV are elderly.

The barbecue manoeuvre, involving stepwise rotations of 90˚ up to a total 270˚ or 360˚ around the yaw axis toward the unaffected ear, is the most commonly used treatment for geotropic horizontal canal BPPV (Figure 4). Horizontal canal BPPV has been reported to have a poorer response to repositioning manoeuvres than posterior canal BPPV, with a remission rate for treatment around of 60-90%. Incorrect identification of the affected ear may be the explanation of this poorer outcome23. Another treatment option for horizontal canal BPPV is the prolonged position manoeuvre which has been particularly recommended when positional nystagmus indicates cupulolithiasis. This treatment involves the patient lying on the side with the affected ear up for 12 hours.

Following a repositioning manoeuvre patients are typically advised to keep the head still and in an upright position for 48 hours with the aim of giving the otoconia time to settle and, thus, prevent recurrence. However, there is no evidence in the literature of post-repositioning advice affecting the outcome of the manoeuvre. On the contrary, in controlled studies, restrictions have failed to significantly affect clinical outcomes with regards to the efficacy of BPPV manoeuvres24,25. There is also variation with regards to the number of repositioning manoeuvres performed in each treatment session. There are two commonly used management strategies: one dictates only one manoeuvre per clinic visit while the other advocates repeated manoeuvres until there is resolution of positional nystagmus. Again, there is no evidence in the literature showing a significant difference between these two approaches with regards to short-term effectiveness or long-term recurrence.

Not infrequently, patients with a characteristic history of BPPV will experience subjective vertigo during the Dix-Hallpike manoeuvre, but there will be no positional nystagmus present. It is well recognised that the development of classical positional nystagmus on the Dix-Hallpike manoeuvre is an erratic sign of BPPV. There is no clear consensus with regards to the management of this group of patients. Some clinicians will not perform a repositioning manoeuvre if there is no demonstrated nystagmus and the reason for this could be the lack of a definite diagnosis. Moreover, absence of the characteristic nystagmus may be taken to indicate resolution of BPPV. In addition, there is a risk (2.5-6%) of causing a “canal conversion” from a posterior to horizontal BPPV26,27. BPPV is frequently inappropriately treated with vestibular suppressant medications28. Regular medical treatment of BPPV, with antiemetics and sedatives, offers very little symptom relief and is not a substitute for particle repositioning manoeuvres29.

BPPV has a high rate of recurrence and in approximately 50% of patients symptoms will reoccur within 40 months after treatment30. Most recurrence (80%) happens within the first year after treatment and recurrence after a symptom-free period of 8 years is very rare31. Nonspecific physical activity has been suggested to protect against BPPV, possibly by relocating loosened debris from the semicircular canals. Accordingly, significantly lower total physical score activity in household and leisure activities has been shown in BPPV patients compared to controls32. Vestibular rehabilitation, Cawthorne Cooksey exercises (CCE), as an adjuvant treatment to repositioning manoeuvres has been shown to significantly improve measures of activities of daily living in the elderly patients33. This could be explained by an additional associated peripheral vestibular pathology or multisensory imbalance, requiring vestibular rehabilitation to obtain cerebral compensation. Evidence suggest that with BPPV the primary intervention should include repositioning manoeuvres to actually treat the condition and this should be supported by vestibular rehabilitation to aid in longer-term functional recovery34. The Brandt-Daroff exercises are a repeated sequence of repositioning manoeuvres first
described for treatment of BPPV.35 Self-administered Brandt-Daroff exercises are the least effective treatment (23% recovery) and are less effective than self-administered canalith repositioning procedure (64% recovery) in the treatment of posterior canal BPPV.36

Repositioning manoeuvres are not always effective, which may be explained by the narrowness of the canal or cupulolithiasis (ie. adherence of the debris to the cupula). An occurrence rate of intractable BPPV of 3.6% has been shown and is more common with apogeotropic nystagmus.37 This may be explained by undetachable cupulolithiasis but intractable BPPV patients have also been shown using three-dimensional MRI, to have semicircular canals with abnormal appearances, possibly related to innate semicircular canal stenosis and/or a plug of otoconial debris, more often than normal controls37. In some of patients with intractable BPPV and severely impairment of the quality of life, surgical treatment may be an option38,39. In a very small number of cases, plugging of the posterior semicircular canal or section of the posterior ampullary nerve should be considered. The section of the posterior ampullary nerve is technically very demanding and there is a significant risk of sensorineural hearing loss. Therefore posterior semicircular canal occlusion has largely become the surgical procedure of choice for intractable BPPV.40 Posterior semicircular canal occlusion has a low risk for hearing loss and has been reported to be a highly effective treatment for intractable BPPV. The majority of patients experience post-operatively a period of dizziness and vertigo, lasting from 48 hours to weeks, probably related to a surgically induced partial canal paresis in the operated ear. However, intractable BPPV is extremely rare and surgical therapy should be applied in exceptional cases only.

Conclusion
Benign paroxysmal positional vertigo (BPPV) is by far the most common peripheral vestibular pathology in the adult population. BPPV affect the quality of life, particularly in the elderly, and is associated with reduced activities of daily living, falls and depression. BPPV is often inappropriately treated with vestibular suppressant medications, which offers very little symptom relief. Unfortunately, delays in proper diagnosis and treatment are still very common and lead to unnecessary prolonged suffering in the patient and often unnecessary costs. The history and the typical burst of nystagmus appearing with positional testing provide for diagnostic criteria of BPPV. The nystagmus seen has characteristic directional features that often allow localisation of the affected side and the semicircular canal involved. Many patients with BPPV will describe presenting symptoms of a more or less constant vertigo and only very careful questioning will reveal that symptom consists of multiple brief attacks. In addition, some patients will go to great lengths to avoid movements that precipitate attacks and may therefore not have suffered any brief vertigo episodes for quite some time prior to consultation. Therefore the Dix-Hallpike manoeuvre should be included in the clinical examination of all patients presenting with vertigo. Although BPPV is usually a self-limiting disorder, treatment with particle repositioning manoeuvres should be offered to all patients of all ages. The particle repositioning manoeuvres are quick and in most patients highly successful. However, if the positional nystagmus is not typical for BPPV or if it fails to respond to positioning treatments, a central cause should be considered and investigated.

References
Allergic Fungal Sinusitis

David A. Gudis MD, Robert T. Adelson MD, James N. Palmer MD
Department of Otorhinolaryngology - Head and Neck Surgery
University of Pennsylvania School of Medicine

Corresponding Author:
James N. Palmer, MD
Associate Professor, Division Chief, Rhinology
Department of Otorhinolaryngology - Head and Neck Surgery
University of Pennsylvania School of Medicine
james.palmer@uphs.upenn.edu

Abstract
Allergic fungal rhinosinusitis (AFRS) is a distinct clinicopathologic entity within the spectrum of chronic rhinosinusitis (CRS) that has become increasingly well understood over the nearly four decades since its earliest recognition. The disease process may represent 10% of all CRS cases, and is notable for its distinguishing features and their influence on diagnosis and management. We review the clinical presentation of AFRS as well as the current understanding of disease pathogenesis. The characteristic radiographic findings are detailed and their potential use in pre-operative identification of AFRS are discussed. Notable aspects of disease histopathology are described with emphasis on the role of fungal culture. Management of AFRS requires a comprehensive approach with surgical clearance of eosinophilic mucin and creation of widely patent sinonasal anatomy in addition to medical modulation of the immune response that drives recurrent disease.

Key Words
Allergic Fungal Rhinosinusitis, Allergic Fungal Sinusitis, Chronic Rhinosinusitis, Eosinophilic Mucin, Nasal Polyposis

Introduction
Allergic fungal rhinosinusitis (AFRS), originally described as a sinonasal correlate to allergic bronchopulmonary aspergillosis (ABPA), is now recognized as a distinct clinicopathologic entity. AFRS was first reported in 1976 by a pulmonologist who described a patient with ABPA presenting with extensive nasal eosinophilic polyposis, edema, and aspergillus maxillary sinusitis1. Millar and others further delineated the disease process, noting that just as patients with allergic bronchopulmonary aspergillosis suffer from thick mucoid impaction of the bronchi and eosinophilic pneumonia, those with AFRS were characterized by their inspissated tenacious mucin and chronic eosinophilic inflammation2-4. Now thought to play a considerable role in as many as 5 to 10% of patients with chronic rhinosinusitis (CRS), AFRS is a specific and potentially dangerous disease process for which aggressive and comprehensive management is essential5.

Clinical Presentation
Patients with AFRS typically present with routine symptoms of chronic rhinosinusitis with polyposis, including progressive nasal congestion, nasal airway obstruction, hyposmia/anosmia, facial pain and pressure, thick rhinorrhea and post-nasal drip. Complaints of vision changes, diplopia, other neurologic symptoms including unusual or severe headaches, or CRS refractory to standard surgery and antibiotic therapy should prompt the clinician to consider the diagnosis of AFRS. Unlike those with invasive forms of fungal sinusitis, patients with AFRS are immunocompetent with a very high prevalence of atopy6,7. They tend to be younger than those with routine CRS, with a mean age between 21 and 33 years8. Asthma or reactive airway disease is present in as many as 64% of patients with AFRS7.

In the United States there is a demographic association whereby patients with AFRS are more likely to be of lower income level, a finding that has been noted in other countries as well8,9. African Americans are more likely to develop AFRS than other groups, and are more likely to present both at a younger age and with more advanced disease as evidenced by bony erosion of the skull base or orbit10. Additionally, males are more likely than females to present with bony erosion11. Whether African American patients or males develop bone erosion earlier in the natural history of AFRS or simply come to medical attention later than other groups remains an unanswered question, yet the clinician should exert special caution in those populations known to have more frequent skull base involvement. A strong geographic association has also been identified, whereby patients in southern regions of the United States who undergo sinus surgery have a
greater incidence of AFRS. This geographic variation by climate is thought to exist globally, a belief supported by diverging incidences of AFRS reported in series of patients from different regions around the world.

On gross examination the practitioner may rarely note sequelae of extensive or aggressive disease. Facial asymmetry or edema, malar flattening, and orbital or periorbital changes including proptosis or telecanthus can indicate bony erosion or remodeling as a result of a benign yet insidious process. Nasal endoscopy characteristically reveals extensive mucosal edema, inflammation, and nasal polyposis which may be unilateral or asymmetric. Characteristic eosinophilic mucin, a thick tenacious mucous that is tan or dark green in color, may also be appreciated on endoscopy, particularly in a patient with a history of prior sinus surgery and widened sinus ostia amenable to inspection in the office setting. When the diagnosis of AFRS is suspected, or in any patient with signs or symptoms concerning for bony erosion or expansion, computed tomography (CT) scan is indicated. Many practitioners maintain a low threshold for pursuing magnetic resonance imaging (MRI) as well, particularly when CT indicates such erosion and further evaluation of the skull base is necessary.

Pathophysiology
There is considerable debate regarding the pathophysiology, and therefore the diagnostic criteria, of AFRS. It is commonly believed that the process begins when an atopic individual is exposed to ubiquitous fungal antigens and the sinonasal mucosa becomes colonized via normal respiration. The host then develops an inflammatory response consisting of both a Gell and Coombs Type I IgE-mediated hypersensitivity reaction (allergy) and a Type III hypersensitivity reaction (immune complex). The chronic mucosal inflammation leads to persistent edema and obstruction of sinus ostia with stasis of inflammatory eosinophilic conglomerates and fungal antigens. This cyclical inflammatory process leads to progressive accumulation of eosinophilic mucin and mucosal polypoid changes within and surrounding an obstructed sinus. Controversy surrounds the distinction between AFRS and routine CRS, as the role of fungus in routine CRS continues to be elucidated. Furthermore, the subset of patients with findings consistent with AFRS but no fungal bodies isolated from surgical specimens has led some investigators to further label this disease process as eosinophilic mucin rhinosinusitis, to distinguish it from cases in which fungi are identified pathologically and are therefore considered eosinophilic fungal rhinosinusitis.

In AFRS, the chronic inflammatory process in the obstructed sinus frequently leads to bony expansile remodeling and erosion with potentially disastrous consequences. While the incidence of bony erosion in AFRS varies quite widely by series, it has been demonstrated that it occurs most commonly in the ethmoid sinuses, particularly along the lamina papyracea into the orbit. However, bony erosion can involve any paranasal sinuse, with subsequent complications including visual changes and visual loss, intracranial and cerebral intraparenchymal extension, seizures, cavernous sinus thrombosis, various cranial neuropathies, and others.

The anterior cranial fossa is the most frequent site of skull base erosion, although such bony changes have been identified in the middle and posterior cranial fossas as well. Encouragingly, the sequelae of bony erosion, even when dramatic, often resolve and undergoes remodeling to a more natural state after successful management. We have previously reported a patient with AFRS who presented with diplopia and bilateral abducens nerve palsy secondary to extrasphenoid extension into the cavernous sinus; his symptoms and cranial nerve function gradually resolved completely within months of treatment.

Diagnosis
A constellation of clinical, radiologic, histopathologic and immunologic features are required to establish a diagnosis of AFRS. While a number of proposed diagnostic criteria have been proposed, the five criteria set forth by Bent and Kuhn criteria remain the most widely accepted:

- Evidence of Type I hypersensitivity reaction to fungi
- Nasal polyposis
- Characteristic radiographic findings
- Eosinophilic mucus without fungal invasion on histopathologic analysis
- Positive fungal stain of surgical specimen

Importantly, the diagnosis of AFRS requires pathologic examination of material recovered from the paranasal sinuses. Therefore, AFRS is not a clinical diagnosis like CRS, and typically requires surgical procedures to provide specimens that to establish the diagnosis. Researchers with an appreciation for the common features of AFRS have sought to establish a sensitive and specific method of ascertaining a diagnosis of AFRS prior to surgery. Dhiwakar et al demonstrated 70% sensitivity and 100% specificity for the preoperative diagnosis of AFRS when the patients have the triad of hyperattenuation on CT imaging, nasal polyps, and elevated titers of anti-Aspergillus IgE antibody. Improved understanding of the characteristics of AFRS may allow preoperative
establishment of an accurate diagnosis, enabling proper counseling and perioperative medical management.

**Radiology**

The unique pathology of AFRS results in characteristic radiographic findings, and are indispensable tools for proper management of this disease process. CT scans readily demonstrate opacification of the involved paranasal sinuses with heterogenous areas of hyperattenuation within corresponding to the collections of thick eosinophilic mucin and inflammatory debris within the sinus cavity. The hyperdense regions most likely result from the combination of inspisated mucin and secretions, accumulated fungal elements, heavy metals and calcium salt precipitates that result from chronic inflammation or are concentrated by fungal elements.

In routine CRS, it is common to see on CT scan hyperdense thickened bone surrounding a chronically inflamed sinus, reflecting the process of neoosteogenesis. In AFRS, however, while neoosteogenesis can occur, a smooth thinning of bone surrounding the affected sinus is also frequently identified (Figure 1&2). The progressive accumulation of mucin and debris in the chronically obstructed sinus is postulated to cause pressure atrophy of the bony partitions, which leads to the expansile remodeling and the ultimate erosion of bone that is often seen. The expansile remodeling of AFRS differentiates this process radiologically from sinus malignancies and invasive fungal disease, as the later two processes demonstrate bone erosion in the absence of sinus expansion.

While bone remodeling occurs in 20-90% of AFRS cases, reviews of AFRS from tertiary care medical centers report orbital or skull base erosion in 44-56% of cases. Orbital involvement is more common than skull base erosion and these bony changes are most frequent with ethmoid sinus involvement. Findings of bone compromise on CT imaging...
should prompt MRI to evaluate orbital and skull base involvement prior to surgery. MRI, in conjunction with CT, can provide reliable indications of fungal contents and assist in the planning of more complicated operations involving erosion of the normal orbital and skull base barriers. T1-weighted images (Figure 3) may show a combination of low, intermediate, or high signal intensity of the affected sinus contents. T2-weighted images (Figure 4) show a characteristic low signal intensity or signal void, a finding attributed to the high protein and low water content of eosinophilic mucin. The high concentration of the various metals involved in fungal metabolism that may contribute to hyperattenuation on CT are also thought to contribute to T2-weighted image signal void on MRI. The inflamed mucosa is generally hypointense or isointense on T1-weighted images and hyperintense on T2-weighted images. Additionally, the inflamed mucosa will enhance with gadolinium contrast administration. When evaluating a patient with suspected AFRS, it is critical that all sequences of the MRI are considered in the context of the corresponding CT scan, as the T2-weighted signal void mimics normally aerated sinuses.

Pathology and Microbiology
Gross surgical pathology in AFRS patients reveals inflamed and edematous mucosa with extensive polyposis. Bony fragments in regions of expansile remodeling are often thinner and more brittle than the osteitic fragments resected in routine CRS. Affected sinuses are frequently full of eosinophilic mucin, a thick, tenacious, viscous substance of a tan or dark green color. Histopathology of the eosinophilic mucin is critical to establishing a diagnosis of AFRS. Hematoxylin and eosin (H&E) stains (Figure 5) reveal hypertrophic edematous sinus mucosa with a chronic inflammatory infiltrate abundant in pyknotic and degranulated eosinophils within a background of more lightly staining lamellated sheets of mucin. Deeply eosinophilic and needle-shaped Charcot-Leyden crystals can be found within the mucin and cellular debris, and these extracellular structures are characteristic to AFRS. The Charcot-Leyden crystal is a pair of hexagonal pyramids joined at their bases by lysophospholipase, an enzyme synthesized by eosinophils. The mucosal epithelium may be desquamated, and the basement membrane thickened. Fungal elements are oftentimes sparse and, in some cases, impossible to detect by H & E staining, in contradistinction to many of the other disease processes of fungal rhinosinusitis. Silver stains, such as Grocott’s or Gomori’s Methenamine Stain (Figure 6) are specific for fungi, and can be helpful when fungal elements are in low numbers or difficult to detect. Fungal elements must not invade mucosa or bone, as AFRS is a noninvasive category of fungal rhinosinusitis. Branching fungal hyphae are generally seen scattered...
within the degranulated sheets of eosinophilic debris. The dematiaceae fungi, such as Bipolaris and Fusarium, are most frequently cultured in AFRS, followed by Apergillus species. They are also the antigens against which patients’ type I hypersensitivity reaction is directed\textsuperscript{16,32}. The yield of fungal cultures (64-100\%) is highly variable and AFRS is diagnosed in cases with negative fungal cultures\textsuperscript{16}. Conversely, the presence of fungal bodies on pathology or a positive fungal culture does not confirm the diagnosis of AFRS, as benign colonization is nearly ubiquitous\textsuperscript{33}.

**Treatment**

While there are no published prospective studies comparing treatment modalities, similar management strategies have emerged from various investigators’ experiences and retrospective case reviews. By appreciating the fundamental feature of disease pathogenesis to be an immunologically mediated hypersensitivity to fungal antigens, we have addressed AFRS by (1) surgical ventilation of the paranasal sinuses and complete removal of eosinophilic mucin and (2) medical modulation of the immune response with corticosteroids and immunotherapy to forestall the allergic drive toward recurrent disease.

Treatment generally begins with endoscopic surgery: wide sinusotomies, complete debridement of polyps and compromised mucosa, and extirpation of all eosinophilic mucin, leaving widely patent and well-ventilated sinuses. Frequently, the surgeon will find the expansile nature of the disease process to have pathologically enlarged the sinus ostia, enabling one to follow the mucin and polyps to the areas of disease\textsuperscript{32}. Widely patent sinonasal anatomy will facilitate post-operative examination and monitoring of disease in the office setting.

Surgery alone, without post-operative medical management, leads to unacceptably high rates of recurrence\textsuperscript{34,35}. Modulation of the pathologically aggressive immune response can occur both through immunotherapy and/or the use of corticosteroids. Patients treated with fungal immunotherapy for a period of one to three years following surgery showed a significant decrease in their rate of recurrence\textsuperscript{7}, reduced rates of re-operation, and less total office visits\textsuperscript{36}. In addition, patients receiving immunotherapy statistically had less mucosal edema as noted on endoscopy and reported better quality of life\textsuperscript{7}.

As in many other inflammatory processes of the airway including ABPA, systemic corticosteroid therapy has thus become a mainstay of treatment as well, with studies supporting its safety and efficacy\textsuperscript{37}. Many practitioners will continue systemic steroids for weeks to months post-operatively. With frequent outpatient post-operative evaluations for debridement and surveillance endoscopic examinations, the steroid taper regimen can be tailored to the patient’s progress, healing, and tolerance of potential medication side effects. The patient should continue aggressive post-operative sinonasal irrigation indefinitely to flush the accumulation of fungal antigens and eosinophilic debris from surgically ventilated sinuses. Given the favorable side effect profile of topical corticosteroids, many practitioners will include them, at various concentrations and delivery methods, in their post-operative treatment protocols. There inadequate evidence to endorse or refute systemic antibacterial or antifungal agents, leukotriene inhibitors or macrolide antibiotics in the management of AFRS, though medical interventions that dampen the overall inflammatory state within the sinonasal region may eventually prove useful in these patients. Anecdotal experience and case series suggest that many investigators achieve favorable results with a course of systemic antibacterial agents and no systemic antifungal agents.

**Conclusion**

Allergic fungal rhinosinusitis plays a role in a significant portion of the population suffering from chronic rhinosinusitis, and as more practitioners become familiar with its presentation and diagnosis that percentage is likely to increase. Because of the potentially devastating complications that arise from the erosion of the orbit and skull base, practicing Otorhinolaryngologists should become familiar with the disease process, its workup and management. While active investigation continues to elucidate the pathophysiology and optimal treatment of AFRS, an aggressive combined medical and surgical management approach is essential to achieve disease.
Prescribing Information

(Please refer to the full Summary of Product Characteristics before prescribing Avamys Nasal Spray Suspension (fluticasone furoate 27.5 micrograms metered spray).

Uses: Treatment of symptoms of allergic rhinitis in adults and children aged 6 years and over. Dosage and Administration: For intranasal use only. Adults: Two sprays per nostril once daily (total daily dose, 110 micrograms). Once symptoms controlled, use maintenance dose of one spray per nostril once daily (total daily dose, 55 micrograms). Reduce to lowest dose at which effective control of symptoms is maintained. Children aged 6 to 11 years: One spray per nostril once daily (total daily dose, 55 micrograms). If patient is not adequately responding, increase daily dose to 110 micrograms (two sprays per nostril, once daily) and reduce back down to 55 micrograms daily dose once control is achieved.

Contraindications: Hypersensitivity to fluticasone furoate, its active substance or excipients. Side Effects: Systemic effects of nasal corticosteroids may result in clinically significant adrenal suppression. Consider additional systemic corticosteroid cover during periods of stress or elective surgery. Caution when prescribing concurrently with other corticosteroids. Growth retardation has been reported in children receiving some nasal corticosteroids at licensed doses. Monitor height of children. Consider referring to a paediatric specialist. May cause irritation of the nasal mucosa. Caution when treating patients with severe liver disease, systemic exposure likely to be increased. Nasal anti-cholinergic agents may result in the development of glaucoma and/or cataracts. Close monitoring is warranted in patients with a change in vision or a history of increased intraocular pressure, glaucoma or cataracts. Pregnancy and Lactation: Fluticasone furoate nasal spray is contained in breast milk. Only use if the expected benefits to the mother outweigh the possible risks to the foetus or child. Drug interactions: Caution is recommended when co-administering with inhibitors of the cytochrome P450 3A4 system, e.g. ketoconazole and ritonavir. Presentation and Basic NHSS code: Avamys Nasal Spray Suspension: 110 sprays. B044. Marketing Authorisation Number: EU/1/07/434/003. Legal category: POM. PL holder: Glaxo Group Ltd. Greenford, Middlesex, UB6 0NN, United Kingdom. Last date of revision: January 2010.

Date of preparation: March 2011. UK/FF/0098/11


Contact us

GlaxoSmithKline

T 0800 221 441
F 020 8930 4328

gsk

Allergic rhinitis relief

Whatever the reason whatever the season

Not actual size
Paediatric upper respiratory tract symptoms are common and for the majority of children they are self limiting and resolve without sequelae. For a small number of children they can result in complications and it is important to be alert to their clinical features and know how to manage them.

The presenting symptoms and signs of rhinosinusitis which parents mention are varied. Fever, malaise, nasal blockage and mucopurulent discharge are common. Also included are snuffles in a baby, snoring, mouth breathing, feeding problems, bad breath, cough and hyponasal speech. It is often striking how concerned the parents are whilst the child often appears unconcerned about their symptoms. Facial pain and headache are rare symptoms in children with rhinosinusitis. Upper respiratory tract infections are common in childhood and occur on average 8 times per year\(^1\). Figure 1. Drowsiness, vomiting, headache, seizure or eye symptoms should raise suspicion of secondary complications\(^2\).

The main factors that influence paediatric rhinosinusitis are the frequency of upper respiratory tract infections, the relatively immature immune system and the prevalence of underlying conditions such as allergic rhinitis and adenoidal hypertrophy. Frequently there is a history of a preceding acute viral rhinitis with fever, malaise and serous nasal discharge, which then becomes mucopurulent before settling spontaneously around 10 days. Children often have a protracted period of nasal obstruction and discharge with up to 13% aged 1-3 years having symptoms for more than 15 days\(^3\). Children under the age of three and a half years rarely blow their nose hence stagnant secretions collect in the nasal airway to become colonised with nasal commensals that discoulor them. Acute bacterial involvement of the sinuses produce similar symptoms to a viral infection but with a more marked fever. The common pathogens are Streptococcus pneunoniae, Haemophilus influenzae, and Moraxella catarrhalis. The majority of bacterial infections resolve spontaneously\(^4\).

Infection on its own is not an adequate explanation for the protracted inflammation which some children have in their paranasal sinuses. A humoural or cellular response at the mucosal level may lead to more protracted mucosal inflammation and secretions. Adenoidal hypertrophy is common with a tendency to spontaneous involution by the age of 8-10 years old. The prevalence of allergic rhinitis in children is approximately 20%\(^1\). While most parents recognise hay fever or seasonal allergic rhinitis, few are aware that many children who have allergic rhinitis can have symptoms all the year round because they are allergic to perennial allergens such as house dust mite or pet allergens. Nasal polyps in children are uncommon. The term “a nasal polyp” is not a diagnosis but a sign of inflammation of the lining of the nose that can be due to a range of diverse disease. Bilateral polyps are usually associated with cystic fibrosis but primary ciliary dyskinesia, immunodeficiency or chronic infection may also be responsible. A sizable proportion will be antrochoanal polyps and many of the remainder are idiopathic. It is important to exclude any underlying cause so this can be addressed\(^1\).
Anterior rhinoscopy may show a clear nasal discharge in the early stages of a viral rhinosinusitis. The presence of coloured secretions does not necessarily imply current infection as it is often stained by white cells in the recovery phase (non-infective) of a viral or bacterial infection or by eosinophilic infiltration in allergic rhinitis. Purulent rhinitis alone is not equivalent to sinusitis. The adenoid can be examined using an angled mirror but a strong gag reflex or a frightened child may prevent this from being done. It often helps to tell a child that you want to look at their teeth as they understand this and will open their mouths. Nasal endoscopy has little to offer in a child under approximately 8 years as visibility is often restricted and it can upset the child. Assessment of the eye, testing for colour vision and acuity, eye movements and pupil reflexes and examination for signs of intracranial sepsis should be carried out where complications are suspected.

Refractory cases warrant a full blood count with differential, immunoglobulin assays and culture and sensitivity may be warranted. Blood cultures are more helpful in a younger patient and if taken prior to administering either enteral or parenteral antibiotics. Culture swabs of the nasal airway are frequently contaminated by commensals from the nasal vestibule and are unlikely to contribute to management. Obtaining an antral specimen for culture requires a general anaesthetic and an antral washout which has not been shown to be of therapeutic benefit at three months. Plain sinus radiographs have little place in the routine management of rhinosinusitis, as a “thickened mucosa” is a non-specific finding and may occur in asymptomatic patients. Such films may have a role in the management of acute maxillary and frontal sinusitis which is unresponsive to medical treatment to help confirm the diagnosis and degree of pneumatisation prior to drainage. A lateral soft tissue plain radiograph is the most reliable method of assessing adenoid size but is unlikely to influence the management in most children. Figure 2. If allergy is suspected, skin tests can be carried out in co-operative children after about the age of 5 years. Figure 3. An alternative is to test for specific IgE especially in children who are taking antihistamines or who have eczema or dermatographism. CT may provide excellent images but it has its problems: the dose of radiation, the need for sedation or general anaesthesia, but most important of all, the significance of CT image findings. CT is not much better at diagnosing rhinosinusitis than plain sinus radiographs. In asymptomatic children there is mucosal thickening or opacification in approximately 50% on CT scan. Anatomical variations such as a concha bullosa or agger nasi air cells are present equally in a normal population without sinusitis, the host’s immunity or mucosal response to pathogens is therefore likely to be of primary importance, and not the presence of anatomical variations.

In children who do not respond to conservative management or who repeatedly fail to improve, even temporarily with medical management, it is worth considering whether there is an immunological defect. The majority of children with an immunodeficiency who have severe sinusitis have inadequate humoral defences rather than cell mediated problems. As many immunodeficiency diseases are hereditary it is worth asking about first degree relatives, or whether the patient has also had recurrent pneumonias, cellulitis, candidiasis, chronic diarrhoea or failure to thrive. Reduced immunoglobulins to pneumococcal, haemophilus or tetanus antigen are a marker of reduced immunity.
The most simple and practical test of ciliary function is the saccharine clearance test which is done by placing a quarter of a saccharine tablet under the anterior end of the inferior turbinate. But this test is crude in comparison to a brushing or biopsy looking at ciliary movement or the electron microscopic appearance. Any biopsy should be taken from an area of healthy looking mucosa otherwise a false positive biopsy will be obtained. An alternative if the nasal mucosa cannot be rendered healthy, even for a short period is to do a tracheal biopsy.

One of the main reasons for a baby or child to have a runny nose is that ciliary function is impaired for up to two weeks after a viral upper respiratory tract infection. The best way to clear the nose of mucus under these circumstances is nose blowing or saline sprays or douching. Unfortunately most children under the age of three and a half years are poor at blowing their nose. Saline sprays are effective at cleaning the nose and may improve mucociliary clearance. The saline mechanically removes mucus and helps patient comfort. Saline sprays may also help reduce the tenaciousness of secretions and they can be repeated as frequently as needed to clear the nose without causing any harm. A short course of topical decongestants may be beneficial in older children.

Antibiotics are not always required as the infection is frequently viral. They may be necessary in those patients with moderate or severe pain or tenderness and purulent rhinorrhea lasting more than seven days or those with severe symptoms regardless of the duration of illness. The antibiotic chosen should be the most narrow spectrum agent available against the likely pathogens. Amoxicillin is the first choice unless the child has had antibiotics within the previous month, if the area has a high prevalence of beta-lactamase resistant Haemophilus influenzae, or if there are any associated complications of sinusitis. One of the most disputed questions is whether antibiotics make any difference. Several studies have found no difference between those treated by antibiotics and control groups when they are followed up for more than twelve weeks.

In children with perennial allergic rhinitis with a single allergy to house dust mite rigorous allergen avoidance may provide some help; although the evidence base for this is not strong. For symptoms of nasal obstruction due to allergy regular age-appropriate topical nasal steroids work best. Antihistamines help the symptoms of sneezing and itching. Leukotriene receptor antagonists are of questionable value allergic rhinitis.

Surgery is rarely required in paediatric rhinosinusitis unless there is an underlying condition or a complication develops. The frontal sinus can be trephined if there is intense frontal pain and a completely opaque sinus indicating that there may be pus under pressure. The maxillary sinus can be washed out to help speed the resolution of the infection but there is no longer term benefit. There is no evidence that endoscopic frontal sinus surgery speeds recovery and the latter may indeed lead to stenosis and adhesions.

There is evidence for adenoidectomy as an initial surgical intervention for chronic rhinosinusitis in children who have not responded to medical treatment. Enlarged adenoids physically obstruct the nasal airway, impeding drainage of secretions. Secretions harbour pathogenic bacteria which proliferate rapidly after viral infection. Following adenoidectomy children with large adenoids showed a reduction in the number of episodes of infective rhinosinusitis per year. However, adenoid hypertrophy normally resolves of its own accord about the age of 7 years old and it is rarely justified as a solitary surgical procedure.

Maxillary antral washout is rarely performed now in children as over 70 percent of children have involvement of their ethmoid sinuses in chronic rhinosinusitis and irrigation of the maxillary antrum alone rarely clears the symptoms.

Endoscopic sinus surgery in acutely infected patients is difficult because the associated hyperaemia causes marked bleeding making views poor and the risk of producing adhesions and stenosis of the frontal recess are increased. Endoscopic techniques can reduce the surgical morbidity and achieve better symptomatic control than conventional
surgery in specific intranasal pathology such as mucocoeles, encephaloceles, allergic fungal sinusitis and benign tumours. Few studies of ESS in children treated for rhinosinusitis report more than an 80% improvement in symptoms and when these results are compared with the reported improvement which occurs without any treatment surgery does not compare favorably.

The complications of infective rhinosinusitis occur rarely and the incidence is unpredictable. Complications include mucocoeles, osteomyelitis, periorbital cellulitis and intracranial infections. Any periorbital swelling warrants admission, parenteral antibiotics, detailed assessment and monitoring of vision, and CT scanning if there is a suspicion of involvement of the postseptal compartment or if the patient fails to respond within 24-36 hours. Contemporary guidelines for the management of orbital cellulitis advise against the use of CT in the first instance if there is no chemosis, proptosis, painful or decreased extraocular movements, an afferent pupillary defect or visual impairment. If any of these features develop, or there is no clinical response to the appropriate antibiotics after 48 hours, then CT is warranted. If there is a postseptal collection of pus it needs draining urgently as compression in this area due to a subperiosteal abscess can cause blindness.

Intracranial infection secondary to infective sinusitis is rare and sporadic. The unusual intracranial complications of sinusitis occur most frequently just before, or in the early teens and usually present with an altered mental state, headache, fever, seizure, vomiting, a unilateral weakness/hemiparesis or a cranial nerve sign. These justify an urgent MRI or CT scan with contrast. The importance of imaging before a lumbar puncture cannot be overemphasised as otherwise the brainstem can be compressed if there is raised intracranial pressure from an abscess and a lumbar puncture is done. Of particular note is the finding that almost 50% of patients with an intracranial infection presented with a periorbital cellulitis or frontal swelling. Therefore it is important to recognise that because a collection of pus presents anteriorly it does not preclude any intracranial involvement. Intracranial infections secondary to rhinosinusitis occur sporadically and whilst it appears that this cannot be prevented, early recognition and treatment is essential to reduce any subsequent morbidity or mortality.

The symptoms associated with rhinosinusitis are usually self-limiting and become progressively less common in older children. There is no evidence that the majority of children who have persistent symptoms attributed to rhinosinusitis develop into adults with chronic sinus disease (the exceptions are those with cystic fibrosis, ciliary dyskinesia and immune deficiencies). Therefore, any treatment that is recommended whilst the child’s immune resistance is maturing or an enlarged adenoid is shrinking should have few side effects or be associated with few complications. The first line treatment should involve harmless measures such as teaching nose blowing, saline sprays, short courses of topical decongestants and probably most of all, an explanation to the parents. Allergen avoidance in children with coexisting allergic mucosal disease will help, as will regular topical nasal steroids for symptoms of obstruction and non-sedative antihistamines for itchy eyes, sneezing and rhinorrhea. Compliance with regular topical nasal medication is often poor, particularly under the age of 6 years. Children with an allergic nasal airway have an increased chance of having asthma and vice versa. If antibiotics are given for persistent purulent rhinorrhea or postnasal drip they should be given with the expectation that re-infection is likely to occur within the next few weeks. The place of radiology in the management of children with rhinosinusitis is very limited and is confined to the few who develop the complications of sinusitis or in whom an atypical infection is suspected. The adage of “primum non nocere” or “do no harm” should underlie the management of paediatric sinusitis.

References
A mucocoele is an epithelial sac containing mucus which fills the sinus. Unlike a blocked sinus it is capable of expanding. They cause local destruction, result in bone resorption and can result in displacement of adjacent structures, most commonly the orbital but rarely the intracranial contents. If they get infected, they can present as acute infected mucopyoceles. Mucocoeles are commonly idiopathic but may occur secondary to infection, trauma, nasal polyposis or neoplasms. There is often a time delay between the initiating event and the mucocoele becoming symptomatic. Mucocoeles are a result of several interactive processes; obstruction, inflammation and bony remodelling.

**Epidemiology**

The most common location of mucocoeles is frontal sinus although they can occur in any of the paranasal sinuses. Their incidence is approximately 65-89% in the frontal sinus, followed by 8-30% in the ethmoid sinuses and less than 5% in the maxillary sinus. They are rarely found in the sphenoid sinus.

The majority of mucocoeles present in the age group of 40-60 years old, although they can present at any age. Very rarely they present in the paediatric population. Most of the paediatric mucocoeles are idiopathic, although an association between mucocoeles and cystic fibrosis has been noted. Mucocoeles present equally in both the sexes. They can cause skull base destruction and intracranial extension in 10-15% of cases.

**Histology**

The sinus mucoperiosteum forms the epithelial lining and is commonly stratified columnar or cuboidal epithelium though squamous metaplasia occasionally occurs. There is an increased number of fibroblasts and inflammatory infiltrate of lymphocytes and monocytes. There is also a rise in mucus producing goblet cells.

There are a number of theories as to the additional stimulus required to initiate the cycle of bone remodelling. The mucocoele is capable of producing bone resorbing factors and inflammatory mediators which are either absent or found in much lower levels in normal or obstructed sinuses. Prostaglandin E2, prostacyclin and collagenase produced by fibroblasts are found in the capsule in higher amounts than normal sinus mucosa. Additionally an increased level of leukotrienes, IL-1, IL-1 and tumour necrosis factor have been found with upregulation of vascular adhesion molecules, e-selectin and I-CAM. Active bone resorption and new bone formation seem to facilitating expansion of the mucocoele as apposed to pressure and bony erosion. Expansion occurs at the site of least resistance and extension is predominantly infraorbital or intracranial. Rarely, they can erode through the front wall of the frontal sionus and present lumps on the forehead or eye brow.

**Presentation**

Diplopia is the most common presenting feature occurring in up to 95% cases. It is primarily at the extremes of gaze in the vertical plane and may be ignored by the patient as it initially causes minimal symptoms. Unilateral proptosis occurs in up to 91% of patients, this is usually painless and slowly progressive. Decreased ocular mobility, particularly on upward gaze is present in around 55% of patients. With reduced visual acuity occurring in only 5% cases, blindness is unusual.

The optic nerve is relatively long compared to the orbital axis this allows proptosis to slowly evolve before compromising visual acuity. A small proportion present with frontal swelling. Frontal headache is a less common feature and epiphora rarely occurs. Mucocoeles may become infected and present as a pyocele.

**Examination**

Externally, mucocoeles may present with a swelling of the face or forehead. Proptosis and some restriction or precipitation of diplopia is not uncommon when the orbit is involved. On endoscopy an expanded mass may be present in the nasal cavity, though that is rare. Endoscopy is usually normal in these patients except when they occur.
secondary to other pathology such as polyposis, rhinosinusitis, neoplasm such as an osteoma or malignant sinonasal lesion. Scars may be visible from previous external drainage procedures or a fistula can be evident in the upper lid region if an inadvertent external drainage has been attempted. Rarely, mucocoele extending to the orbital apex may lead to an acute presentation with visual disturbance, including diplopia and blindness.

**Imaging**

Frontal sinus mucocoeles are apparent on plain x ray as an expanded sinus with loss of the scalloped margin. In addition there is loss of translucence and sclerosis at the margins with occasional microscopic calcification. However, the investigation of choice is CT scan of the sinuses.

CT scanning with reconstruction allows assessment in the axial, coronal and sagittal plain giving a three dimensional view of the mucocoele. This can be invaluable in assessing ophthalmological and intracranial extension. Figure 2. CT may also help distinguish between benign and malignant processes. Mucocoeles most frequently arise in the frontal and ethmoid sinuses and show an expanded sinus containing no air. The bone may be normal, sclerotic, thinned or eroded. Mucocoeles appear as a homogenous isodense mass (10-18 HU) with either no enhancement with contrast or enhancement only of the lining. Figure 4.

MRI is recommended if there is expansion into the orbit or cranium. Figure 3. It is also indicated where there is uncertainty about the primary pathology, or there is a known neoplastic lesion. Figure 4. A mucocoele usually has low T1 and high T2 signal. Post contrast MRI can differentiate between mucocele and solid neoplasia. The mucocele demonstrates peripheral enhancement only whereas neoplastic lesions would show a non enhancement of the whole lesion.

**Microbiology**

Mucocoeles are not considered an infective process however culture may be positive in up to 52% of cases. Antibiotic therapy may affect the number of positive cultures. A number of organisms have been identified such
as Staphylococcus aureus, Staphylococcus albicans and Haemophilus influenzae. Patients may not have clinical signs of infection. Less commonly, infection with pseudomonas may occur in cystic fibrosis or immunocompromised patients. Antibiotic therapy is not recommended except in acute pyocele presentation.

**Classification**

Frontal sinus mucocoeles present in different sizes and can have variable extent and expansion. The following classification system is proposed to help standardizing assessment and management of frontal sinus mucocoeles.

**Type 1** Limited to frontal sinus (with or without orbital extension)

**Type 2** Frontoethmoidal mucocoeles (with or without orbital extension)

**Type 3** Erosion of the posterior sinus wall
- A - Minimal or no intracranial extension
- B - Major intracranial extension

**Type 4** Erosion of the anterior wall

**Type 5** Erosion of the anterior and posterior wall
- A - Minimal or no intracranial extension
- B - Major intracranial extension

**Treatment**

The treatment of mucocoeles is surgical. The philosophy of mucocoele surgery is to perform the least destructive procedure required to achieve adequate drainage and prevent recurrence. Surgical approaches described in literature range from marsupialisation of the mucocoele leaving the lining intact to radical exenteration and obliteration. The approach used is determined by location of the mucocoele, associated pathology (e.g. nasal polyposis or osteoma), previous surgical procedures and the anatomy of the paranasal sinuses. Preoperative assessment and planning is paramount.

Adjuvant antibiotic treatment is indicated in the presence of infection. Extensive drainage surgery should be avoided during an acute infective episode.

An endoscopic approach is the procedure of choice in mucocoeles which can be widely marsupialized via an endonasal route. It has the advantage of not leaving an external scar, and does not disrupt the trochlea or supraorbital nerve supply. However, it may be more difficult to achieve drainage in a lateral frontal sinus mucocoele or where hypertrophic bone occludes the recess. There is often a residual bony deformity due to the expansion which requires time to remodel.

In the long term, circumferential scarring and stricture formation in the frontal duct can result in stenosis, sinusitis and mucocoele recurring.

The terminology for endoscopic frontal sinus drainage surgery can be confusing with many names describing essentially similar procedures. Figures 5a-d. Frontal Sinostomy or Draf I procedure establishes frontal sinus drainage by addressing the cells in the frontal recess, in particular the ager nasi cell and frontoethmoidal cells to widely open the natural osteum. A Draf IIa enlarges the natural osteum by opening the frontal sinus floor from...
lamina papyracea to the middle turbinate. A Draf IIb extends the osteum from the lamina papyracea to the nasal septum. A Draf III procedure is synonymous with endonasal median drainage, modified Lothrop’s and frontal drill out. This resection opens the frontal sinus floor from ipsilateral to contralateral lamina papyracea including removing the upper nasal septum17.

An external approach may be indicated in cases with uncertain pathology, revision surgery that is unsuitable to an endoscopic approach, where malignancy is an underlying cause of the mucocoele formation, when the mucocoele is lateral to the orbital contents or when the mucocoele arises in the poorly accessible supraorbital cells. Coronal incision with osteoplastic flap and frontal trephination are the commonest modalities of external approaches as the Lynch-Howarth approach has discredited as an acceptable approach for frontal sinus surgery.

If drainage procedures have failed then sinus obliteration may be considered however it may be extremely difficult to gain microscopic clearance of the mucocoele sac in areas where there has been bony erosion leaving the sac abutting periorbita or dura. This raises the possibility of further mucocoele formation over time. Where it has not been possible to restore normal sinus drainage and obliteration has failed a Riedel’s procedure may be the only remaining option however with the obvious cosmetic deformity it should be a last resort13.

Although, there may be significant areas of bone resorption in the posterior table of the frontal sinus, skull base or orbit, provided the mucosal lining is intact it is not necessary to repair areas of bony dehiscence. The lining of the sinus returns to normal appearance with mucociliary clearance re-established within a matter of weeks10,18. Failure of proptosis and diplopia to resolve may indicate a residual, recurrent mucocoele, or failure of bone remodelling11.

### Complications

The rate of major complications is very low with endoscopic mucocoele surgery. One of the largest series by Har El

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Recurrence</th>
<th>CSF leak</th>
<th>Infection</th>
<th>Diplopia</th>
<th>Flap necrosis</th>
<th>Cosmetic deformity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic Draf IIa, IIb, III</td>
<td>0.9-2.3%</td>
<td>0.9%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>None</td>
</tr>
<tr>
<td>Lynch-Howarth fronto-ethmoidectomy</td>
<td>11%</td>
<td>5%</td>
<td>1-10%</td>
<td>32%</td>
<td>N/A</td>
<td>6% Webbing</td>
</tr>
<tr>
<td>Osteoplastic flap</td>
<td>3%</td>
<td>6%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>3-5% frontal bossing, bone depression</td>
</tr>
<tr>
<td>Sinus obliteration</td>
<td>3 – 35%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
reports of 108 cases shows only one case each of CSF leak and recurrence following endoscopic marsupialisation with mean follow up of 4.6 years. Hartly and Lund report no complications or recurrence in a small paediatric series of 7 patients who underwent endoscopic drainage of mucocoeles. Proptosis resolves in around 75% of patients and improves in the remainder. Diplopia resolves in around 67% of cases where it is present. It is important to exclude residual problems as a cause of persistent symptoms.

Summary

Mucocoeles are uncommon and most frequently present with orbital symptoms. Frontoethmoidal mucocoeles predominate. Treatment is primarily surgical and should be approached systematically. The aim is to marsupialize the mucocoele and provide adequate sinus drainage and to prevent recurrence. Where this is not possible the aim should be to remove any functioning sinus mucosa to prevent recurrence. Mucocoele recurrence is uncommon and the majority of ophthalmic symptoms resolve postoperatively.

References

The Reliability of Patient Outcome Scores in Rhinology

Ms Claire Hopkins, FRCS (ORL - H&N)
Consultant Otolaryngologist, Guy’s Hospital,
Great Maze Pond
London
SE1 9RT

Introduction
The success of surgery has traditionally been judged by the surgeon – based on postoperative examination, histology or radiological findings. Increasing patient empowerment has brought to the spotlight the patient’s own evaluation of their health-related quality of life (HRQOL) before and after surgical interventions, and there is now growing acceptance that patients’ views are essential in the delivery of high quality care.

Patient Reported Outcome Measures (PROMs) are measures of HRQOL that are self-rated and reported directly by the patient. They usually refer to a single time point or clearly defined preceding period, thus ‘outcome’ measure in this setting is a misnomer. The impact of medical care can be determined by comparing repeated measures before and after the intervention. Clinical measures often correlate poorly with PROMs, and fail to predict changes in PROMs following treatment. In addition, individual patients may report very different levels of HRQOL despite having similar disease burden. This has lead clinicians to question both the reliability of patient rated measures and the growing demands of the Department of Health to collect such data.

Patient-Rated Outcome Measures
Quality of life is measured using one of a growing number of ‘instruments’; typically these are questionnaires that allow quantitative assessment of otherwise subjective results. Patients are required to rate the impact of their disease across a number of specified ‘domains’ or areas of interest. Individual questions are scored according to severity or impact of disease, and then scores are combined to produce an overall total. Scores can be used to follow patients with chronic disease, compared before or after an intervention at an individual patient level, or across different groups of patients, thus quantifying the amount of change.

Generic versus disease-specific outcome measures
Some PROMs have been developed for particular conditions or treatments (disease-specific) while others are designed for use in all patient groups or healthy individuals and measure patients’ perception of their general health (generic measures).

Generic PROMS, such as the SF-36, allow comparison between conditions or treatments, and therefore can be used to determine the impact of different diseases on patient groups, the relative cost utility of different interventions and to inform commissioning decisions. Using the SF-36, chronic rhinosinusitis has been shown to have a negative impact on several aspects of quality of life, and has a greater impact on social functioning than chronic heart failure, angina or back pain.

The EQ-5D measures HRQOL across domains; walking and mobility, ability to self-care, ability to perform usual activities, pain and anxiety or depression, and has been recommended for future use by a working group of the
DoH. While suitable for surgical procedures such as hip and knee arthroplasty, for which it is currently being used by the DoH, global measures such as the EQ-5D often lack the sensitivity to assess changes in health status in rhinological conditions. This is of concern if such measures are used for demand management to ration healthcare.

The Glasgow Benefit Inventory (GBI) is a validated generic instrument that has been widely used in otolaryngology. It is a post-intervention questionnaire that is administered once only, and has been used to show benefit from functional and cosmetic septorhinoplasty (+58.3%), endoscopic sinus surgery (+237%), endoscopic DCR (+16.8%) and septoplasty (+11.3%). Although once only administration of the instrument is likely to increase compliance, it means that baseline data is not collected and therefore precludes controlling for this in comparative studies. It also fails to add clinical understanding of the severity of patients’ symptoms prior to treatment, which may otherwise help guide treatment.

Disease specific PROMS in rhinology
There are a rapidly growing number of instruments designed to measure patients’ perception of HRQOL in direct relation to rhinological disease. These disease specific instruments readily identify the most important symptoms to patients, quantify the severity of all commonly associated symptoms, focus the consultation, and provide a useful clinical record; thus may help facilitate the patient’s visit. They can help define the aims of treatment, and are likely to be more sensitive to small but clinically relevant changes in outcome than global measures.

Rhinosisinusitis
A recent literature review identified 15 disease-specific instruments designed for use in patients with rhinosinusitis (either acute or chronic). Both the Taskforce on Rhinosinusitis and the European Position Paper on Nasal Polyposis have recommended the collection of PROMs, but have been unable to advocate a single outcome tool suitable for all studies, and the choice will depend partly on the clinical setting. Morley and Sharp, on appraisal of the available measures concluded that the SNOT-22 was the most suitable tool in terms of reliability, validity, responsiveness and ease of use. An earlier systematic review, prior to publication of the SNOT-22, recommends the RSOM-31 for rhinosinusitis, a longer form version of the same tool, and the RQLQ for rhinitis. This paper also presents an excellent assessment of the psychometric properties of each tool.

The SNOT-22 was used to collect prospectively the outcomes of 3,128 patients undergoing a range of surgical procedures for chronic rhinosinusitis, recruited by the National Comparative Audit of Surgery for Chronic Rhinosinusitis and Nasal Polyposis. This is the largest published outcomes study to date in CRS, and therefore provides useful benchmarking data against which future studies may be compared. Significant reductions in SNOT-22 scores were achieved by surgery, and maintained across a 5-year period (Fig 1). Psychometric validation has been completed, and normative data using the SNOT-22 also collected.

Nasal obstruction and septal surgery
The Nasal Obstruction Septoplasty Effectiveness (NOSE) questionnaire is a validated 5-item instrument for use in patients with nasal obstruction, and has been used to measure improvements in QOL in septoplasty, functional septorhinoplasty and nasal valve surgery. The SNOT-22 has also been used in septoplasty, although it has not been validated for use in this patient group.

Rhinoplasty and facial appearance
Perhaps more so than in any other aspect of rhinology, patient satisfaction and quality of life must be the measure against which successful aesthetic facial plastic surgery should be judged. Patient satisfaction will be achieved by not only meticulous surgical technique, but also by clearly defining which aspects of cosmesis concern the patient. The Rhinoplasty Outcomes Evaluation (ROE) is the only QOL instrument designed specifically for rhinoplasty, and has been fully validated. There are few published studies including patient rated satisfaction following rhinoplasty. Three studies show significant improvement in ROE scores following rhinoplasty.

Organ Specific PROMs
Wilson and colleagues argue that the disease specific measures highlighted above suffer from the need to diagnose the appropriate disease before the measure can be applied, and therefore have developed a ‘general nasal patient inventory’. The resulting 45-item questionnaire has the benefit of capturing many different symptoms associated with a range of rhinological conditions. The
large number of items results in a higher respondent burden that may reduce compliance, but it will be useful for studies wishing to compare different rhinological conditions and their impact on quality of life.

**Collection of PROMs**

In the UK, collection of pre and post-operative PROMs data is now a legal requirement for health care providers following joint replacement, hernia and varicose vein operations\(^23\), and the scope is likely to be widened to include other procedures. In the meantime, we as individual surgeons are under increasing pressure to produce our own outcomes data. It is hoped that as collection of PROMs become compulsory, health care providers acknowledge the time required to do so, and remunerate it appropriately. In the meantime, PROMs may be incorporated into clinical practice with little disruption to the clinic by encouraging patients to complete questionnaires whilst waiting to be seen. Data collection may be undertaken on a simple proforma, allowing the data to be entered onto central databases at a later stage, by non-clinical personnel.

**Reliability of patient rated outcomes**

Clinician rated outcome measures are often thought to be more reliable than those rated by the patient, and are thus more readily accepted by clinicians. However, clinicians are also prone to error, and may be biased by preconceived ideas of disease severity, or the surgery they have performed. Even ‘hard’ outcome measures such as revision surgery rates can be greatly biased by the surgeon’s attitude to further surgery.

We must remember that it is most frequently impairment of their quality of life that drives our patients to seek treatment for rhinological conditions. There is little point demonstrating an improvement in radiological appearances of the sinuses if this is not accompanied by improvement in symptoms. We should trust patients to be honest about their symptom severity, and value their rating of disease burden.

**Correlation with clinician rated measures**

Several publications have demonstrated the lack of correlation between PROMs in chronic rhinosinusitis and objective measures, such as the radiological Lund-Mackay scoring system\(^24-25\). Similarly, a recent systematic review has demonstrated no correlation between sensation of nasal obstruction and measurements of cross-sectional airflow using rhinometry\(^26\).

The relationship between biological, physiological and radiological variables and symptoms is complex. Physiological variables can be profoundly abnormal in some asymptomatic patients, while others may report severe symptoms in the absence of change in biological markers of disease. Studies in many medical specialties demonstrate that patient reported measures of symptoms are poorly correlated with clinical measures. In studies of benign prostatic hypertrophy there was no association between urodynamic indices of obstruction and obstructive symptoms\(^27\). Studies of asthma and COPD have found little or no correlation between subjective dyspnoea and FEV\(_1\)\(^28\).

It has been proposed that patients’ symptoms and quality of life are the result of an interaction between many factors, in which biological or physiological variables are only a piece of the final jigsaw (Figure 2)\(^29\). Response to disease is modified by many patient factors, including individual characteristics and the patient’s environment. For example, studies have shown the gender appears to modify symptom severity in sinonasal disease, with women reporting higher SNOT-22 scores than men for the same level of disease severity on cross sectional imaging\(^30\). Cultural expectations, age, socio-economic status and co-morbidities are amongst other factors that may modify the impact of disease. Clinicians probably overestimate the impact that measurable biological variables have on symptoms and functioning.

It is therefore not surprising that there should be little correlation between a patient-based symptom severity-scoring systems. The absence of correlation does not suggest that either patient rated or objective scores are invalid, but that they are measuring different aspects of the disease process, and therefore are useful adjuncts in outcome measurement.

Where reducing the impact of symptoms on the quality of life of the patient is the primary aim of treatment, PROMs may be more useful in guiding treatment and measuring the resulting outcome. Clinician-rated measures may however provide additional feedback to the surgeon in terms of technique.

**Predicting outcome**

Detractors of the use of PROMs as a primary outcome measure also argue that they do not predict the outcome of surgical intervention. For example, Kennedy\(^31\) has reported that symptomatic improvement following FESS surgery does not correlate with resolution of mucosal disease in patients with chronic rhinosinusitis, and therefore symptomatic improvement alone may not be a reliable outcome measure. However, for the reasons discussed above, it is unlikely that a patient rated measure will
predict outcome measured using a clinician rated ‘biological’ marker, but patient rated scores are strong predictors of symptomatic improvement following surgical intervention\(^\text{15}\).

Clinical applications of PROMs
In the clinical setting, repeated measures map the individual patient’s journey, and allow improvements or exacerbations to be readily identified. For example, using repeated SNOT-22 measures a ‘snotogram’ can be constructed which highlights the impact of treatment (Figure 3). This was produced using an electronic database developed on behalf of the British Rhinological Society (www.rhinodataset.co.uk), which also allows comparison of outcomes against national averages.

Limitations of PROMs
Quality of life measures are not a substitute for measuring clinical outcomes but are an adjunct to them. For example, symptomatic improvement following septoplasty could be combined with assessment of the nasal airway, such as nasal inspiratory peak flow. In addition, quality of life is not the only way to measure patient centred outcomes; measures of disability, social interaction and support, and psychological well-being may be more appropriate in some settings.

Scores from quality of life measures are usually presented as population means. While this is useful in testing one treatment against another in groups of patients, it is of less value in clinical practice. It is much more difficult to interpret scores on an individual patient basis, for example, is a score above the mean considered abnormal? Should intervention be restricted to those with scores above a certain point? In order to answer this, some studies have attempted to define the ‘minimally important difference’ but again, this applies values derived from the whole
population to individuals who may differ widely in their responses.

Finally, there is concern that routine collection and publication of outcome data may encourage surgeons to become risk averse, and refuse treatment to the most high risk cases. However, it is hard for a surgeon to predict which patients may derive most symptomatic benefit, as for reasons stated above, this may not relate to markers of disease severity. There is also no evidence of case selection in cardiothoracic surgery following publication of mortality data.

Summary
With impending revalidation, it is very likely that all surgeons will be required to produce and publish individual outcomes data. Routine collection of PROMs is likely to become mandatory for health care providers. Patients now rightly expect their doctors to record outcomes of clinical care. We should embrace this opportunity, and use this patient rated information to enhance the doctor-patient relationship and focus communication. Careful use in cohort studies, or within randomised trials may identify important differences in outcomes, between treatments or providers, although it is still important to recognise the limitations of the outcome tools. Specialty wide national databases, such as The British Rhinology Society database, are likely to facilitate data collection, and comparison with other health care providers. PROMs can become a useful clinical tool to improve outcomes from rhinological surgery.

References
2 www.sf-36.org
10 Morley AD, Sharp HR. A review of sinonasal outcome scoring systems - which is best? Clin Otolaryngol 2006; 31, 103-109
19 Hellings PW, Trenite GJN. Long-term patient satisfaction after revision rhinoplasty. Laryngoscope. 2007; 117: 985-998
Common Genetic Syndromes in Otolaryngology

Introduction
Genetic syndromes affecting the head and neck are not uncommon. With the advent of newborn universal hearing screening, it is quite likely that the ENT surgeon may be the first clinician diagnosing an underlying syndrome. It is therefore vital that the ENT surgeon recognises patterns of common syndromes affecting the head and neck to organise relevant investigations and plan future management.

Materials and Methods
This is a review article based on a literature search performed on Medline in April 2011. The article also draws its source from clinical experience gained from a tertiary paediatric ENT referral unit in Scotland.

Conclusion
Syndromic children need to be managed in a multidisciplinary setting. Early recognition of various anomalies in the head and neck is vital to long term treatment outcomes in these children.

Keywords
paediatric-ENT syndromes

Common genetic syndromes in ORL-HNS
Otolaryngologists with a paediatric practice need to be aware of common genetic syndromes affecting the head and neck as this is vital for requesting appropriate investigations, seeking suitable referrals and planning further management. Also not uncommonly, the otolaryngologist can be the first clinician to diagnose a syndromic child.

Definitions

Syndrome
A syndrome is defined as multiple defects in one or more tissues thought to be the result of a single cause. The classic example is Down’s syndrome where a single defect (Trisomy 21) leads to a series of anomalies such as small stature, cardiac malformations, small ears, slanted palpebral fissure etc.

Sequence
A sequence is defined as a series of abnormalities occurring in a non-random pattern where a single embryological event is the cause of such defects. An example is Di-George sequence occurring due to malformation of the 3rd and 4th pharyngeal pouch resulting in defects affecting the thymus, parathyroids and heart.

Association
An association is defined as a group of defects occurring together more often than by absolute chance alone. These abnormalities do not occur as part of an established malformation. The VACTERL association is a recognised disorder which includes Vertebral anomalies, Anal atresia, Congenital heart defects, Tracheo-oesophageal fistula, Renal and Limb abnormalities.

Down’s syndrome is the commonest genetic syndrome encountered in ENT practice. The reader is asked to refer to a previous edition of ENT masterclass for a detailed discussion. Down’s syndrome will not be further discussed
year book 2011 volume 4 number 1

in this chapter. A detailed discussion of all genetic syndromes is outside the realms of this chapter and therefore we have discussed the commoner syndromes with particular emphasis on their clinical presentation and practical management.

**Syndromes associated with hearing loss**

**Conductive hearing loss:** Kartagener, Treacher-Collins, Goldenhaar and Turners syndrome

**Presentation**

*Primary ciliary dyskinesia* along with situs inversus, chronic recurrent sinusitis and bronchiectasis is known as Kartagener syndrome. Conductive deafness is usually mild and secondary to middle ear effusion. Due to mild hearing loss, hearing rehabilitation is often not required. If needed, the first line of treatment for hearing rehabilitation should be hearing aids as grommet insertion in these patients can result in troublesome otorrhoea.

**Treacher-Collins syndrome (TCS):** TCS occurs due to a developmental abnormality of the first and second branchial arch. Inherited in an autosomal dominant pattern, the gene currently implicated is TCOF. ENT features include microtia/dysplastic ears, conductive hearing loss secondary to ossicular malformation, pre-auricular sinuses/fistula, cleft palate, mandibular and midfacial hypoplasia.

**Goldenhaar syndrome** is hemifacial microsomia (figure 1) associated with vertebral anomalies. Like TCS, this syndrome also occurs due to a developmental abnormality of the first and second branchial arch. Children with TCS and Goldenhaar syndrome may require bone conduction or bone anchored hearing aids due to dysplastic ears. In Goldenhaar syndrome, the unaffected ear is an important determinant in hearing rehabilitation.

**Turners syndrome (45XO):** Occurs due to absence of a sex chromosome. General features include short stature, infertility, webbing of neck and a low posterior hairline. Deafness in Turners syndrome may be conductive or sensorineural.

Glue ear is a very common occurrence in these children. Children with Turners syndrome are also prone to develop cholesteatoma and therefore close surveillance is required. High tone sensorineural hearing loss is well recognised and usually occurs between the third and fourth decade.

**Syndromes associated with sensorineural hearing loss:** Ushers, Brachio-oto-renal, Pendred, Waardenburg, Alport, CHARGE, Jervell-Lange-Nielsen and Alström

**Presentation**

Ushers syndrome is an autosomal recessive disorder characterised by hearing loss, retinitis pigmentosa and vestibular dysfunction. There are three variants namely Types I, II and III. Types I and II are differentiated by the presence or absence of vestibular dysfunction respectively and Type III occurs with progressive hearing loss which can be post lingual in onset. Early aggressive intervention of hearing impairment is essential as patients with retinitis pigmentosa can have progressive vision deterioration.

**Branchi-Oto-Renal (BOR):** An autosomal dominant disorder characterised by abnormalities of the branchial arches, ears and kidneys. The genes implicated are EYA1, SIX1 and SIX5. Renal abnormalities recognised include duplex kidneys, hydronephrosis and agenesis. ENT features include preauricular pits/dysplastic pinna, branchial fistula and sensorineural deafness secondary to mondini dysplasia. Due to BOR, audiometry is essential for all children presenting with branchial or preauricular anomalies. If audiometry is abnormal a renal ultrasound should be requested.

**Pendred syndrome:** Characterised by stepwise progressive sensorineural hearing loss and congenital hypothyroidism. It constitutes 7.5% of all causes of congenital syndromic hearing loss. Anatomically an enlarged vestibular aqueduct is seen on CT and patients may develop progressive hearing loss following seemingly trivial head injuries.

**Waardenburg syndrome** is another common cause of syndromic hearing loss inherited in an autosomal dominant pattern. Mutations have been identified in PAX3, MITF, EDNRB, EDN3 and SOX10. Other features include a high nasal bridge, white forelock of hair, heterochromia of the iris, skin hypopigmentation, limb anomalies and Hirschprung’s disease.

Figure 1: Child with Goldenhaar syndrome. Note dysplastic right pinna.
**Alport syndrome** has a variable inheritance (X-linked/Autosomal dominant or recessive) characterised by renal involvement (glomerulonephritis) and sensorineural hearing loss. Mutations have been identified in COL4A4, COL4A3 and COL4A5. Hearing loss affects 83% of males and 50% of females.

**Jervell-Lange-Nielsen syndrome** is as well recognised cause of sensorineural hearing loss and is inherited in an autosomal recessive manner. It is also known as prolonged Q-T syndrome. The primary abnormality is seen in the potassium channel gene KCNQ1. Acute cardiac events such as ventricular tachycardia and ventricular fibrillation are seen. A history of sudden unexplained deaths or syncope events in the family should raise clinical suspicion of this condition.

**CHARGE** is a genetic disorder characterised by Coloboma of the iris, congenital Heart Defects, choanal Atresia (figure 2), retarded growth, Genitourinary and Ear anomalies. Mutations have been identified in CHD7 in approximately 60% of cases. ENT features include choanal atresia, microtia, ossicular malformation, conductive/ sensorineural deafness and inner ear malformations such as hypoplastic or absent semicircular canals.

Due to coexisting anomalies, every child with choanal atresia should undergo a renal ultrasound, echocardiogram, audiometry and ophthalmology assessment.

Diagnosis is confirmed by direct flexible nasendoscopy examination and CT scanning aids surgical planning. Surgical approach is either by a transpalatal or transnasal approach using a 120 degree endoscope placed in the mouth and positioned behind the soft palate. The atretic septum is perforated and enlarged using powered instruments. Stents should be placed postoperatively and remain for at least 6 weeks.

**Alström syndrome** occurs with short stature, obesity, diabetes mellitus, cardiomyopathy and progressive hearing loss. It is inherited in an autosomal recessive manner. Renal, liver and pulmonary disorders are recognised.

**Management**

Investigations and treatment of all children with syndromic hearing loss should be planned in a multidisciplinary setting with specialist input from clinical geneticists, audiologists, Otolaryngologists, paediatric physicians and ophthalmologists.

Counselling should be offered to immediate family members of syndromic children as inheritance patterns vary and this could provide useful information on the likelihood of future occurrences. Blood tests are not routinely performed in the assessment of syndromic hearing loss but should be guided by history and examination findings.

High resolution CT scan of the temporal bones (1 mm slices) and MRI of the inner ears provide useful information about the ossicles, cochlea, internal auditory meatus and cerebello-pontine angle. They also help to diagnose other causes of hearing loss such as an enlarged vestibular aqueduct or mondini dysplasia (Pendred syndrome).

**Syndromes associated with airway abnormalities**

**Sleep disordered breathing/Obstructive sleep apnoea**

A significant proportion of syndromic children will present with sleep disordered breathing including obstructive sleep apnoea. Clinically children may present with habitual snoring, witnessed apnoeas and restless sleep. Daytime symptoms include poor concentration, irritability and behavioural symptoms.

Factors contributing to SDB in syndromic children include generalised hypotonia (Prader-Willi), Midfacial hypoplasia (Craniosynostosis), small retracted mandible (Pierre-Robin sequence), Macroglossia (Beckwith-Wiedmann) or adenotonsillar hypertrophy alone.

**Airway abnormalities based on anatomical site**

1) **Obstruction involving the nasal cavity**: Choanal atresia [CHARGE(see above)], Piriform aperture stenosis [Solitary median maxillary central incisor syndrome (SMMCI)]

**Solitary median maxillary central incisor syndrome (SMMCI)** is a rare midline developmental anomaly of unknown cause associated with nasal cavity defects. General features include microcephaly, holoprosencephaly,
congenital heart defects, cleft lip/palate, hypopituitarism, oesophageal/duodenal atresia and ambiguous genitalia. EN T features include a central maxillary incisor, pyriform aperture stenosis (PAS) and choanal atresia.

As neonates are obligate nasal breathers, these children can present with acute onset respiratory distress worse whilst feeding. The diagnosis is obvious on inspection with a bony slit like nostril and a single central tooth bud in the upper gum (figure 3).

Piriform aperture stenosis can present with life threatening respiratory distress. The diagnosis is suspected in a neonate with acute respiratory distress and difficulty passing a nasotracheal or nasogastric tube7. Less severe forms present with intermittent episodes of apnoea and cyanosis relieved by crying spells. The diagnosis is confirmed with a CT scan (figure 4). A pyriform aperture width of <11mm is diagnostic. Treatment depends on severity of symptoms and can either involve conservative measures such as nasal decongestants, nasal steroid drops or NPA insertion and/or surgical management16. Surgical technique is through a sublabial approach and debriding the bony overgrowth and widening the pyriform aperture. Nasal stents are placed postoperatively to maintain airway patency and removed 6 weeks later.

2) Obstruction at level of tongue base and pharynx: Macroglossia (Beckwith-Wiedmann syndrome, Mucopolysacharidosis), small retracted mandible (Pierre-Robin sequence, Sticklers syndrome), Midfacial/maxillary hypoplasia (Craniosynostosis).

Beckwith-Wiedmann syndrome occurs as a result of mutations in the growth promoting gene located on chromosome 11p158. Clinical features include macroglossia, ear lobe crease, posterior helical pits, skeletal overgrowth, gastrochisis, hypoglycaemia and renal anomalies. Children with obstructive sleep apnoea may require a nasopharyngeal airway or rarely a tracheostomy. Macroglossia may be treated with an anterior wedge resection of the tongue which improves cosmesis but is not so effective for airway obstruction9. Early mandibular distraction may provide airway relief as well. However most airway pathology in these patients resolve with growth.

Pierre Robin sequence is a developmental anomaly presenting with mandibular hypoplasia and cleft palate. ENT features include retrognathia, airway obstruction, feeding difficulties, failure to thrive and a small open postured mouth.

Sticklers is a genetic collagenopathy syndrome (figure 5). Inherited in an autosomal dominant pattern, Children with Sticklers syndrome also present with a Pierre-Robin sequence type anomaly. ENT features include a flattened facial appearance, cleft palate, micrognathia and upper airway obstruction. Patients particularly suffer with
skeletal abnormalities such as arthritis, scoliosis, hypermobile joints and double jointedness.

**Craniosynostosis** syndromes are inherited in an autosomal dominant pattern and include Crouzon, Apert, Muenke and Pfeiffer which are FGFR gene related craniosynostosis however Saethre-Chotzen results from mutation in the TWIST gene.

General features of craniosynostosis include proptosis, hypertelorism, syndactyly (Apert syndrome) and broad toes/thumbs (Pfeiffer syndrome). Specific ENT abnormalities include external ear deformity (small/low set ears), airway obstruction, ear canal atresia, hearing loss and (conductive/sensorineural). Clinical presentation also involves obstructive sleep apnoea and in severe cases can cause raised intracranial pressure. Nasopharyngeal airway and tracheostomy should be considered for airway obstruction. Surgical correction of facial abnormality usually involves midfacial advancement procedures.

3) **Obstruction at level of larynx and trachea:** Laryngeal cleft (Opitz-Frias), Tracheo-oesophageal fistula (Opitz-Frias, Pallister Hall syndrome), Laryngeal webs (Velocardiofacial syndrome).

**Velocardiofacial syndrome** (VCF) also known as DiGeorge or Shprintzen syndrome is a 22q11.2 microdeletion syndrome and inherited in an autosomal dominant pattern. General features include delayed developmental milestones, cardiac anomalies, short stature, immune deficiency and parathyroid dysfunction. ENT features include cleft palate, velopharyngeal incompetence and anterior glottis webs (Figure 6). VCF is surprisingly common and may present primarily to the ENT surgeon with recurrent acute otitis media due to immunodeficiency. From a clinical perspective, any child with a laryngeal web needs to have a FISH (fluorescein in situ hybridisation) test for VCF.

**Opitz-Frias syndrome** is a congenital dysmorphic syndrome and presents with delayed developmental milestones, congenital heart defects, hypospadias, hypertelorism, laryngeal cleft and tracheo-oesophageal fistulas.

**Mucopolysaccharidosis (MPS)** are metabolic disorders inherited in an autosomal recessive pattern except Hurlers syndrome which is X-linked. MPS are lysosomal storage disorders and their clinical features include skeletal abnormalities, coarse features, delayed physical/mental development and organomegaly. ENT features include obstructive sleep apnoea, recurrent sinusitis/ear infections, atlanto-axial joint instability and deafness. First line surgical management for OSA involves adenotonsillectomy with tracheostomy in selected patients. Due to atlanto-axial joint instability, the clinician should be extremely careful whilst positioning the head during surgery.

**Investigations of airway disorders**

Depending on the severity of symptoms, the following tests should be considered.

**Sleep studies**

Polysomnography is the gold standard test for sleep apnoea and can differentiate central vs. peripheral causes of sleep apnoea. The variables measured include heart rate, oxygen saturation, respiratory effort, electrocardiography and videotaping with sound. Apart from having a diagnostic value, sleep studies also help to monitor effectiveness of treatment following airway surgery.

**Microlaryngoscopy and Bronchoscopy (MLB)**

A formal Microlaryngoscopy and bronchoscopy under general anaesthetic should be performed in syndromic children with complex airway problems. Direct visualisation of the airway can identify abnormalities such as laryngeal webs (Velocardiofacial) and laryngeal cleft or TOF (Opitz-Frias).

**Conclusion**

This review has highlighted the common paediatric syndromes and their ENT management. A multidisciplinary approach is required for these children to identify all potential anomalies. Early identification of various anomalies can help in early diagnosis and can improve the quality of life of these children.
References
Assessment and Management of Congenital Atresia of the Ear

Christopher Loh (MBBS, MRCS, DOHNS), Ray Clarke (BSc DCH FRCS FRCS(ORL))
ENT Department, Alder Hey Children's NHS Foundation Trust, Alder Hey Hospital, Eaton Road, West Derby, Liverpool, L12 2AP

Keywords
microtia, congenital, atresia, ear

Introduction
Microtia (Greek for “small ear”) is a congenital deformity where the pinna is small and underdeveloped (microtia) or absent (anotia). It can be unilateral (Fig. 1, 2) or bilateral. It has a prevalence of 2.5 in 10000 births1. Unilateral microtia is far more common than bilateral microtia (4:1). In unilateral microtia, the right ear is most commonly affected and it is more common in males than females. The reason and mechanism for this is not understood. Canal atresia or stenosis is also frequently associated with microtia and in addition to the aesthetic issues, presents problems of hearing loss.

Classification
Although there are many classification systems for microtia, the Marx classification2 (Table 1) is the most widely used Canal atresia is frequently associated with the more severe forms of microtia.

Jahrsdoerfer proposed a scoring system for patients with canal atresia in order to try to determine suitability for canal atresia surgery3.

Aetiology
The embryology of the pinna, ear canal, middle ear cleft and labyrinth is well described4 and is beyond the scope of this article. However, it is important to note that microtia can be associated with abnormalities of the ossicles, middle ear cleft and labyrinth.

In the majority of cases, microtia presents as an isolated deformity. Usually, the aetiology is unknown. However, it can present as part of a spectrum of abnormalities in syndromes such as Branchio-oto-renal, hemifacial microsomia, Goldenhar and Treacher Collins. Teratogens such as thalidomide and maternal rubella have been implicated in microtia. In addition, retinoids such as isotretinoin used for the treatment of acne, have also been implicated.

There are reports of familial microtia with varying patterns of inheritance5. However, there have also been reports of identical twins where only one twin had microtia6. These findings suggest that both genetic and environmental or intrauterine events are important in the development of microtia.

Immediate Management - Investigations
All patients with microtia should undergo hearing assessment within the first few weeks of life. Audiometric
brainstem responses can be done in most babies without a general anaesthetic and should identify hearing thresholds in the microtic and uninvolved ear. Both air and bone conduction thresholds should be assessed. A decision can then be made with regards to providing appropriate audiological rehabilitation.

A CT scan of the temporal bones does not affect the immediate management of the patient and thus can be left to a later date (Fig. 3).

An abdominal ultrasound can be carried out to identify babies with Branchio-oto-renal syndrome.

**Immediate Management – Hearing**  
In microtia with canal atresia, there is usually a severe conductive hearing loss in the affected side. However, inner ear function is usually normal, resulting in some ability to hear on the affected side.

The hearing in the contralateral ear is usually normal, and if so, parents should be reassured that speech and language development should proceed normally. However, if there is glue ear, an air-conduction hearing aid can be provided.

In bilateral microtia, it is important to provide amplification to the patient early with a form of bone conduction hearing aid. The BAHA Softband® is one such bone conduction aid which has proven popular and successful for use with younger children and babies (Fig. 4). The BAHA Softband is an elastic band similar to a sweat band used in sports. The BAHA® sound processor attaches onto the Softband via a connector disc sewn into the band. Importantly, the Softband comes in a variety of patterns and colours! Such hearing aids can also be useful in the patient with unilateral microtia to reduce the head shadow effect and improve the localisation of sound.

**Later And Continuing Management**  
The child with microtia should have regular audiological surveillance. A child is likely to develop otitis media with effusion (OME) in an unaffected ear at some point in their first few years. This would necessitate either provision of a temporary air conduction hearing aid or adjustment or an existing air conduction hearing aid. A ventilation tube may be necessary if any worrying retraction pockets develop.

Canal stenosis, more so than canal atresia, can lead to cholesteotoma. A review by Jarhsdoerfer and Cole in 1990 showed that cholesteotoma can occur in up to 91% of children over the age of 12 with a canal stenosis 2mm or narrower7. However, there were no cases of cholesteotoma in children under three years of age. Thus, a high resolution CT scan of the temporal bone should be carried out in cases of canal stenosis between the age of five and ten years. Repeated CT scans are not required in patients with canal atresia due to the rarity of cholesteotoma in this group.

**Later Management – Surgery**  
Whilst a child with microtia will often present to the ENT surgeon within the first several months of life, a decision with regards to surgical intervention is left for several years. There is, of course, much parental anxiety and a desire for corrective surgery early on. The options for correcting the cosmetic deformity are autologous...
reconstruction or a prosthetic implant. There is also the third option of doing nothing. In this, it is important that the child participates fully in the decision as to which route to take, with guidance from clinician and parent. The patient and parents have to be fully informed of the risks and benefits of each option as the effects of surgery are something that the child has to live with for the rest of his or her life.

Although there are psychological issues for the patient with microtia, most children do not seem to be unduly affected until the age or 6 or 7. The other important reason to wait until the child is older before surgery is allow the child to grow physically.

In unilateral microtia, any reconstruction should be based on the principle of symmetry with the non-microtic ear. The pinna reaches about 85-90% of its adult size between the ages of six and eight and surgery is not usually considered before this age.

**Surgery – Reconstruction**

Pinna reconstruction using the patient’s own costal cartilage can be considered the gold standard in care for the patient with microtia. It is imperative that the child and their costal cartilage be of an adequate size to create a framework for a reconstructed pinna. This usually happens at around 9 or 10 years of age. It is a procedure of at least two stages placed around six months apart.

At the initial stage, a template of the framework is made from the normal ear. The costal cartilage is harvested, usually on the opposite side of the microtia and using the cartilage from ribs 6, 7 or 8. The surgeon is more of a sculptor at this stage of the operation, using a good aesthetic eye to carve the framework to match the template and photos of the normal ear. The framework is then inserted underneath a pocket of non-hair bearing skin in the appropriate position. Some skin and cartilage remnants from the microtic ear may have to be excised at this point. However, enough tissue should be left to fashion a lobule. Suction drains are placed and left under a head bandage. The head bandage and suction drains are left for about a week.

At the second and subsequent stages, the cartilage framework is angled away from the mastoid using a wedge of cartilage banked from the previous operation. A skin graft is then used to cover the posterior surface of the newly reconstructed pinna. This is highly demanding surgery and should only be undertaken by those with appropriate training and expertise.

**Surgery – Prosthesis**

Two percutaneous abutments need to be placed in good quality cortical bone. Osseointegration should be checked before any skin and soft tissue remnants are removed, which would make autologous ear reconstruction impossible. The benefits of a prosthesis are a realistic looking pinna that exactly matches the opposite side. However, the prosthesis has a fixed lifespan and needs to be changed every two years. In addition, as the skin / implant interface is prone to irritation, the patient and family are committed to daily lifelong care of the implant site.

**Surgery for Canal Atresia And Middle Ear Abnormalities**

Canal atresia surgery is highly specialised and technically demanding. The aim of canal atresia surgery is to achieve serviceable hearing. The serious complications of such surgery include the small risk of facial paralysis, sensorineural hearing loss or a dead ear, and a re-stenosis requiring further surgery. With such risks, the excellent hearing results achieved by a bone anchored hearing aid is a more attractive option is the majority of cases.

**BAHA**

As mentioned throughout this article, the BAHA® is a good option for patients with bilateral or unilateral microtia with canal atresia. It provides excellent hearing rehabilitation with good speech discrimination scores. BAHA® surgery is usually carried out after the age of five to ensure adequate thickness of cortical bone, although some centres carry our surgery on children aged 2 to 3. As BAHA® surgery can be performed before autologous ear reconstruction, the location of the abutment must be planned to allow space for a reconstructed pinna.

**Conclusion**

When a surgeon first meets a baby with microtia, he or she will be able to look forward to establish a long and hopefully rewarding relationship with patient and family. A team should be available to provide surgical expertise, audiological assessment and rehabilitation and psychological support throughout the patient’s journey. Although there is sometimes parental desire to expedite surgery, the decision should be patient-led with as much information and support provided to help with the decision making. As such, surgery should be delayed until the patient is old enough to contribute to the decision-making process, which will affect him or her for the rest of his life.
References


Paediatric Obstructive Sleep Apnoea

Premjit S Randhawa MRCS, DOHNS, Antony A Narula MA FRCS FRCSEd
Department of Otolaryngology, St Mary's Hospital, Praed Street, London W2 1NY

Corresponding Author:
Premjit Randhawa
Department of Otolaryngology, St Mary's Hospital, Imperial Healthcare NHS Trust
Praed Street, London, W2 1NY
Tel: 0207 8867566   Email: prandhawa13@hotmail.com

Key Words
tonsillectomy; adenoidectomy; obstructive sleep apnoea; sleep disordered breathing; paediatric

Abstract
OSA is the severe end of the spectrum of sleep related breathing disorders (SRBD). It has an incidence of around 2% in the general population and if left untreated can lead to significant cardiovascular, neurocognitive, developmental and behavioural problems. Adenotonsillectomy is effective in the majority of children with OSA and prevents long-term complications. Children who undergo surgery for OSA show a growth spurt post-surgery as well as an improvement in school performance, behaviour and overall quality of life in the short and long term. Children with OSA are however at risk of developing post-operative respiratory complications which if managed in the wrong environment can lead to significant morbidity and mortality. At present however, no one diagnostic test is sensitive enough or specific enough to identify this group of children pre-operatively.

Key words
obstructive sleep apnoea; polysomnography; tonsillectomy; adenotonsillectomy; sleep study; respiratory complications

Introduction
Obstructive sleep apnoea (OSA) is defined as a disorder of breathing during sleep characterized by prolonged periods of increased upper airway resistance and recurrent episodes of partial and/or complete upper airway obstruction. This subsequently leads to disruption of normal ventilation and oxygenation during sleep as well as normal sleep patterns. OSA is the severe end of the spectrum of sleep related breathing disorders (SRBD) that encompasses primary snoring, upper airs resistance syndrome and finally OSA. It can lead to significant cardiovascular, neurocognitive, developmental and behavioural problems if left untreated.

Epidemiology
Obstructive sleep apnoea (OSA) has an incidence that is estimated to be about 2% (c.f. primary snoring 12%) and occurs equally in boys and girls. The peak incidence of OSA is between 2 to 8 years of age and parallels with the prominent growth of lymphoid tissue around the upper airway. OSA can occur earlier in children with craniofacial or neurological disorders due to abnormalities in upper airway anatomy. An increase in prevalence has also been noted in adolescents due to rising prevalence of obesity. In the United Kingdom it has been estimated that 27000 tonsillectomies are carried out annually with just under half being carried out for children with symptoms of obstruction.

Pathophysiology
Successful respiration is dependent on a patent upper airway which is determined by the diameter as well as tonicity of the pharyngeal muscles in response to the upper airway pressures generated during respiration. During the waking state, upper airway collapse is prevented by keeping an increased pharyngeal neuromuscular tone. During sleep however, there is reduction in pharyngeal dilator tone and hence a physiological narrowing in the airway and increased upper airway resistance.

The pathogenesis of paediatric OSA is complex and incompletely understood. It involves interplay between functional changes which occur normally during sleep and anatomical factors, both normal and abnormal, which lead to the narrowing of the upper airway and subsequently to partial or complete obstruction.

A generalized reduction of muscular tone begins during Stage N1 of non-rapid eye movement (NREM) sleep and progressively worsens until it is barely perceptible during rapid eye movement (REM) phase of sleep. Children, depending on their age, spend the majority of their sleep time (40-80%) in REM sleep. It is during this stage that
respiration is least stable which makes children even more prone to OSA. Any pathology that causes upper airway narrowing e.g. adenotonsillar hypertrophy or anatomical variation, contributes to the development of OSA.

The main predisposing factor for OSA in children is adenotonsillar hypertrophy which causes a relative narrowing of the upper airway (Figure 1). It is important to understand that adenotonsillar hypertrophy on its own does not necessarily lead to OSA as the variation between pharyngeal muscle tone and anatomy in individuals plays a significant part. Children with anatomical abnormalities e.g. craniofacial patients, Down’s syndrome, achondroplasia and mucopolysaccharidoses are at increased the risk of developing OSA. The RCPCH has stratified the risk of this high risk group of children developing OSA (Table 1). The reduced neuromuscular tones in these children also contribute to the development of OSA.

In obesity, the pathophysiology is related to excessive deposition of fat tissue within the muscles and tissue surrounding the upper airway, reducing airway size and casing increased airway resistance. The reduced lung volumes and decreased central ventilation drive in obese children also contribute to compromised upper airway patency.

Once obstruction occurs, impaired ventilation leads to hypoxia and hypercapnia with subsequent increased respiratory effort and finally arousal from sleep in order to re-establish airway patency. This awakening may be in the NREM stage of sleep where individuals generally feel groggy with worse cognitive function compared to awakening in other stages of sleep. This cycle is then repeated several times through the night, resulting in recurrent hypoxia and fragmentation of sleep.

Clinical Manifestations
Snoring is the most common symptom of presentation and OSA is unlikely in the absence of habitual snoring. If it is present, a more detailed history of sleeping patterns needs to be elicited. Table 2 lists common symptoms elucidated from patients with OSA. The loudness of snoring does not necessarily correlate with degree of apnoea.

Physical examination of a child who presents with symptoms suggestive of OSA should include a general examination of the child as well as a full ENT examination (Table 3). Non-specific findings related to adenotonsillar hypertrophy, such as mouth breathing, nasal obstruction during wakefulness, adenoidal facies and hyponasal speech may be present. It is important to remember that small or moderately enlarged tonsils do not necessarily exclude upper airway obstruction as adenoidal hypertrophy may be more significant than the tonsils themselves. A number of studies have shown that there is no relation between the size of adenoids and tonsils and presence of OSA.

At present, research shows that history and clinical examination have a poor sensitivity for distinguishing
children with primary snoring from those with OSA with a predictive accuracy ranging from 30% to 50%\textsuperscript{14,17-19}.

**Sequelae of OSA**

If left untreated, OSA can lead to significant neurocognitive, behavioural, cardiovascular, and developmental morbidity. The morbidity associated with OSA has been shown to be comparable to children with juvenile arthritis or moderate asthma\textsuperscript{14,20,21}.

Studies have shown an association between OSA and attention deficit hyperactivity disorder (ADHD) and other behavioural problems such as social withdrawal or aggression\textsuperscript{22-24}. The prevalence of inattention and hyperactivity in children with OSA is between 20-30% c.f. 8% ADHD in the general population\textsuperscript{25,26}. Children with OSA have also been shown to perform less well at school and adenotonsillectomy has been shown to improve their performance and also behaviour\textsuperscript{27-31}.

Cardiovascular sequelae such as cor-pulmonale with heart failure, pulmonary and systemic hypertension have also been reported in long standing OSA\textsuperscript{32}. Failure to thrive is a serious complication of OSA and it likely related to a combination of anorexia and decreased oral intake, increased energy consumption from increased work of breathing, and alternations in nocturnal growth hormone secretion patterns\textsuperscript{33,34}. Previous studies have shown that these children undergo a growth spurt after adenotonsillectomy with no long-term sequelae\textsuperscript{35}. Fortunately, complications such as mental retardation, cor-pulmonale and failure to thrive are rarely reported in this day and age due to early diagnosis and treatment.

**Diagnosis**

The ‘ideal’ pre-operative investigations would:

1. Identify patients who have OSA
2. Identify patients who are at increased risk of post-operative respiratory complications so that appropriate precautions can be taken
3. Identify patients who do not have OSA so that unnecessary intervention can be avoided.

Radiographic investigations that have been used to assess the upper airway include lateral neck x-rays, cephalometric measurements, fluoroscopy, CT and MRI. All modalities essentially show that the upper airway in children with OSA is smaller when compared to normal children.

Table 2: Symptoms suggestive of OSA

<table>
<thead>
<tr>
<th>Features during sleep</th>
<th>Snoring</th>
<th>Witnessed apnoeas</th>
<th>Cyanosis</th>
<th>Parental concern about their child’s breathing</th>
<th>Restless sleep</th>
<th>Unusual sleeping posture</th>
<th>Sweating</th>
<th>Enuresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms on waking</td>
<td>Difficult to rouse in the morning</td>
<td>Irritability/bursts of anger on waking</td>
<td>Morning headaches or vomiting</td>
<td>Lack of appetite for breakfast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime features</td>
<td>Mouth breathing</td>
<td>Excessive daytime sleepiness</td>
<td>Hyperactivity/behavioural disturbance</td>
<td>Learning/memory difficulties</td>
<td>Developmental delay</td>
<td>Failure to thrive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Clinical examination findings

- Nasal Obstruction (deviation of the septum or hypertrophic inferior turbinates, nasal polyps)
- Hyponasal voice
- Oedematous or long soft palate or uvula
- Hypertrophic lingual tonsils
- Narrow oropharynx (large tonsils, redundant pharyngeal arches)
- Adiposity or large neck circumference
- Retrognathia
- Maxillary hypoplasia

Figure 2: Lateral X-ray showing enlarged adenoids (arrow)
The lateral neck x-ray is simple to perform and has long been used in the outpatient setting to assess adenoidal hypertrophy and upper airway patency (Figure 2). Although it is useful to assess the presence of adenoidal tissue, it provides no information regarding the presence or severity of OSA.

MRI with 3D reconstruction has been shown to be a valuable tool as it not only allows reconstruction of the upper airway soft tissue and skeletal structure but also allows for dynamic assessment of airflow. Upper airway endoscopy such as nasendoscopy and microlaryngobronchoscopy provide dynamic evaluation of the airway and localisation of the region of obstruction. These investigations are used when assessing the more complex airway.

Healthcare questionnaires have also been developed to help assess the severity of OSA. Although simple and convenient to administer as screening questionnaires, they are not sensitive or specific enough to distinguish primary snoring from OSA.

The most common screening tool used in most departments is single channel continuous pulse oximetry. It is simple to use, relatively cheap and can be done at home or in hospital. Intermittent desaturations during sleep are highly suggestive of OSA and a positive oximetry trend (> 3 clusters of desaturations to below 90%) gives a positive predictive value of 97% for OSA. It unfortunately also has a negative predictive value of 47% as not all apnoeic episodes in children result in desaturation because they occur for short durations. These short desaturation periods are too short to be picked up by oximeters that have a longer latency period. A positive test as such would negate the need for PSG however a negative test in a patient with high index of clinical suspicion of OSA will require further testing which unfortunately would the majority of our patients.

Polysomnography is currently the gold standard investigation for diagnosing OSA and assessing its severity. It involves simultaneously recording a number of physiological variables, which can be selected depending on the clinical context in which the study is being carried out. They typically include respiratory movements, gas exchange, cardiac rate and rhythm, sleep state, and muscle activity (Figure 3). The parameter most commonly used when diagnosing OSA from PSG is the apnoea-hypopnoea index (AHI) which indicates the number of apnoeic and hypopnoic events per hour of sleep.

The American Academy of Sleep Medicine (AASM 2007) has defined an AHI > 1 is the ‘abnormal’ value of choice when analysing PSG results. This value has been adopted as studies have shown that after the first month of life, normal infants and children do not exhibit more than one obstructive episode per hour.

**Treatment**

Adenotonsillectomy is the treatment of choice for most children with OSA. Other surgical treatments that have been advocated include uvulopalatopharyngoplasty, palatal implants, tongue base reduction and orthognathic surgery, all of which are tailored to individual needs of patients. Tracheostomy, which is the definitive treatment for upper airway obstruction should be needed only rarely.

Continuous positive airway pressure (CPAP) is usually employed in patients with neuromuscular diseases, residual disease after surgery or in whom surgery is contraindicated. However, a significant proportion of young children do not tolerate CPAP.

**Discussion**

OSA in children is a common entity and the consequences in terms of neurodevelopment and cardiorespiratory complications are well documented. Adenotonsillectomy is curative in the majority of children and studies have shown that the long term complications are avoided. These children undergo a growth spurt post surgery as well as showing an improvement in school performance, behaviour and overall quality of life in the short and long term.

Children with severe OSA who undergo adenotonsillectomy can run into significant respiratory problems post-operatively as in patients with upper airway obstruction and hypercarbia, hypoxia is the driving stimulus for respiration. Relief of respiratory obstruction by adenotonsillectomy with postoperative oxygen administration may remove the hypoxic drive, resulting in respiratory compromise. The
sedative effects from anaesthesia, including inhaled anesthetics and narcotics, can also decrease the activity of the pharyngeal dilator muscles responsible for maintenance of upper airway muscle tone and patency resulting in postoperative respiratory compromise.  

The rate of respiratory complications post adenotonsillectomy for children with OSA have been reported to vary from 1.3% - 23%. These reported respiratory complications vary from requiring oxygen in recovery to formal airway adjuncts and also intubation and respiratory complications. Anaesthesiology 2002;105:405-412

It is as obviously important to identify children with OSA who are at risk from post-operative complications accurately to prevent unnecessary morbidity. The current goal standard investigation, PSG, is unfortunately not readily available in the United Kingdom. At present there are < 18 units which have facilities to perform full PSG. It has been estimated that a full paediatric PSG costs £1000 per study in the NHS. The test itself is time consuming, requires a child friendly environment with dedicated paediatric staff, on average requiring 1-2 hours to set up, 10-12 hours to record and 3-4 hours to analyse.

In view of recent published guidelines by ENT-UK and the RCPCH regarding the requirement of PSG in a high risk group, the demand for this test will inevitably increase, 4, 55. This will not only strain resources further on centres that perform them but will also increase waiting times for these investigations, potentially delaying surgery for the very group of patients who are at high risk for developing cardiovascular and neurocognitive sequel.

Table 4: Children at high risk of post-operative PICU

| Age < 2 | Wt < 15kg | Severe OSA on polysomnography | Cardiac complications of OSAS (e.g. Right ventricular hypertrophy) | Failure to thrive | Obesity | Prematurity | Recent respiratory infection | Craniofacial anomalies | Neuromuscular disorders |

Clearly, small groups of children e.g. craniofacial abnormalities can be identified in advance (Table 4). However, although it is desirable to select the high risk sub-group from the majority of children, no single investigation can do this accurately and reliably.

References
20. Ruboyianes JM, Cruz RM. Paediatric adenotonsillectomy for obstructive sleep apnea. Ear Nose Throat J 1996;75:430-3
Surgical Management of Primary Hyperparathyroidism

Mr Chee Yean Eng, FRCS (ORL-H&N), Mr M Shahed Quraishi FRCS, FRCS (ORL-H&N)
Department of Otolaryngology, Doncaster Royal Infirmary, Doncaster DN2 5LT
Email: Muhamad.quraishi@dbh.nhs.uk

Abstract
Primary hyperparathyroidism is the commonest cause of hypercalcaemia in the out-patient population. Eighty percent of pHPT are caused by solitary parathyroid adenoma. These patients can undergo minimal invasive parathyroidectomy with excellent cure rate and minimal morbidity. Success depends on pre-operative localisation investigations, intra-operative localisation adjuncts and the use of appropriate surgical approaches and expertise. Negative or discordant pre-operative localisation scans and persistent pHPT cases after initial exploration are best managed in tertiary centres.

Introduction
Primary hyperparathyroidism (pHPT) is the commonest cause of hypercalcaemia in the out-patient population and 2nd only to malignancy in the in-patient population1. The incidence of pHPT is increasing due to better detection since the advent of multichannel serum autoanalysers showing up hyperclaemia in asymptomatic patients2. The clinical incidence of pHPT is around 1 - 3% in women and around 0.3% in men3.

There are 2 types of pHPT. These are sporadic (non-hereditary) and familial (hereditary). Ninety five percent are sporadic pHPT and only 5% are hereditary such as those associated with Multiple Endocrine Neoplasia (MEN) Type 13. Of the sporadic pHPT, 80% are due to solitary adenoma, 15 – 20% due to glandular hyperplasia and 1% due to carcinoma3-6.

Parathyroid surgery is becoming more popular and gradually establishing itself as the acceptable definitive treatment for pHPT. This paper will focus on the surgical management of patients with pHPT and emphasise the importance of pre-operative localisation imaging for minimally invasive parathyroidectomy.

Clinical assessment
Patients presenting to surgeons are typically referred by Endocrinologists and have biochemically confirmed pHPT. Majority of patients with pHPT are asymptomatic (80%) and their hypercalcaemia are picked up incidentally on biochemical screening for other reasons3. These patients are then further evaluated with PTH-assay, 24-hour urinary collection for calcium level, and creatinine clearance/ Glomerular Filtration Rate (GFR). A raised PTH-assay, hypercalcaemia, and hypercalciuria confirm the diagnosis of pHPT.

History should include any symptoms suggestive of hypercalcaemia, which is summarised by the classical rhyme of 'bones, stones, abdominal groans and psychic moans'. Musculoskeletal symptoms may include muscle weakness, fatigue and lethargy, bone and joint pain. Patients may present with recurrent renal or ureteric stones and renal colic. Gastrointestinal symptoms may include abdominal pain, chronic constipation, peptic ulceration and pancreatitis. Psychological symptoms may manifest itself as anxiety, depression and loss of concentration or memory. These neurocognitive symptoms can mimic dementia in the elderly population.

It is important to enquire about risk factors for hyperparathyroidism and hypercalcaemia. These include Lithium therapy and a history of previous neck irradiation.

It is also worth enquiring about family history of hypercalcaemia which could be related to Familial Hypocalciuric Hypercalcaemia (FHH) or Multiple Endocrine Neoplasia (MEN). FHH patients are usually asymptomatic with mild hypercalcaemia and do not require surgery. MEN patients tend to have multiple gland disease (MGD) and are managed differently from those with solitary adenomas.

Less commonly encountered are pHPT associated metabolic and potential cardiovascular manifestations including impaired glucose tolerance or diabetes, hypertension, left ventricular hypertrophy and valvular calcification, and increased risk of premature death3.
Pre-operative localisation investigations

This is highly recommended in order to determine the best surgical approach to achieve cure with minimal risk of complications. With good patient selection and reliable identification of patients with solitary adenoma, Minimally Invasive Parathyroidectomy (MIP) offers a high cure rate, shorter operative time and reduced operative morbidity6-8.

Sestamibi scintigraphy (MIBI)

Technetium99m Methoxyisobutylisonitrile (sestamibi) is the radioisotope used in this metabolic scan. Sestamibi is a monovalent lipophilic cation that diffuses through cell membranes and accumulates almost exclusively within mitochondria9. Parathyroid tissue has a high metabolic rate with high mitochondrial activity, which explains its high uptake of sestamibi9. Positive sestamibi scans tend to be associated with higher PTH level or serum calcium level. Parathyroid adenoma with >20% oxyphil cell content is more likely to be associated with a positive MIBI scan compared to parathyroid adenomas formed mainly of chief cells9.

In the pre-operative setting, variations in techniques include the early/late planar scintigraphy originally described, Dual-phase imaging with single tracer/double tracer, Sestamibi with single photon emission computed tomography (SPECT) and/or CT for better anatomical localisation10, 11.

Sestamibi scan is good at detecting solitary adenoma and has a sensitivity of around 85% and positive predictive value (PPV) of between 91-96%8,10,12. SPECT has been shown to improve sensitivity of scintigraphy from 85% to 92%9. However, it is unreliable in identifying patients with MGD and double adenomas9.

Ultrasound scan (USS)

In experienced hands, preferably a dedicated radiologist, high-frequency USS has an overall sensitivity of 89% and PPV of 98% for localising solitary adenoma9. The abnormal gland is identified by its appropriate anatomical location, enlarged, oval or triangular in shape, and homogeneously hypoechoic13 (Figure 2). Colour Flow Doppler (CFD) also demonstrates peripheral blood flow of the abnormal parathyroid gland14,15 (Figure 3). This is in contrast to vascular pedicle hilar blood flow into a lymph node.

USS also provides the anatomic relationships between the enlarged gland and surrounding structures to guide surgery. Larger and heavier gland size is associated with higher rate of detection by USS. The sensitivity and PPV are reduced in patients with concomitant thyroid nodules or multinodular goitre (85% – 100% vs. 47% - 84%)9.

Figure 1: Sestamibi Dual-phase Iodine-123 subtraction scan

Figure 2: Ultrasound scan showing a solitary large parathyroid adenoma.
USS or MIBI or both

USS is cheaper and avoids ionising radiation exposure when compared to MIBI. It has almost equal sensitivity and PPV for solitary adenoma. Opinion varies as to which is more helpful and should be the first localisation investigation. Nevertheless, it is common practice to have both USS and MIBI scans to help localise solitary adenoma. This is especially true when there is presence of thyroid nodules or multinodular goitre.

MIP in cases with concordant USS and MIBI scans have been reported to have up to 95 – 99% success rate defined by normocalcaemia for variable duration post-operatively. However, it has been noted that up to 16% of patients with concordant USS and MIBI scans can have MGD found on BNE. It is obvious from this that not all enlarged glands have to be removed to achieve surgical success measured by normocalcaemia.

CT-scan, MRI-scan, and PET scan

CT scan and MRI scan play a small role in parathyroid imaging. They are less sensitive compared to MIBI or USS. Nevertheless, CT scan at 3-mm slices with contrast enhancement, the novel four-dimensional computed tomography (4D-CT) or MRI-scan may be able to help localise ectopic or mediastinal glands (up to 71% – 88% sensitivity).

FDG-PET-scan has very good sensitivity (86%) and acceptable specificity (78%) for solitary adenoma. It may be useful in negative or equivocal MIBI and USS localisation scan or before reoperation.

Venous sampling

This is a more invasive procedure and used only when imaging studies have been negative. It may be used in re-operative situation. It has a high overall sensitivity of 93% – 95% in both primary operation setting and re-operative situation. This can help regionalise (neck/mediastinum) and lateralise (right/left) the abnormal parathyroid gland.

In equivocal or negative MIBI and USS, selective venous sampling (SVS) by percutaneous sampling of bilateral internal jugular veins and peripheral arm veins for rapid PTH assay can help regionalise and localise the diseased parathyroid gland. A 1.5 – 2 fold increase in baseline PTH has been shown to have a sensitivity of 75% - 83% and specificity of 88% – 96% to localise the diseased parathyroid gland. USS guided FNA rapid-PTH assay can also help localise the diseased gland more accurately.

Indications for Parathyroid surgery in pHPT

Patients with pHPT who are symptomatic of hypercalcaemia should have parathyroid surgery if there is no other contraindication to surgery.

Asymptomatic pHPT patients who lack specific symptoms or signs associated with hypercalcaemia or PTH excess could be managed according to published consensus guidelines of The Third International Workshop on Primary Hyperparathyroidism held on 13th May 2008 in Orlando, Florida, USA. These are listed in Table 1.

GFR of less than 60ml/min is defined at Stage 3 renal failure and increases serum PTH level and worsens the hyperparathyroid state.

Younger patients should undergo early surgery because they have a greater risk of developing complications of pHPT over time than in those older than. However, this does not preclude surgery in older patients who are deemed suitable and would benefit from definitive surgery.

### Table 1: Indications for asymptomatic pHPT patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium (corrected)</td>
<td>Raised by more than 0.25 mmol/l (1 mg/dl) above upper limit of normal.</td>
</tr>
<tr>
<td>Creatinine clearance/GFR</td>
<td>&lt; 60 ml/min.</td>
</tr>
<tr>
<td>Bone Mineral Density (BMD)</td>
<td>Post-menopausal woman and men over 50:</td>
</tr>
<tr>
<td>T-score: Age-invariant.</td>
<td>• T-score -2.5 or less at the lumbar spine, femoral neck, total hip, or 33% (1/3) radius.</td>
</tr>
<tr>
<td>Z-score: Age-matched.</td>
<td>• Previous fracture fragility.</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 50 years old</td>
</tr>
</tbody>
</table>

GFR of less than 60ml/min (1.73 m2) is defined at Stage 3 renal failure and increases serum PTH level and worsens the hyperparathyroid state.
24-hour urinary calcium level should only used to exclude FHH and no longer an indication for surgery.

Normocalcaemic pHPT are characterised by consistently normal serum calcium level in the face of persistently raised PTH. These patients are typically asymptomatic. The natural history and optimal management are still being investigated.

Surgical approaches to pHPT

The commonly recognised parathyroidectomy surgical approaches are listed and described in Table 2. The traditional BNE is the gold standard and benchmark for other surgical approaches. BNE has been reported to have around 95% of achieving normocalcaemia post-operatively.

Table 2: Surgical approaches to Parathyroidectomy

<table>
<thead>
<tr>
<th>Surgical approaches</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral Neck Exploration (BNE)</td>
<td>Traditional full four-gland exploration. Surgical gold standard. Useful in MGD, recurrent/residual disease, negative or discordant pre-operative localisation investigations.</td>
</tr>
<tr>
<td>Unilateral Neck Exploration (UNE)</td>
<td>Full exploration of one-side of the neck exposing both ipsilateral parathyroid glands. Usually guided by Imaging and/or PTH venous sampling.</td>
</tr>
<tr>
<td>Minimally Invasive Parathyroidectomy (MIP) or Selective Parathyroidectomy (SP)</td>
<td>Selective removal of single parathyroid adenoma. Usually guided by imaging and/or PTH venous sampling. Also known as focused or targeted parathyroidectomy.</td>
</tr>
</tbody>
</table>

UNE was the favoured strategy in the mid-1970s and early-1980s when evidence showed that, with good patient selection, image-guided UNE carries the same success rate in achieving normocalcaemia post-operatively compared to BNE. In addition, UNE was associated with shorter operating time, shorter hospital stay and reduced complication of post-operative hypocalcaemia when compared to BNE (22% vs. 45%).

MIP has gained popularity since the turn of the century with improved pre-operative localisation imaging technique allowing better patient selection. Comparable success rate and reduced post-operative morbidity have been demonstrated with MIP. MIP is now widely accepted as the preferred surgical approach for patients with solitary adenoma. This is typically performed under general anaesthesia as a daycase procedure. The surgical techniques/access for MIP are summarised in Table 3. Current available evidence would favour OMIP which is less complicated, shorter operating time and carries less risk to the recurrent laryngeal nerve, when compared to VAP or EP.

Parathyroidectomy has been shown to have up to 97% patient satisfaction rate. Following successful parathyroidectomy, patients return to normocalcaemia with resolution of hypercalcaemic symptoms. In addition, bone density has also been shown to improve over time with a significant decreased risk of bone fracture in both symptomatic and asymptomatic patients.

Table 3: Surgical techniques/access for MIP

<table>
<thead>
<tr>
<th>Surgical access for MIP</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open mini-incision MIP (OMIP) (Figure 4)</td>
<td>Small horizontal cervical skin incision (approximately ≤ 2.5cm) on neck as guided by imaging.</td>
</tr>
<tr>
<td>Video assisted MIP (VAP)</td>
<td>Rigid endoscope without gas insufflation. Magnified view with optimal lighting.</td>
</tr>
<tr>
<td>Endoscopic MIP (EP)</td>
<td>Rigid endoscope with gas insufflation. Access via midline between the strap muscles or lateral access via the paracarotid gutter. Magnified view with optimal lighting.</td>
</tr>
</tbody>
</table>

Local anaesthesia considerations

Given the short surgical time and minimally invasive surgery of MIP, local and regional block anaesthesia with or without intravenous sedation can also be considered. The local anaesthetic techniques described included local infiltration, superficial cervical block and deep cervical block (Figure 5). All have been shown to be equally effective and safe.

Local anaesthesia has the advantage of avoiding risk of general anaesthesia and intubation, shorter recovery time following the operation, lower post-operative pain, and lower incidence of nausea and vomiting. It can be used for

Figure 4: Small horizontal cervical skin crease incision for Open Minimally Invasive Parathyroidectomy (OMIP).
older patients with severe co-morbidities where general anaesthesia is contraindicated or carries too high a risk. Surgery under local anaesthesia would have a small risk of conversion to general anaesthesia if a more extensive exploration becomes necessary or if the patient became agitated. Bilateral cervical blocks should be avoided to prevent bilateral diaphragmatic paresis.

Good patient selection is absolutely crucial for local anaesthesia. Positive and concordant pre-operative localisation scans, accessible thin long neck, superficial parathyroid glands, and a co-operative patient being ideal.

Contraindications to local anaesthesia include obstructive sleep apnoea (at risk of oxygen destauation with sedation), thick short neck with poor access, uncooperative and anxious patients, and those with posteriorly or inferiorly located parathyroid adenoma.

**Intra-operative localisation techniques**

There is no need for further intra-operative localisation if:

1. The MIBI and USS scans are concordant showing solitary adenoma.
2. The surgeon is certain that the nodule is parathyroid tissue based on location, colour and consistency.

The 4 known modalities in Intraoperative localisation techniques include the use of Intra-operative PTH monitoring (IOPTH), Radio-guided Parathyroidectomy (RGP), Frozen Section and Methylene Blue injection. These can be employed in various situation to improve successful surgery.

**Intra-operative PTH monitoring (IOPTH)**

This is the commonest intraoperative localisation technique. This can be performed from a central or peripheral site but should be consistent for any whole procedure.

The use of IOPTH depends on the results of the pre-operative localisation studies and the surgical approach used. It should be considered if only a single preoperative localisation study was used when performing MIP. It is highly recommended that IOPTH is used in discordant preoperative localisation studies when performing MIP and in reoperative parathyroidectomy.

IOPTH may be helpful in deciding if a biochemical cure has been achieved following MIP for pHPT. The Miami protocol is commonly quoted where cure is defined as greater than or equal to 50% decay from the highest (pre-incision or pre-excision) value within 10 mins after removing the hyperfunctioning gland(s).

**Radio-guided Parathyroidectomy (RGP)**

This is intra-operative localisation of Parathyroid tissue with gamma probe after pre-operative Sestamibi (MIBI) administration. This intra-operative adjunct should only be used when there is a positive MIBI scan and absolutely contraindicated in pregnancy or MIBI allergy/sensitivity. The dose and timing of MIBI administration varies in published literatures. There is currently no comparative studies to demonstrate which, if any, MIBI protocol is more superior.

RGP has been used in BNE, UNE and MIP setting. It has also been used to confirm cure by ex-vivo validation of the excised tissue to be parathyroid tissue (will show increased radioactivity). However, many authors still propose concomitant use of IOPTH and/or Frozen section. As such, the addition of RGP ex vivo validation, on top of frozen section or IOPTH, is unclear and not widely supported.

There is currently not enough evidence to show that RGP improve accuracy or increase cure rate. The use of RGP will add to cost and could potentially prolong surgery. RGP is currently considered as an alternative technique to other intra-operative adjuncts such as IOPTH and frozen section.

**Frozen section**

This is very reliable in differentiating between parathyroid and non-parathyroid tissue (e.g. fat, lymph node, thyroid tissue) with an accuracy of more than 99%. However, it is unreliable for differentiating between adenoma and multiglandular hyperplasia.

**Methylene Blue (MB)**

MB selectively stains parathyroid tissue and can therefore facilitate surgery. This is administered pre-operative via intravenous infusion of MB 7.5 mg/kg body weight, diluted in 100ml 5% dextrose, infused over 60 minutes prior to surgery.

There is currently no evidence to show that MB use improves surgical success. In addition, MB has been shown to have similar chemical structure to Monoamine Oxidase Inhibitor (MAOIs) and the use of MB can be
Management algorithm flowchart and patient selection

![Flowchart]

Associated with significant neurological morbidity including toxic encephalopathy, especially in patients taking selective serotonin reuptake inhibitor (SSRI)\(^{26,32}\). The use of MB is therefore not recommended.

Negative/discordant pre-operative non-invasive localisation imaging

These patients should be referred to tertiary referral centres for consideration of more invasive pre-operative localisation investigations (such as selective PTH venous sampling)\(^{22,26}\). Cross-sectional imaging may help with anatomical localisation. These patients may also benefit from iOPTH, RGP or BNE\(^{7,8,26}\).

Failed initial exploration, persistent and recurrent hyperparathyroidism, and re-exploration

Surgical treatment for sporadic pHPT in experienced hands carries a success rate of more than 95% with morbidity lower than 1\%\(^{7}\).

Persistent HPT is defined as HPT diagnosed within 6 months of initial parathyroid surgery. HPT diagnosed 6 months or more after initial parathyroid surgery should be regarded as recurrent. The most common cause of persistent sporadic pHPT has been shown to be inadequate neck exploration by an inexperienced surgeon evidenced by the missed abnormal gland found in its anatomical position in up to 80% of re-operative cases\(^{7,16,33,34}\). This is followed by failure to locate or remove an ectopic adenoma located at various sites in the neck, superior or middle mediastinum (25\%), supernumerary parathyroid glands (5\%), and MGD (10 – 15\%)\(^{16}\).

Re-exploration should be performed by an experienced surgeon in a tertiary referral centre adopting a systematic approach as described by Harrison and Caron\(^{16,34}\). There is increased risk to the recurrent laryngeal nerve in re-exploration (up to 2.3\%) and hence pre- and post-operative vocal cord checks may be useful\(^{16}\). Normocalcaemia after re-operative surgery in expert centres is achieved in 84 – 98\% of patients\(^{7,16,33,34}\).

Conclusion

Sporadic pHPT due to solitary adenoma forms the majority of patients with HPT. MIP performed by dedicated surgeon supported by accurate pre-operative MIBI and USS can achieve very high cure rate with minimal morbidity. Negative or discordant pre-operative localisation cases, and persistent or recurrent cases are best managed in tertiary expert centres with access to iOPTH.

Acknowledgement: The authors would like to thank Dr David Ward, Consultant Radiologist, Doncaster Royal Infirmary for providing the Radiological Imaging for this article.

References:

Introducing the new NIM-Response® 3.0 Nerve Integrity Monitoring System

At Medtronic ENT, we’re driven to innovate by listening to your needs. The new NIM-Response 3.0 is built upon 20 years of leadership in nerve monitoring, and it delivers advanced monitoring in an easily accessible system.

**Call today to arrange a demonstration.**

For further information please call Medtronic ENT on 01923 212213, fax on 01923 205145 or e-mail entadvert.uk@medtronic.com. You may also consult our website at www.MedtronicENT.com.

- **First and only nerve monitor that fully enables:**
  - Monitoring during bipolar cautery
  - Stim Bur capability, combining electric drill with stimulation
  - Artifact detection software to help eliminate noise
  - Incrementing Probe capability that allows surgeons to adjust stimulus levels
- Easier to use, redesigned software with three simple environments: Setup, Monitoring, and Reports
- Reports Wizard easily documents patient’s EMG activity

Peace of mind for you • Peace of mind for your patient
Management of Cervical Chyle Leaks

Anil Joshi, MRCS, MS, Iain J. Nixon, FRCS (ORL-HNS) Karen Harrison-Phipps FRCS C Th, Jean-Pierre Jeannon FRCS (ORL-HNS), Richard Oakley FRCS (ORL-HNS), Ricard Simo, FRCS (ORL-HNS)
Departments of Otorhinolaryngology Head and Neck Surgery and Thoracic Surgery, Guy’s and St Thomas’ NHS Foundation Trust, London

Address for correspondence
Department of Otorhinolaryngology Head and Neck Surgery, 3rd Floor Southwark Wing, Guy’s Hospital, St Thomas Street, London SE1 9RT
Email: aniljoshient@yahoo.com
Phone: 07860448830, 02071882215

Abstract:
Chyle leaks in the neck can occur due to trauma, surgeries in the chest and neck. It is commoner on the left than the right. Their incidence is much higher in salvage surgeries and can be difficult to manage. There are complex factors such as the amount and duration of leak, patient’s condition with respect to fluid, electrolytes, immune and infection status and also the condition of the post-operative neck wound that dictate the choice of treatment. Hence there appears to be no clear consensus on the ways to manage in troublesome leaks. We review the literature and discuss some of the ways in managing post-operative chyle leaks. We also aim to provide a management algorithm that helps to address this challenging complication of CL management.

Key Words
Chyle leak; Neck dissection; Video assisted thoracoscopy (VATS)

Introduction
Chyle leak (CL) or lymphatic fistulae are infrequent but troublesome complications following neck dissections for metastatic neck disease. It occurs when either the thoracic duct (TD) or one of its tributaries are damaged during the surgery or secondary to infection and poor healing of the tissues in the post-operative period. It is also more common following salvage surgery. Chyle leak can occur on both sides of the neck although in the left side is much more common. A thorough understanding of the anatomy of the lymphatic system in the neck, chest and abdomen is imperative so the identification and ligation of the duct or its tributaries can be undertaken at the time of surgery and therefore minimizing the risk of fistula formation in the post-operative period. Chyle leak may result in delayed healing of tissues, loss of electrolytes and fluid imbalance as well as secondary infection. There are no standard protocols available in the surgical peer-reviewed literature to manage CL and there does not appear to be a consensus as to how to address them in a systematic manner. Treatment varies from conservative approaches such as correction of fluid and electrolytes, fat free diet and total parenteral nutrition, to surgical exploration the neck, transthoracic ligation of the duct or embolisation.

The aim of this paper is to review the current literature and to provide a structured overview of the anatomy of the thoracic duct, physiology of chyle, incidence, diagnosis and current management options on the management of CL. We also aim to provide a management algorithm that helps clinicians to address this challenging complication of CL management.

Anatomy of the thoracic duct
Gaspare Asellio first described the lymphatic system in 1622. Jean Pecquet discovered the thoracic duct and outlined its pathway in 1647. The thoracic duct is the largest lymphatic vessel in the body. It is 36-45cm long and has a diameter of 2-3mm. It enters the chest and crosses between the internal jugular vein and the anterior scalene muscle. Although its termination can vary, it commonly enters at the junction of the left subclavian and left internal jugular veins (Figure 1). Embryologically, the thoracic duct is bilateral; hence it’s multiple anatomical variations. Some of these include irregular levels to cross between left and right, thoracic duplicates and triplicates in more than 40% of cases and termination in the internal Jugular, subclavian or left brachiocephalic veins. One should also have an understanding of the right lymphatic duct as injury to this could potentially cause a chyle leak on the right side.
Physiology of the chyle

Chyle is an odourless, alkaline fluid consisting of lymph from interstitial fluid and emulsified fat from intestinal lacteals. It contains 1%-3% fat, mostly in the form of triglycerides, and 3% protein. Albumin content is higher in chyle than in plasma but it contains a total protein level only half that of plasma. Around 2 to 4 litres of chyle flows through the thoracic duct every day, and total volume is affected by increased interstitial fluid pressure. It has been observed that upon consumption of fat, long-chain triglycerides enter blood via chyle whereas medium-chain triglycerides are absorbed into the portal system directly.

Incidence

Injury to the thoracic duct occurs in 1-2.5% of patients who undergo neck dissections. The site of injury is commonly at the termination of the duct at its entry in the internal jugular vein. Seventy-five percent of cases occur on the left side. The incidence is higher in cases where metastatic lymph nodes develop in level IV such as in thyroid or hypopharyngeal cancers. Other potential causes of CL in the neck and chest include penetrating trauma, cervical rib resection, oesophagectomy, cervical and thoracic node biopsy and resection of lung. It is also more common following salvage surgery.

Diagnosis

At the time of the surgery, the TD should be identified and ligated to prevent CL. If the TD is inadvertently injured, chyle will escape, and it would be obvious to the surgeon, but on occasion the CL will cease spontaneously following retraction of the TD to within the soft tissues of the neck. It is therefore imperative that the CL is identified and dealt with before the end of the procedure. This is best achieved, by tilting the head of the patient downwards and asking the anaesthetist to perform a Valsalva maneuver. The increased intra-thoracic pressure will make, in most cases, the CL evident and once this is done the ligation can be carried out.

In the post-operative period CL is diagnosed by persistent drainage from the neck wound, milky colour of drain fluid and fullness or increasing swelling of the neck. CL may cause symptoms of hypovolemia, electrolyte imbalance, protein loss, lymphopenia, metabolic acidosis and loss of fat-soluble vitamins leading to malnutrition, immune compromise and infection. It can cause delayed or non-healing of the wound and localised infection due to fluid stasis, leading to flap necrosis and prolonged hospitalisation.

Biochemical analysis of the fluid including a chylomicron level of more than 4%, triglycerides level of more than 110mg/dl and elevated lymphocyte count is diagnostic. Other investigations include lymphoscintigraphy, Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and injection of methylene blue.

With regards to the output volume, there is no current useful classification that aids clinical management. Some authors suggest the figure of 600ml in 24h as a mark of severity to address the CL surgically although there exists significant diversity of opinion. The authors have devised a protocol to help with the management of CL and classified the leaks in 3 categories. Low output (<500ml in 24h), intermediate output (between 500 and 1000 mls in 24 h) and High output (>1000 mls in 24 h). This standardization has helped construct a protocol that has benefited medical, dietetic and nursing staff to effectively address CL management (Figure 2).

Protocol

Management of chyle leak can be both conservative and surgical (Table 1). The choice of the treatment will depend

Figure 1: Anatomy of the thoracic duct

Figure 2: Flow chart for management of post-operative chyle leak as per the Head and Neck Unit Standard Operational Policy GSTT 2011.
Conservative measures
- Bed rest
- Laxatives
- Fluid and electrolyte management
- Free drainage surgical drains
- Wound pressure dressing
- Antibiotic prophylaxis

Nutritional and Medical measures
- Free fat diet or free fat enteral nutrition (in patients receiving enteral nutrition)
- Octreotide
- Tetrahydrodrolipstatin (Orlistat®)
- Etilefrine
- Tetracycline injection
- Povidon-iodine sclerotherapy

Surgical management
- Surgical re-exploration and ligation
- Video-assisted thoracoscopic ligation

Table 1. Post-operative Management of Chyle Leaks

<table>
<thead>
<tr>
<th>Conservative measures</th>
<th>Nutritional and Medical measures</th>
<th>Surgical management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bed rest</td>
<td>Free fat diet or free fat enteral nutrition</td>
<td>Surgical re-exploration and ligation</td>
</tr>
<tr>
<td>Laxatives</td>
<td>Octreotide</td>
<td>Video-assisted thoracoscopic ligation</td>
</tr>
<tr>
<td>Fluid and electrolyte management</td>
<td>Tetrahydrodrolipstatin (Orlistat®)</td>
<td></td>
</tr>
<tr>
<td>Free drainage surgical drains</td>
<td>Etilefrine</td>
<td></td>
</tr>
<tr>
<td>Wound pressure dressing</td>
<td>Tetracycline injection</td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis</td>
<td>Povidon-iodine sclerotherapy</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Post-operative Management of Chyle Leaks

on the amount and duration of leak, the patient’s condition with respect to fluid, electrolytes, immune and infection status and also the condition of the post-operative neck wound. These multiple factors might be the reason why standard guidance is difficult to find.

Conservative, Nutritional and Medical Management.

The principle behind the medical management would be to decrease the chyle flow thereby allowing the fistula to close spontaneously. Regular draining of the wound, adequate bed rest and maintaining a strict fluid balance is of paramount importance. Pressure dressings over the supraclavicular fossa whenever possible and putting any suction drainage into free drainage will help the spontaneous healing of the CL. Nutritional therapy helps in closure of fistula in almost 80% of the cases9. Dietary management includes either a fat-free diet enteral nutrition (EN) or a total parenteral nutrition (TPN).

Fat-free diet, either orally if possible or via NGT feeding in patients unable to have oral intake in the immediate post-operative period should be attempted first. Unfortunately, the currently available fat-free enteral feeding nutritional supplements have by and large poor levels of proteins and this can affect healing. A multidisciplinary approach with head and neck dieticians is imperative. TPN should be the next step before considering surgery, however there is no clear-cut advice in the literature regarding when and for how long should TPN be administered. There is evidence that using Medium chain triglycerides (MCT) diet can help in fistula closure. In a study by Lucente et al of 574 neck dissections, six chyle leaks were diagnosed and all were successfully treated with MCT based diet10. Consideration must be also given to the cost of treatment and the complications of TPN. In a comparative study between TPN and EN by Ramos W et al, use of TPN was associated with quicker fistula closer, improved nutritional response and reduced duration of treatment11.

Other methods of conservative management include use of octreotide, a somatostatin analog that works by decreasing the absorption of triglycerides leading to a decrease in lymphatic flow, tetrahydrodrolipstatin (orlistat®), a pancreatic lipase inhibitor, vasoconstrictor agent etilefrine and local tetracycline12 or povidone-iodine sclerotherapy. A study by Kalomenidis I in 2006 with intravenous infusion of somatostatin showed cessation of chyle leak by day five13.

Surgical Management.

A. - Intra-operative management . As indicated, once the TD leak has been identified, it should be ligated. The method of ligation is controversial. Some authors suggest non-absorbable sutures such as silk, which in turn produce an inflammatory reaction that may help healing of the CL. Other authors suggest the use of metallic staples which avoid direct handling of the TD, reducing the risk of tearing the lymphatics preventing further leakage (Figure 3). These ligatures must be multiple and the Valsalva maneuvre should always be done at the end of the procedure to ensure adequate control of the CL. The use of electrical diathermy should be avoided as this only works with haemoglobin and not in lymphatics. The protection of the duct must be also ensured. This is achieved by using absorbable dressings such as Surgicel or Surgicel Fibrillar®, Fibrin Glue® or muscle flaps from the neighbouring tissues such as the sternocleidomastoid muscle or the strap muscles if available15. If significant concern still persists, patients should be put on free-fat diet for a period of 48 to 72h to decrease intra-ductal pressure and prevent leakage.

B. - Post-operative management. In the post-operative period, surgical management is indicated if the conservative measures fail and the CL persist over a period of 5 to 10 days. This is usually the case in high output volume fistula.

Figure 3: Ligation of the thoracic duct in the left neck with surgical clips.
Again, there is no consensus in the literature reviewed as to what amount constitutes high output or when to pursue surgical intervention. Also, re-exploration of the post-operative neck carries increased morbidity. By and large, a surgical approach is usually taken in failed medical management after a week to ten days or in cases of high output leaks. In a study by Crumley et al, in 1976 suggested surgical management if the chylous drainage is more than 500 mL per day for 4 consecutive days or if the collection cannot be controlled with pressure dressings and aspirations.

Nussenbaum B, et al in 2000, performed a retrospective analysis of 15 chyle leak cases over a period of five years. Ten cases were managed conservatively with an average time to drain removal of 7.1 days. Patients with high output fistulae of more than 1000ml/day all required surgical intervention. They suggested that peak 24 hour drainage is predictive of medical management failure. However another study by de Gier et al in 1996 did not believe that volume of drainage is the only factor in deciding the mode of management. Surgery was performed only when medical management failed after 30 days or if complications arose during the course.

Nussenbaum B, et al in 2000, performed a retrospective analysis of 15 chyle leak cases over a period of five years. Ten cases were managed conservatively with an average time to drain removal of 7.1 days. Patients with high output fistulae of more than 1000ml/day all required surgical intervention. They suggested that peak 24 hour drainage is predictive of medical management failure. However another study by de Gier et al in 1996 did not believe that volume of drainage is the only factor in deciding the mode of management. Surgery was performed only when medical management failed after 30 days or if complications arose during the course.

AA. Re-exploration of the neck. Re-exploration of the neck in failed medical management has been suggested. If undertaken it should be performed before the 10th post-operative day when the fibrosis is not yet fully established. Re-exploring the neck after a CL is often very difficult and it might not be possible to identify the duct due to post-operative changes in the tissue including inflammation, infection or fibrosis. If re-exploration is undertaken, the use of the surgical loops or the operating microscope may help intraoperative identification. The operator must be experienced and the tissue handling very delicate to avoid further damage of the vessel. Application of clips, ligation, use of gelfoam, fibrin glue and rotating a muscle such as the sternomastoid to suture over the site have all been tried with good reported success.

AB. Video-assisted thoracoscopic ligation. Thoracoscopic ligation of the thoracic duct provides a safe and an efficient means of treating chyle leaks refractory to repeated surgical and medical interventions. Gunnlaugsson CB et al in 2004 developed a systematic approach toward chyle leak after reviewing the literature. They used a threshold of greater than 500ml/d of leak for more than 4-7 days of medical management for surgical intervention. In selected cases where identification or ligation of the duct in the neck was difficult, they considered thoracoscopic ligation of the thoracic duct. Also, a video-assisted thoracic surgery (VATS) approach avoids the surgical morbidity associated with open thoracotomy and decreases hospital stay. This is the preferred approach by the authors as it provides a safe and efficacious approach to CL without disturbing the neck wound (Figure 4).

Management of CL in salvage surgery.
The risk of CL in post-radiotherapy neck dissections is higher than in primary surgery. A critical approach must be exerted to ensure that the TD is identified, ligated and secured during surgery as indicated. The use of the harmonic scalpel has been advocated as it appears to reduce the seroma rate, lymphoedema and chyle leak. Exploring the neck to stop the leak can cause more morbidity due to reduced vascularity of these tissues. It can result in non-healing of the flaps leading to large neck fistulae, infections and even carotid blowout. In such cases of failed medical management, we recommend ligation of the thoracic duct in the chest through VATS rather than exploring the neck as demonstrated by the case report.

Conclusion:
• Chyle leak can potentially be a serious complication following neck dissection.
• Care must be taken when operating in the supra-clavicular area on both sides.
• A step-wise approach towards the management of chyle leak is essential and this includes a strict bed rest, fluid balance and diet management.
• On failed medical management, surgical intervention should be considered.
• A VATS approach is recommended in cases of leaks in post-radiotherapy neck dissection.

References:
Shoulder Dysfunction after Neck Dissection

Nilesh Vasan, MD and Jesus E. Medina, MD
University of Oklahoma Health Sciences Center

Correspondence Address:
Dr. Jesus E. Medina
Department of Otorhinolaryngology
920 Stanton L. Young Blvd. WP 1290
Oklahoma City, OK 73104

Introduction
Removal of the spinal accessory nerve (SAN) during a radical neck dissection results in significant morbidity. The resulting denervation of the trapezius muscle, one of the most important shoulder abductors, causes destabilization of the scapula with progressive flaring of it at the vertebral border, drooping, and lateral and anterior rotation. The loss of the trapezius function decreases the patient's ability to abduct the shoulder above 90 degrees. Paralysis of the trapezius muscle causes a clinical syndrome characterized by weakness and deformity of the shoulder girdle, usually accompanied by pain. (Figure 1)1. The shoulder pain appears to be secondary to increased supportive demands on and strain of the levator scapulae and rhomboid muscles. Furthermore, adhesive capsulitis of the glenohumeral capsule may result in a 'frozen shoulder'2 leading to chronic disability.

Avoidance of his cumbersome sequela, by preserving the SAN, has been one of the reasons for the development of the modified radical3 and selective neck dissections4 that are commonly used today. Interestingly, varying degrees of shoulder dysfunction can occur, even when the SAN is preserved during a neck dissection. Therefore, it is important for a surgeon to understand the anatomy of the SAN, the risk factors associated with nerve dysfunction resulting from neck dissection, and the importance of early diagnosis and rehabilitation when a dysfunction occurs.

Anatomy
Spinal Accessory Nerve
Below the jugular foramen, the external branch of the spinal accessory nerve is located medial to the digastric and stylohyoid muscles and lateral or immediately posterior to the internal jugular vein. Occasionally, the uppermost portion of the nerve is posterior-medial to the vein. From here, the nerve runs obliquely downward and backward to reach the medial surface of the sternocleidomastoid muscle near the junction of its superior and middle. Although the nerve can continue its downward course entirely medial to the muscle (18%), more commonly it pierces the SAN and appears in the posterior border of it (82%)5. Here, the nerve is always located above the point where the greater auricular nerve turns around the posterior border of the SCM, also known as Erb’s point6. The mean distance between Erb’s point and the spinal accessory nerve is 10.7 mm, SD +/- 6.3. It then runs through the posterior triangle of the neck and crosses the anterior border of the trapezius muscle. The mean distance between this point and the clavicle is 51.3 mm, SD +/- 17. Two anatomic characteristics of this portion of the nerve are relevant to avoid injuring it during a neck dissection. First, the spinal accessory nerve is rather superficial as it courses through the middle and low posterior triangle of the neck, and it can be easily injured while elevating the posterior skin flaps. Second, the nerve does not enter the trapezius muscle at the anterior border of it but courses along the deep surface of it in close relationship with the transverse cervical vessels. Therefore, isolating the nerve to the level of the anterior border of the trapezius does not ensure its preservation during surgical dissection below this point, particularly in a bloody operative field.

Nerves to the Levator Scapula
The nerves to the levator scapulae, which vary in number from 1 to 3, branch off the 4th and 5th cervical nerves and travel posteriorly and inferiorly. They cross the anterior border of the levator scapulae and remain on the surface of
it for a short distance. These nerves are under the fascia of the muscle; thus, in the course of any neck dissection, but especially in a RND or a MRND, it is crucial to keep the plane of dissection superficial to the fascia of the levator in order to preserve these nerves. Understandably, a greater degree of shoulder disability may result from a radical neck dissection when the nerves to the levator scapulae muscle are severed.

Physiology
The trapezius is a fan-shaped muscle composed of upper, middle, and lower segments, each of which functions in a different but complementary manner. The trapezius and the other muscles that insert on the scapula stabilize and control the shoulder girdle during arm movement. The levator scapulae acts synergistically with the upper division of the trapezius to elevate the scapula; the rhomboid assists the middle part of the trapezius in retracting and stabilizing the scapula against the posterior thoracic cage. The simultaneous action of the upper and lower divisions of the trapezius muscle results in a unique rotatory action of the scapula. The upward rotation of the scapula, in combination with abduction of the arm at the glenohumeral joint, permits elevation of the arm beyond 90 degrees at the shoulder level.

The action of lever scapulae is to raise the medial angle of the scapula and incline the neck to the corresponding side with rotation of the neck in the same direction. With the trapezius muscle, the levator scapula makes a shrug possible.

Analysis of shoulder function
Leipzig et al7 provided the first objective data regarding shoulder dysfunction following neck dissection. They rated prospectively the degree of shoulder dysfunction in 109 patients undergoing various types of neck dissection. They found that impairment of function of the shoulder can occur after any type of neck dissection. However, it occurred more frequently when the spinal accessory nerve was extensively dissected or resected.

Subsequent studies, using objective measures of preoperative and postoperative strength, range of motion measures, and electromyography (EMG) of the trapezius muscle,8 showed that patients who underwent radical neck dissection had a significant permanent decrease in trapezius muscle strength and denervation of it on EMG, which did not improve with time. Conversely, moderate to severe EMG abnormalities were noted in as many as 65% of the patients who had a MRND and moderate EMG abnormalities were noted in 22% of those undergoing supraomohyoid neck dissections. However, in most of these patients, trapezius muscle strength and evidence of trapezius denervation improved by 12 months.

Cappiello et al compared both clinically and with electrophysiologic analysis, using electromyography (EMG) and electroneurography (ENG) to assess shoulder function after SND of levels II-IV and II-V9. At 12 month follow-up, both groups demonstrated mild to moderate weakness in shoulder function but more so in the SND II-V group. EMG and ENG abnormalities were more prevalent with posterior triangle dissection but were noted also in patients that had (level IIb) dissection9. Interestingly, these electrophysiologic findings did not correlate with subjective symptoms or clinical findings of shoulder dysfunction.

Several recent observations suggest that dissection of sublevel IIb is not necessary in patients with larynx, oropharynx and hypopharynx cancer in the clinically N0 neck10,11. Dissection of the nodes in level IIb requires, in most patients, a more extensive manipulation of the spinal accessory nerve; thus, avoiding a level IIb dissection can decrease the risk of postoperative dysfunction of this nerve, as has been suggested by a recent electromyographic study12.

Shoulder function and quality of life (QOL)
Kuntz and Weymuller1 assessed 84 patients pre operatively and 6 and 12 months post neck dissection and found that Quality of Life (QOL) scores were worse in patients who had a RND than in patients who had mRND and SND. Similar results have been reported by others, who, in addition to questionnaires, used objective measures such as the arm abduction test (AAT)13-17. These studies also found that preservation of the cervical plexus contribution to the SAN did not decrease shoulder morbidity significantly13.

Rehabilitation
In a recent multicenter study of 224 patients undergoing neck dissection Nibu et al2 assessed the impact of immediate postoperative rehabilitation and type of neck dissection on postoperative QOL, in comparison to a previous cohort of 74 patients who did not receive rehabilitation2. Participants completed a questionnaire and completed the AAT 1, 3, 6 and 12 months after surgery. They found that at 12 months, ATT was significantly better in patients in whom the SAN was preserved even if the sternocleidomastoid muscle was resected. They also found that postoperative rehabilitation resulted in better shoulder function and QOL after neck dissection2.

Chida et al18 studied prospectively ten patients with accessory nerve palsy after radical neck dissection. Every patient received occupational therapy. Patients were evaluated before and after therapy for the existence of resting and motion pain, active and passive range of motion (ROM) during shoulder flexion and abduction. The occupational therapy program consisted basically of passive ROM exercises, active-assistive ROM exercise,
sanding and wiping exercises. These were combined with relaxation techniques. Occupational therapy resulted in significant improvement of shoulder function. However, the beneficial effects were modest in regards to shoulder pain. Resting pain was relieved in two of the seven patients who received therapy and was unchanged in the remaining five. Motion pain was severe in every patient at the initial evaluation. Although the motion pain disappeared in one case, there was little change in the remaining nine patients. McNeely et al\textsuperscript{19} conducted a pilot study to evaluate the effects of progressive resistance exercise training (PRET) on shoulder dysfunction caused by spinal accessory neurapraxia or neurectomy in patients with head and neck cancer. Twenty patients were randomly assigned to PRET or standard care intervention. Subjects assigned to the PRET group exercised three times per week for 12 weeks. The goal of the exercise program was to enhance scapular stability and strength of the upper extremity. Active shoulder external rotation, shoulder pain, and overall score for shoulder pain and disability were significantly better in the PRET exercise group.

At our institution, patients who undergo neck dissection and have any shoulder discomfort or weakness postoperatively are given a pamphlet with the following exercises. They are designed to increase the movement and strength of the neck, arms, and shoulders. Patients are directed to perform each exercise ten times, twice per day.

**Figure 1:** With arms extended at right angles to the body, rotate them in a clockwise direction.

**Figure 2:** Position yourself next to a wall and walk your fingers up the wall as high as possible (A). When you cannot progress any higher, step closer to the wall and slide your hand as high up as possible (B). Take care to keep your elbow straight at all times.

**Figure 3:** Lie on the unoperated side, facing straight ahead with your head supported by your arm. Flex your chin to your chest and repeat the exercise ten times.

**Figure 4:** Lie on your back, looking ahead. Twist your head first to the right, then to the left as far as possible.

**Figure 5:** Lie on your back with your arm at the side of your body. Move the arm until it is extended as far as possible from your side without raising it from the bed. Then move your arm back to your side. The elbow must be kept straight at all times.
backward until the back of your hand rests on the bed. Your side and your elbow bent to a ninety degree angle. Slowly raise and lower your arm. Keep your elbow straight at all times.

Conclusion

The available evidence clearly indicates that any neck dissections can result in shoulder dysfunction as a result of paresis or paralysis of the SAN. Although this appears to be reversible, it behooves us to make every effort to avoid undue trauma to the nerve (particularly stretching) during any neck dissection in which the nerve is preserved. Other measures that may be useful in minimizing shoulder dysfunction after neck dissection are to preserve the nerves to the levator scapula muscle and to avoid dissecting level IIb, when appropriate. Furthermore, every patient that undergoes a neck dissection must be questioned about the function of the shoulder and must be evaluated by a physical therapist early in the postoperative period. Should any deficit be detected, early physical and occupational therapy are recommended since they are useful to improve range of motion and to strengthen alternative muscles to compensate for the loss of trapezius function.

Reference List


Figure 6: Lie on your back with your arm at right angles to your side and your elbow bent to a ninety degree angle. Slowly roll your arm forward until your palm rests on the bed, then backward until the back of your hand rests on the bed.

Figure 7: Lie on your back with the arm on the operated side extended at the side of your body. Slowly raise and lower your arm. Keep your elbow straight at all times.
Evidence based Management of Glottic Laryngeal Dysplasia

Paul Nankivell\textsuperscript{1,2} BA, BM BCh, MRCS
Hisham Mehanna\textsuperscript{1,2,3} PhD, BMedSc, MBChB, FRCS, FRCS (ORL-HNS)

\textsuperscript{1}Institute of Head and Neck Studies and Education (InHANSE)
University Hospitals Coventry and Warwick, Coventry, UK

\textsuperscript{2}Department of Otorhinolaryngology/Head and Neck Surgery
University Hospitals Coventry and Warwick, Coventry, UK

\textsuperscript{3}Department of Otorhinolaryngology/Head and Neck Surgery
Birmingham Heartlands Hospital, Birmingham, UK

Corresponding Author
Professor Hisham Mehanna
Director and Honorary Professor
Institute of Head and Neck Studies and Education, University Hospitals Coventry and Warwickshire
Clifford Bridge Road, Coventry, CV2 2DX, UK
Fax: 02476 966915 Email: Hisham.mehanna@uhcw.nhs.uk

Abstract
Dysplasia affecting the larynx can undergo malignant progression. Detection and treatment of this premalignant stage before invasion is therefore desirable, but carries potentially significant morbidity. Predicting which of the relatively small proportion of lesions will progress is currently based on histological grading; however this has a poor prognostic ability at an individual patient level. No biomarkers have yet been proven to reliably improve on existing predictive methods. In addition, lack of evidence for the most effective treatments and follow-up strategies has led to a lack of consensus, and consequently, varied management approaches. This in turn, makes analysis of data and outcomes from different individual centres difficult to compare. A recent consensus meeting of UK ENT surgeons and pathologists will hopefully help lead to a more co-ordinated and scientific approach to improving the management of this condition.

Keywords
Laryngeal, treatment, management, biomarkers, follow-up

Introduction
The clinical importance of laryngeal dysplasia lies in its malignant potential. These lesions continue to pose a great clinical challenge, partly because of the lack of knowledge regarding the natural history of the condition, but also because of the wide variability in diagnosis, management and follow-up strategies employed. This inconsistent approach was recently highlighted in a questionnaire survey to UK ENT surgeons on their management of laryngeal dysplasia\textsuperscript{1}. The findings of this survey confirmed a wide variability in management, and prompted the convening of a workshop bringing together both pathologists and surgeons and the publication of consensus guidelines on several key aspects of management\textsuperscript{2}. The findings of both the study and the guidelines will be discussed in greater detail throughout this review. It is important to point out at the outset however, that there is little high quality evidence for the management of glottic laryngeal dysplasia.

Definitions and presentation
Dysplasia is defined by the World Health Organisation, (WHO) as, ‘A precancerous lesion of stratified squamous epithelium characterized by cellular atypia and loss of normal maturation and stratification’\textsuperscript{3}. In the head and
neck, these changes occur most commonly in the oral cavity and glottic larynx. Dysplasia is graded histologically by quantifying the degree of cellular and architectural abnormality above the epithelial basement membrane using haematoxylin and eosin stained sections. Although a variety of histological grading systems are currently in use, the most widely used WHO classification divides dysplastic lesions into five categories: hyperplasia, mild, moderate and severe dysplasia, or carcinoma in situ (CIS). Dysplasia often presents in the larynx as leukoplakia, a term that a recent working group suggested be used for ‘white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer’. The most common clinical presentation is with hoarseness of voice. However, neither clinical history nor appearance of the lesion are reliable indicators of the presence or absence of dysplasia.

**Epidemiology**

Epidemiological data is relatively lacking for dysplasia affecting any anatomical site in the head and neck, but is particularly so for the larynx. Laryngeal leukoplakia is reported to affect between 2 and 10 per 100,000 person years for females and males respectively. In the same cohort, the rates of newly diagnosed laryngeal cancer were 0.3 and 7 per 100,000 person years for females and males. The proportion of white patches biopsied containing dysplasia has been quoted as ranging from 6-90%. A review of 12 studies attempted to clarify this and demonstrated that around half (54%) of the 2188 laryngeal leukoplakia biopsies contained no dysplasia, with around a third showing mild/moderate dysplasia and 15% severe dysplasia/carcinoma in situ.

**Malignant transformation**

The natural history of laryngeal dysplasia is not well characterized. An assumption is often made of a linear progression from keratosis through mild and moderate dysplasia to more severe dysplasia and then invasive disease. Whilst there does appear to be evidence for the progressive accumulation of genetic changes during the pre-malignant phase, there is no good observational evidence to support this theory of linear progression morphologically or histologically. This may be in part because the rates of malignant progression in the few studies that have practiced a watch and wait policy for severe dysplasia/CIS have demonstrated unacceptably high transformation rates.

The rates of malignant transformation reported in the literature vary widely, from 2 to 74%. This may in part reflect the heterogeneity of the severity of dysplasia in the cases included. It may also represent the well-documented inter-rater variability in reporting dysplasia lesions among pathologists. A recent systematic review, performed by our group, examined the malignant transformation rate in 940 patients from 9 studies. 137 patients progressed to cancer, giving a malignant transformation rate of 14% (95% CI 8-22%). This is similar to the rate of 12% (95% CI 8-18%) found in our systematic review of oral dysplasia. When divided into two groups (mild/moderate versus severe/CIS) the transformation rate was shown to be significantly greater in the higher-grade group (30% versus 11% p<0.0002). From the same review, seven studies assessed the mean time to transformation, which for all grades combined was shown to be 5.8 years (range 1.8–14.4 years). There was no evidence that grade of dysplasia affected the duration to transformation, although the quality of this data was noted to be poor. Notably, the duration to transformation was as long as 14 years in one study, and therefore the available evidence does not support the practice of early discharge of patients with dysplasia.

**Pathological considerations in the management of laryngeal dysplasia**

**Grading**

Dysplasia grading systems assess the degree and severity of architectural and cytological change in the tissues. There are several grading systems in use, including Laryngeal Intraepithelial Neoplasia (LIN) and Ljubljana, although the most commonly used system is the WHO classification. This last system classifies dysplasia into hyperplasia, mild, moderate and severe dysplasia, or carcinoma in situ (CIS). Severe dysplasia and CIS may be considered the same with regards to management decisions. To date, this is the best predictor of future malignant behaviour, with higher grades of dysplasia associated with increased rates of progression to cancer. However, lower grades of dysplasia do also transform to malignant disease, and higher grades can remain static. To compound this problem considerable inter and intra-rater variability has been shown amongst pathologists grading dysplasia cases. These limitations make this method of predicting future outcomes imperfect; yet it remains one of the most important factors in clinical decision making.

**Biomarkers**

The inadequacies of histological grading may be improved by examining the differential expression of proteins or genes in those dysplastic lesions likely to transform to cancer compared to those that may regress. There are many studies of such prognostic biomarkers, however most have only used a cross sectional design with no longitudinal follow-up. We undertook a systematic review of biomarkers that demonstrated prognostic ability for laryngeal dysplasia. 13 markers from 9 studies were
identified with good follow-up data\textsuperscript{20}. Only 4 markers had any ability to predict future malignant transformation, (p53, Cortactin, Cyclin D1 and Ki67)\textsuperscript{21-23}. Each of these studies had small numbers of patients however, and although one study did show p53 to have a prognostic ability, a meta-analysis of the 5 studies examining this biomarker failed to confirm this. Therefore, there is currently no good evidence for the routine use of biomarkers in the management of laryngeal dysplasia.

**Surgical considerations in the management of laryngeal dysplasia**

In an attempt to help reduce variability in treatment, and encourage more uniformity we have based our discussions in this section on the recent ENT-UK consensus guidelines for the management of laryngeal dysplasia\textsuperscript{2}.

**Specialist vs. non-specialist**

The survey of UK ENT surgeons suggested that only around \textasciitilde{}60\% of the cases of laryngeal dysplasia were being managed by surgeons with a head and neck subspecialty interest, and that around half of those managing the condition were involved in less than 10 cases per year\textsuperscript{1}. To address this obvious anomaly, the consensus guidelines recommended that there should be a nominated individual within the head and neck team who develops an interest in the condition and its management. This concentration of cases would increase the expertise of those involved and aim to reduce the variations in management\textsuperscript{2}.

**Diagnosis**

Single or multifocal lesions should ideally undergo excision biopsy, thereby providing diagnosis and treatment by one procedure. In large confluent lesions, this may not be practical because of the high potential morbidity of removing large areas of laryngeal mucosa. In these cases, there should be mapping of the lesion by multiple biopsies, with a low threshold for re-biopsying any suspicious areas\textsuperscript{2}. There are two important aspects of the initial management to consider: specimen orientation and documentation. Endoscopically resected laryngeal specimens pose a particular challenge for accurate pathological reporting, owing to their small size. This makes it difficult to use more routine methods of fixing tissue for orientation. Use of an anatomically constructed dehydrated cucumber mount enables biopsies to be better orientated and preserved for histopathological processing and reporting\textsuperscript{24}. Alternatives include cardboard paper with an adhesive surface to enable mounting and orientation of the specimen.

Precise documentation of laryngeal lesions is fundamental and a key recommendation from both the questionnaire survey and consensus meetings. Photographic documentation allows the anatomical and morphological characteristics of a lesion to be captured for both initial assessment and ongoing monitoring.

**Treatment modality**

Currently there is insufficient high quality data to be able to specify the optimal treatment for laryngeal dysplasia. The options include surgical intervention, radiotherapy and photodynamic therapy (PDT). The severity of dysplasia grade appears to be the most influential factor in deciding which to employ. What little data exists on the role of PDT in treating laryngeal pathology appears encouraging, however it predominantly examines malignant rather than premalignant laryngeal lesions\textsuperscript{25-27}. Surgery may involve total excision or include a biopsy for diagnosis and then a period of watchful waiting. This approach may be performed with cold steel instruments or LASER. Some centres use the LASER to perform ablation of the lesion rather than excision. However, the latter leaves no specimen for histological assessment and may lead to more significant voice dysfunction afterwards\textsuperscript{2}. Although still performed, vocal cord stripping has no real place in the treatment of this condition, except in a very small number of selected cases with widespread severe grade disease. For severe dysplasia/CIS there is no clear evidence for any benefits of radiotherapy over surgical excision. A study from the Netherlands suggests the localisation and extent of the disease may influence the decision, with bilateral vocal cord or anterior commissure involvement leading to over 90\% of respondents favouring radiotherapy\textsuperscript{28}. Our meta-analysis showed a trend, but no statistically significant difference between those lesions treated surgically, (either with cold steel or LASER) and those where biopsy or radiotherapy had been performed\textsuperscript{29}. The heterogeneous nature of the two groups may account for the lack of statistical significance. The UK consensus is for surgical excision where possible, and to reserve the use of radiotherapy to cases with limited access or high grade dysplasia that recurs several times\textsuperscript{2}. Despite this, the roles of surgery and radiotherapy remain to be defined more clearly.

**Risk factor avoidance**

Smoking is well documented as a principal risk factor in the development of laryngeal dysplasia as well as laryngeal cancer\textsuperscript{29,30}. Despite this, there is no evidence that in patients with dysplasia, smoking cessation reduces the risk of these lesions progressing to cancer\textsuperscript{18,31}. Furthermore, the risk of developing new lesions may also be as great in those that stop smoking. Yet all patients should receive advice to stop smoking and be encouraged to quit, as it will reduce the risk of developing de novo second primary cancers. The aetiological role of alcohol and laryngopharyngeal reflux is less compelling; however advice to
reduce the former and treatment for the later may still be warranted. There is no evidence for the role of the Human Papilloma Virus (HPV) as a risk factor in laryngeal premalignancy and cancer32-35.

Follow-up
The evidence that laryngeal dysplasia may transform to malignancy many years after initial diagnosis may indicate the need for lifelong follow-up. However, following up all patients indefinitely may be costly, and sometimes may not be practical. In view of the fact that there is no evidence that any surveillance strategy reduces transformation or detects it earlier, a pragmatic approach may be to stratify patients into high and low risk groups with follow-up tailored to the two groups2. Those of high risk may be patients with severe dysplasia/CIS on initial biopsy, or those with less severe dysplasia but with ongoing symptoms of hoarseness, visible lesion on the vocal cord or continued exposure to carcinogenic risk factors i.e. smoking. These patients should be managed in a manner similar to a cancer follow-up regime, namely that is, monthly for the first year, two monthly for the second year, three monthly for the third year, and six monthly in years four and five. As for documentation at the time of diagnosis, photo-documentation is advised to allow for accurate disease monitoring. Patients considered low risk may be discharged after a minimum of six months, however they should be counselled carefully to return if there is any recurrence or worsening of symptoms such as hoarseness. Furthermore, there is a case for patients who already suffer from hoarseness as a result of their condition or treatment to undergo long-term follow-up as they may not undergo appreciable voice change till a lesion is significantly bigger.

Conclusion
Laryngeal dysplasia, as a premalignant lesion should be considered and managed in a manner similar to head and neck cancers – that is by dedicated head and neck surgeons with higher risk cases discussed in multi-disciplinary meetings. A careful diagnostic work-up including risk factor documentation, photo-documentation of the larynx and accurate specimen orientation are key. Currently the advocated treatment of choice where possible, is complete surgical excision by either cold steel of LASER, and advice on risk factor avoidance. Research is much needed into the epidemiology and natural history of the condition, along with prognostic biomarkers, effectiveness of different treatment options and follow-up regimes. The recent publication of a consensus guideline is an important first step and will hopefully lead to more valuable research output in the future.

References
The Current Role of Chemotherapy/ Biotherapy in the Primary Management of Advanced Squamous Cell Carcinoma of the Head and Neck

Pol Specenier and Jan B Vermorken
Department of Medical Oncology, Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Belgium
Email: pol.specenier@uza.be

Abstract
Concurrent cisplatin-based chemoradiotherapy (CRT) is considered standard for patients with resectable disease when organ preservation is desired, and, as adjuvant treatment, for patients with high risk pathological findings at surgical resection, and for patients presenting with unresectable disease.

The TPF combination can be considered the new standard regimen whenever induction chemotherapy (ICT) is considered appropriate. Despite its increased use since the introduction of the TPF regimens, the respective roles of ICT and sequential treatment, i.e. ICT followed by concurrent CRT or BRT have not been established yet.

The majority of patients presenting in a more advanced disease stage will eventually relapse either locoregionally and/or at distant sites. A few patients with a locoregional recurrence can be salvaged by surgery or reirradiation. Most patients with recurrent or metastatic disease only qualify for palliative treatment. Treatment options in these patients include supportive care only, single agent chemotherapy, combination chemotherapy or targeted therapies either alone or in combination with cytotoxic agents.

Several of the more traditionally used combination chemotherapy regimens have demonstrated higher response rates in randomized trials than either single agent cisplatin or methotrexate, but they did not have impact on survival. In the EXTREME trial, the addition of cetuximab to the combination of cisplatin or carboplatin and infusional 5-FU has led for the first time to a significant improvement in overall survival in patients with recurrent/metastatic SCCHN. This regimen is recommended for recurrent/metastatic disease patients in good performance status, who otherwise would have been able to tolerate platinum-based combined chemotherapy regimens.

Introduction
Squamous cell carcinoma of the head and neck (SCCHN) is considered to be the final stage of a multi-step process evolving from normal histology to hyperplasia, dysplasia, carcinoma in situ, to invasive carcinoma. Particular chromosomal alterations appear to be associated with distinct stages of tumor progression. Underlying genetic instabilities including the loss of heterozygocity (LOH) of certain chromosomes (3p14, 9p21, 17p13, 8p, 11q, 13q, 14q, 6p, 4q27, 18q21, and 10q23) and amplification or deletion or up-regulation or downregulation of certain oncogenes or tumor-suppressor genes, including epidermal growth factor receptor (EGFR), p53, Rb, p65, cyclooxygenase 2 (COX-2), p16, cyclin D1, and phosphatase and tensin homolog (PTEN), MYC, MET, PIK3CA, are genetic alterations which can occur in each of the pathological stages of this disease1,2.

Locoregionally Advanced SCCHN
Up to 60% of the patient present with locoregionally advanced (LA) disease at diagnosis, the options for treatment currently rests between surgery and post-operative radiotherapy or a combined modality therapy with salvage surgery as an option for patients whose disease has not responded or who develop a late recurrence.

Concurrent Chemoradiation
Concurrent cisplatin-based chemoradiation (CRT) is to be considered standard therapy for patients with resectable disease when organ preservation is desired, and, as adjuvant treatment, for patients with high risk pathological findings at surgical resection or for patients with unresectable disease.

Concurrent CRT was adopted as standard of care for LA-SCCHN after the publication of a large meta-analysis which was later updated and extended to a total of 17,346 patients treated in 93 randomized trials3,4. Chemotherapy also improves survival when added to hyperfractionated or...
accelerated radiotherapy which in itself is superior to conventional radiation alone\textsuperscript{5,8}.

Multiple randomized phase III trials demonstrated a survival benefit for CRT over radiation alone, administered either as definitive treatment or in the adjuvant setting, after surgery, for high risk patients. The best studied and most widely used regimen, which can be considered the standard comparator for randomized trials, is cisplatin 100 mg/m\textsuperscript{2} on days 1, 22, and 43 during radiotherapy\textsuperscript{9}. Blanchard et al\textsuperscript{10} performed a mixed treatment comparison (MTC) meta-analysis to the Meta-Analyses of Chemotherapy and Radiotherapy in head and neck cancer. The analysis suggested that altered fractionated concomitant chemoradiotherapy (AF-CRT) leads to the highest probability of survival in non-metastatic SCCHN.

\textbf{Bio(chemo)radiation}

Bonner et al\textsuperscript{11,12} randomized 424 patients with stage III or IV nonmetastatic squamous cell carcinoma of the oropharynx, hypopharynx or larynx to radiotherapy alone or to radiotherapy in combination with weekly cetuximab during radiotherapy. There was a significant increase of the median duration of locoregional control (24.4 vs. 14.9 months, \( p = 0.005 \)) and the median OS (49 vs. 29.3 months, \( p = 0.018 \)). There was no difference in grade 3/4 acute toxicity except for acneiform rash and infusion reactions, which occurred in 17 and 3\% of the patients, respectively. In particular, the grade 3/4 radiation related mucosal toxicity did not lead to an increased incidence of radiation dermatitis. However, a large number of cases of severe radiation have been reported after more widespread use outside clinical trials\textsuperscript{11-19}. Thus far, a head to head comparison of CRT and cetuximab-based bioradiation is lacking.

Walsh et al\textsuperscript{20} retrospectively reviewed acute toxicity with cetuximab and radiotherapy, comparing it with a matched cisplatin and radiotherapy group. The cetuximab group experienced significantly more toxicity: grade > 3 oral mucositis (\( p = 0.014 \)), grade > 3 skin dermatitis (\( p = 0.0004 \)), > 10\% weight loss (\( p = 0.03 \)), and enteral feeding requirement (\( p = 0.05 \)) (80), although the compliance with bioradiation was significantly better (\( p = 0.05 \)).

In the TREMPLIN trial\textsuperscript{21}, patients with stage III-IV carcinoma of the larynx or hypopharynx who were candidates for total laryngectomy, were treated with 3 cycles of induction chemotherapy (docetaxel and cisplatin both 75 mg/m\textsuperscript{2} on day 1 and 5-fluorouracil 750 mg/m\textsuperscript{2}/day on days 1-5). Hundred and sixteen patients who obtained at least a partial response after induction chemotherapy, were randomized to receive conventionally fractionated irradiation (70 Gy in 35 fractions of 2 Gy over 7 weeks) with either cisplatin 100 mg/m\textsuperscript{2} on day 1, 22, and 43 or weekly cetuximab at the recommended dose. There was no difference in larynx preservation rate 3 months after treatment, which was the primary endpoint of this phase II study. Only 43\% of the patients in the cetuximab arm were able to receive the chemotherapy as scheduled versus 71\% in the cetuximab arm. Grade 3 in field skin toxicity occurred in 24\% and 52\% of the patients with cisplatin and cetuximab, respectively (\( p < 0.001 \)). There were more locoregional failures after cetuximab (21.4\% versus 11.7\% with cisplatin) but at the end, locoregional control was equal between the two arms as the majority of the failures in the cetuximab arm could be salvaged with surgery. Grade 1 renal dysfunction at last evaluation was observed in 22.4\% and 0\% of the patients, respectively (\( p < 0.001 \)).

In Radiation Therapy Oncology Group (RTOG) study 0522\textsuperscript{22}, the addition of cetuximab to cisplatin-based chemoradiation did not improve the outcome. In that large phase III trial, 895 evaluable patients with stage III-IV carcinoma of the oropharynx, larynx, and hypopharynx were randomized to receive concurrent accelerated radiation (72 Gy in 42 fractions over 6 weeks and cisplatin 100 mg/m\textsuperscript{2} on day 1 and 22 with or without weekly cetuximab at the recommended dose. Over 90\% of patients received 2 cisplatin cycles in both arms and 74\% of the patients received the loading and 6 or more doses of cetuximab in the combination arm. The median follow-up was 2.4 years for surviving patients. There were no significant differences in progression-free survival (PFS) (HR: 1.05, 95\% CI: 0.84-1.29; \( p = 0.66 \)), which was the primary endpoint of the study. There was no difference in overall survival (OS) (HR: 0.87, 95\% CI: 0.66-1.15; \( p = 0.17 \)), death within 30 days of therapy (2.0\% vs. 1.8\%, \( p = 0.81 \)), and total grade 3-5 adverse events (92\% vs. 90\%, \( p = 0.30 \)). However, patients in the combination arm had higher rates of grade 3-4 mucositis (43\% vs. 33\%, \( p = 0.004 \)) and in field skin reactions (25\% vs. 15\%, \( p < 0.001 \)).

\textbf{Induction chemotherapy - Organ Preservation Studies}

Induction chemotherapy has some appealing theoretical advantages such as optimal drug delivery to the tumor through undisrupted vasculature, early eradication of micrometastases and improved tolerance of cytotoxic drugs\textsuperscript{23}. Moreover, induction chemotherapy offers the opportunity of assessing tumor response and thereby selecting the patients for organ preservation\textsuperscript{24}.

Organ preservation was pioneered by the Veterans Affairs Laryngeal Cancer Study Group\textsuperscript{25} who randomized 332
patients between laryngectomy and induction chemotherapy followed by definitive radiation. After a follow-up of 33 months the estimated two-year survival was 68% for both treatment groups. The larynx was preserved in 64% of the patients in the induction chemotherapy arm. There were significantly more distant metastases in the surgery group and more locoregional recurrences in the chemotherapy group. After the publication of the results of the trial, induction chemotherapy followed by radiation was widely adopted as an alternative for total laryngectomy for patients with LA carcinoma of the larynx who responded to induction chemotherapy with cisplatin/infusional 5-fluorouracil (PF) followed by definitive radiotherapy in case of a complete response at the primary tumor site after two or three cycles. Less well responding patients underwent radical surgery followed by radiotherapy. After a median follow-up of 51 months, there was no difference in local or regional failure rate. There were fewer distant metastases in the induction-chemotherapy arm (25% vs. 36%). Median OS was 25 months in the immediate-surgery arm versus 44 months in the induction-chemotherapy arm. So, the survival in the chemotherapy arm was not jeopardized. Moreover, about half of the patients who were still alive at three years had retained functional larynges.

Lefebvre et al\textsuperscript{26} randomly assigned 202 patients with T2, T3 or T4 tumors of the pyriform sinus or aryepiglottic fold to immediate surgery followed by radiotherapy or induction chemotherapy with cisplatin/infusional 5-fluorouracil (PF) followed by definitive radiotherapy in case of a complete response at the primary tumor site after two or three cycles. Less well responding patients underwent radical surgery followed by radiotherapy. After a median follow-up of 51 months, there was no difference in local or regional failure rate. There were fewer distant metastases in the chemotherapy arm (25% vs. 36%). Median OS was 25 months in the immediate-surgery arm versus 44 months in the induction-chemotherapy arm. So, the survival in the chemotherapy arm was not jeopardized. Moreover, about half of the patients who were still alive at three years had retained functional larynges.

RTOG protocol 91-11\textsuperscript{27} was a second generation larynx preservation trial, with radiotherapy alone as a control arm. Five hundred forty-seven patients with stages III or IV SCC of the glottic or supraglottic larynx carcinoma and candidates for total laryngectomy as curative treatment, were randomized to be treated with cisplatin/infusional 5-fluorouracil (PF) induction chemotherapy (ICT) followed by conventionally fractionated radiotherapy, conventionally fractionated radiotherapy concurrently with cisplatin 100mg/m\textsuperscript{2} on days 1, 22 and 43 of the radiotherapy, or conventionally fractionated radiotherapy alone. At first reporting, the median follow-up was 3.8 years. At two years, the proportion of patients who had an intact larynx was significantly higher in the concurrent CRT arm than in the ICT arm and the radiotherapy alone arm (88% vs. 75% and 70%). Locoregional control rate was 78% with concurrent CRT, 61% in the ICT arm and 56% with radiotherapy alone. Updated results of RTOG 91-11 were presented at the Annual Meeting of ASCO in 2006 after a median follow-up of 6.9 years for surviving patients\textsuperscript{28}. At five years, there was no difference in laryngectomy-free survival between the ICT arm and the concurrent CRT arm. However, the larynx preservation rate and the locoregional control rate were still significantly better in the concurrent CRT arm. The distant metastasis rate was low in all three arms with a trend favoring both chemotherapy arms. Disease-free survival was significantly better with either induction or concurrent chemotherapy. There was an excess in non cancer-related deaths in the concurrent CRT arm. Overall survival was still not significantly different between the three arms but showed a trend in favor of the ICT arm.

**A new standard induction regimen**

The earlier mentioned meta-analysis of chemotherapy in locoregionally advanced head and neck cancer failed to demonstrate a survival advantage for induction chemotherapy followed by locoregional treatment compared to locoregional treatment alone and in fact indicated superiority of concurrent CRT over the sequential use of chemotherapy followed by locoregional treatment\textsuperscript{3,4}. However, when the meta-analysis was restricted to the trials using the PF regimen, consisting of cisplatin 100mg/m\textsuperscript{2} on day 1 followed by 5-fluorouracil 1000mg/m\textsuperscript{2}/day administered as a continuous infusion over five days, then also the sequential use of chemotherapy followed by irradiation was significantly better than radiation alone (in absolute terms 5% better survival at 5 years)\textsuperscript{29}. However, the PF ICT regimen is no longer standard. Indeed, the superiority of TPF (PF + docetaxel) and PPF (paclitaxel + PF) has been demonstrated in multiple large randomized phase III trials and by the outcome of an individual patient-based meta-analysis conducted by Blanchard et al\textsuperscript{30}.

Hitt et al\textsuperscript{31} randomized 382 patients with stages III or IV SCCHN to three 3-weekly cycles of either PF (arm A) or cisplatin (100 mg/m\textsuperscript{2} on day 1), paclitaxel (175 mg/m\textsuperscript{2} on day 1) and 5-fluorouracil (500 mg/m\textsuperscript{2}/day as a continuous infusion on days 2–6) (PPF) (arm B) as induction regimen. The primary objective was to compare the complete response rate which was 14% in arm A and 33% in arm B (p < 0.001). Patients with a complete response or a partial response of at least 80% at the primary tumor site were treated with CRT (conventional radiation, 70 Gy and cisplatin 100 mg/m\textsuperscript{2} on days 1, 22 and 43). The other patients were treated according to the institution’s guidelines. Median time to treatment failure was 12 months in arm A and 20 months in arm B (p = 0.003). Patients in arm B had a trend to longer OS although the difference was not significant. However, the difference in median OS (26 vs. 36 months) was statistically significant for patients with unresectable disease. After a median follow-up of 23 months, 175 patients had disease progression or a relapse. Only 14% of them had distant metastases. Fifty-three percent of the patients in arm A and 16% in arm B experienced grade 2, 3 or 4 mucositis during induction chemotherapy (p < 0.001).
Vermorken et al\textsuperscript{32} randomized 358 patients with locoregionally advanced unresectable SCCHN between four cycles of PF or TPF (docetaxel 75 mg/m\textsuperscript{2} and cisplatin 75 mg/m\textsuperscript{2} on day 1 followed by 5-fluorouracil 750 mg/m\textsuperscript{2}/day on days 1-5 administered as a continuous infusion). After induction chemotherapy, all patients with stable or responsive disease were irradiated (conventionally fractionated, hyperfractionated or accelerated). After a median follow-up of 32.5 months, PFS (primary endpoint) was found significantly longer in the TPF arm (11 vs. 8.2 months, \(p = 0.007\)). After a median follow-up of 51 months, median OS in the TPF arm was 18.6 months vs. 14.2 months in the PF arm (\(p = 0.0052\)). Estimated three year OS was 36.5 \% for TPF and 23.9 \% for PF. A recent update of the study after a median follow up of 8.5 years confirmed the earlier efficacy data\textsuperscript{33}. Grade 3/4 neutropenia was more frequent with TPF (76.9 \% vs. 52.5 \%), while thrombocytopenia was more frequent with PF (17.9 \% vs. 5.2 \%) and there were less toxic deaths observed in the TPF arm (2.3 \% vs. 5.5 \%). Moreover, the quality of life was better preserved in the TPF arm\textsuperscript{34}.

Posner et al\textsuperscript{35,36} randomized 539 patients to TPF (docetaxel 75mg/m\textsuperscript{2} and cisplatin 100 mg/m\textsuperscript{2} on day 1 followed by 5 FU 1000 mg/m\textsuperscript{2}/day for 4 days) or PF. Eligible were patients with resectable disease, with low cure rate probability, patients with unresectable disease, and patients who were candidates for organ preservation. After three cycles patients received CRT with weekly carboplatin. After a median follow-up of 42 months the median OS (primary endpoint) was 70.6 months in the TPF arm versus 30.1 months in the PF arm (\(p = 0.0058\)). Three-year OS and PFS were 62\% and 48\%, respectively. Grade 3/4 neutropenia was more common in the TPF arm than in the PF arm (84\% vs. 56\%).

Pointreau et al\textsuperscript{37} randomized 220 patients with operable stages III or IV carcinoma of the larynx or hypopharynx who were candidates for total (pharyngo)laryngectomy between the European TPF and PF. After three cycles, patients with a less than 50\% tumor reduction and/or persistent larynx fixation underwent total laryngectomy followed by radiotherapy while the responders received radiation alone. The primary endpoint of the study was the three year larynx preservation rate. The overall response rate was 80\% with TPF and 59.2\% with PF. Larynx preservation after induction was offered to 80\% of the patients in the TPF arm and to 57.6\% in the PF arm. After a median follow-up of 36 months, the three year actuarial larynx preservation rate was 70.3\% with TPF and 57.5\% with PF (\(p = 0.03\)). Overall survival was not different between the two arms of the study.

### Sequential Treatment

Multiple phase II trials as well as the randomized trials by Posner et al and by Hitt et al clearly demonstrated the feasibility of TPF or PPF induction chemotherapy followed by concurrent CRT\textsuperscript{31,35,36}. However, all the above-mentioned randomized trials compared two different induction regimens and were not designed to study whether sequential use of ICT and concurrent CRT was superior to concurrent CRT alone. At least five large randomized phase III trials comparing TPF induction chemotherapy followed by CRT to CRT alone were started. Two of these trials were closed prematurely due to lack of accrual or lack of funding.

The final analysis of the trial conducted by the Spanish Head and Neck Cancer Cooperative Group was presented at ASCO 2009\textsuperscript{38}. In that trial, patients were randomized to receive either TPF or PF induction chemotherapy followed by concurrent CRT or concurrent CRT alone. The data presented suggested that the sequential approach improved time to treatment failure, time to progression and locoregional control. Despite the clever design of the study, the analysis unfortunately suffered from a number of methodological flaws which hampered the interpretation of the results.

Paccagnella et al\textsuperscript{39} published the results of the phase II portion of an Italian multi-center trial. Patients were randomized to receive three cycles of TPF followed by conventional radiotherapy concurrently with two cycles of PF or the same CRT alone. The complete response rate was 50\% in the induction arm and 21.2\% in the CRT arm. This trial has subsequently been taken into a phase III trial, which is expected to complete recruitment in the first quarter of 2011. Pending the results of the randomized trials and clarification of the issues raised in the Spanish trial, concurrent CRT still remains the standard treatment for patients with LA-SCCHN.

### Nutritional status

Malnutrition is frequently reported in patients with SCCHN. Pretreatment malnutrition has been reported to be associated with an increased risk of locoregional failure\textsuperscript{40}. Rutter et al\textsuperscript{41} retrospectively analyzed the impact of timing of percutaneous endoscopic gastrostomy (PEG) tube placement on clinical endpoints in 111 patients undergoing concurrent CRT. Early PEG tube placement was correlated to reductions in weight loss during CRT (\(p < .001\), \(R = 0.495\)), hospitalization for nutritional deficits (\(p = .011\), \(R = 0.262\)), and magnitude of persistent weight loss at 6 weeks post-CRT (\(p = .003\), \(R = 0.347\)). No differences were seen in PEG complication or dependence rates with earlier placement\textsuperscript{41}. Prophylactic PEG has
been reported to reduce the cumulative incidence of treatment interruption caused by toxicity, a decreased weight loss and a better HRQoL after 6 months. However, prophylactic PEG has also been reported to be associated with significantly higher rates of late esophageal toxicity.

**Late toxicity**

Xerostomia and impaired swallowing are the most commonly late therapy-induced self-reported toxicities in patients who were treated with radiotherapy either alone or in combination with chemotherapy. Prognostic factors for swallowing dysfunction at 6 months include T3-T4 tumors, bilateral neck irradiation, weight loss prior to radiation, oropharyngeal and nasopharyngeal tumors, accelerated radiotherapy and concomitant CRT. Messmer et al prospectively investigated the evolution of xerostomia over time after radiotherapy for head and neck cancer. Xerostomia at rest did not change significantly over time whereas the difficulties with speaking improved and the difficulties with eating worsened. Subjective xerostomia had not reached a steady state even more than 5 years after radiotherapy.

**Follow up**

Kothari et al prospectively analyzed 1039 consecutive outpatient consultations of head and neck cancer patients representative for a population treated by a multidisciplinary management team. Suspicion of recurrence was observed in 10% of the patients seen routinely but in 68% of the patients who had requested an unscheduled appointment. Most recurrences were found within the first follow-up year (54%). Recommended follow up (33) includes a history and physical exam at progressively longer intervals over time. Thyroid-stimulating hormone (TSH) should be checked regularly in irradiated patients, and post-treatment imaging of the primary and the neck is recommended within 6 months of treatment in patients with T3-T4 and/or N2-N3 disease. Further imaging is not routinely recommended for asymptomatic patients.

**Conclusions**

The management of SCCHN is complex and requires a multidisciplinary approach.

For the 60% of the patients who present with locoregionally advanced disease, combined modality therapy is generally recommended. Concurrent cisplatin-based CRT is to be considered standard for patients with unresectable disease, for patients with resectable disease when organ preservation is desired, and, as adjuvant treatment, for patients with high risk pathological findings at surgical resection.

Thus far, a head to head comparison of CRT and cetuximab-based bioradiation is lacking.

The TPF combination can be considered the new standard regimen whenever induction chemotherapy is considered appropriate. Despite its increased use since the introduction of the TPF regimens, the role of induction chemotherapy and that of sequential treatment, i.e. induction chemotherapy followed by chemoradiation, has not been established as yet.

The majority of patients presenting in an advanced disease stage will eventually relapse either locoregionally and/or at distant sites. A few patients with a locoregional recurrence may be salvaged by surgery or reirradiation.

**Reference**


Globus – a Diagnosis still Shrouded in Mystery in 2011

Paul M. Weinberger MD and Gregory N. Postma MD
Georgia Health Sciences University, Center for Voice, Airway and Swallowing Disorders
1120 15th Street, Augusta, GA 30912

Introduction and background
The condition today known as “Globus Pharyngeus” was described as early as 2500 years ago by Hippocrates (reviewed in1). Originally termed “Globus Hystericus” in 17042, there was an implication that the disorder was largely confined to females (greek hystericus = relating to the uterus). While earlier physicians attributed globus to essentially a supratentorial or psychogenic disturbance, the intervening years have moved away from this explanation while still yielding surprisingly slow progress towards discovering the true pathophysiologic causes. By 1968, the term “hystericus” was dropped and the modern “globus pharyngeus” was coined by Malcomson. Treatments for globus have ranged from plausible to potentially dangerous, including Magnolia Bark extract3, anti-reflux therapy 4, and even performing a partial epiglottectomy5.

Symptoms of globus primarily center around a perception of a lump in the throat, as if food or other material is trapped. It is generally perceived in the midline of the throat between hyoid bone and sternal notch, but can also include more lateralized paramedian sensations6. It should be emphasized that these symptoms specifically do not include dysphagia (difficulty swallowing) or odynophagia (pain when swallowing)7. Indeed, as will be discussed in the section on Diagnosis, these latter symptoms exclude globus and point to the potential for a more serious condition.

Key Points
1. To have a diagnosis of globus pharyngeus, symptoms such as dysphagia and odynophagia must not be present.
2. Globus is extremely common.
3. Globus may be, but is not always, associated with reflux disease.
4. Barium swallow (esophagography) and sedated esophageal endoscopy (rigid or flexible) are not recommended in the routine evaluation of globus, unless indicated for other reasons such as dysphagia, weight loss, etc.
5. In-office unsedated fiberoptic laryngoscopy (flexible trans-nasal, or rigid trans-oral) laryngoscopy is indicated in the workup and evaluation of a patient with globus.
6. In-office transnasal unsedated esophagoscopy (TNE) is an emerging diagnostic tool, and can be valuable in the evaluation of a patient with globus.

Epidemiology
The prevalence of globus in normal, healthy individuals has been estimated to approach 46% in most studies6, 8, 9. Globus is a universal disorder, and anecdotally appears to equally affect patients from around the globe including the United States, Japan, Greece, and the United Kingdom. Age distribution is generally middle-aged adults (4th and 5th decade) with globus uncommon in patients under the age of 206, 9, 10. Gender distribution is roughly equal9, 11 although more females with globus seek medical attention6. Globus is an extremely common chief complaint among patients seeking ENT referrals, accounting for up to 4% of initial ENT evaluations12.

Pathophysiology
Numerous etiologies for globus have been proposed, starting with the psychiatric derivations of the original term “globus hystericus.” As initially described, globus was thought to originate from purely psychogenic causes including repressed emotions, leading one author to propose the disorder could be secondary to “holding back tears 13.” While the “hystericus” has been dropped from modern terminology, there does remain some association between globus pharyngeus and anxiety or depression.
Several studies have demonstrated higher levels of depression and anxiety in patients with globus compared to controls\textsuperscript{14-16}. Contrarily, in a prospective study of 88 globus patients, there was an equivalent rate for depression and anxiety compared to a reference “normal” population of general medical outpatients\textsuperscript{17}.

One possible link between globus pharyngeus and psychiatric morbidity may be response to stress. Two studies have shown that patients with globus report a significant stressful life event in recent months, compared to controls\textsuperscript{18, 19}. Globus patients are less likely to have a “close confiding relationship,” compared to controls\textsuperscript{19}. Strong emotion can worsen globus symptoms\textsuperscript{9}, but this has not been replicated in experimental conditions using artificial stressors\textsuperscript{14}.

In contrast to the largely circumstantial evidence linking globus to psychiatric conditions, there is a more substantive link between globus and gastroesophageal reflux disease (GERD) / extra-esophageal reflux (EER), although definitive causation has not been demonstrated. In a prospective study of over 2000 patients, Hori et al. found the odds ratio for experiencing reflux symptoms in patients with globus is 11.6 (95% CI 7.1-19.1)\textsuperscript{20}. Globus patients have been shown to have increased esophageal acid exposure compared to controls\textsuperscript{21}, although another group found no such correlation\textsuperscript{22}. The relationship between reflux and globus is complex, and illustrates the difficulty in separating correlation from causation. Both globus and reflux are very common in the general population, affecting up to 46% and 39% of the population respectively\textsuperscript{6, 9, 23}.

Because of this, retrospective cohort studies are very likely to show a statistically significant correlation between the two symptoms, but this association merely proves that the two commonly occur together. In fact, there may be a third factor, which is the true linkage between the two. For example, one could imagine a hypothetical scenario where obesity (which is a known risk factor for reflux) could somehow also, and separately from the reflux, predispose a patient to globus sensation. Nevertheless, there is decent evidence that some – but not all - globus may indeed be causally related to reflux\textsuperscript{21,22,24-27}.

Other conditions that are commonly identified in globus patients on radiographic studies have been incorrectly attributed a causal role in globus pharyngus. The presence of a prominent cricopharyngeal bar in globus patients is similar to that seen overall in patients undergoing barium swallow for various reasons (up to 17%)\textsuperscript{11,28}. While some early studies showed higher upper esophageal sphincter (UES) pressures in globus patients compared to controls\textsuperscript{29}, subsequent studies using improved techniques have failed to confirm this\textsuperscript{14,30}. Similarly, presence of a hiatal hernia has been demonstrated in between 30-50% of globus patients\textsuperscript{31, 32}, but hiatal hernia is quite common in western populations, present in up to 50% of asymptomatic patients\textsuperscript{33-35}.

One interesting association that may account for a small percentage of patients with globus is the finding of a heterotopic gastric mucosa (“inlet patch”) in several case reports\textsuperscript{36-38}. Ablation of inlet patch has been shown to improve globus symptoms\textsuperscript{39}, and indeed a large prospective study of over 2000 endoscopies found that presence of inlet patch was an independent risk factor for globus\textsuperscript{20}. These data notwithstanding, the incidence of inlet patch, even in globus patients, ranges from 5-13% so certainly the majority of globus is not caused by an inlet patch\textsuperscript{20,40,41}.

As mentioned above, there may be a third factor which relates to both reflux and globus. One plausible explanation involves the role of altered visceral sensation. While space constraints preclude an exhaustive discussion of this important topic, we will summarize current knowledge. The prospective endoscopy study mentioned above had an interesting, and unexpected additional finding: absence of symptoms from reflux, more so than presence of reflux or inlet patch, were the most strongly associated with globus pharyngeus\textsuperscript{20}. Thus, altered visceral afferent sensation may be important in globus. Supporting this idea, Kwiatek et al. has previously shown that globus patients have an exaggerated respiratory UES response tracing on manometry\textsuperscript{42}. Additionally, Chen et al. demonstrated that globus patients have heightened perception of esophageal stimuli (balloon distension and electrical stimulation) compared to normal controls\textsuperscript{43}. These patients also localized symptoms at or above the sternal notch, even when stimulation occurred in the distal esophagus. Further studies of the role of visceral hypersensitivity in globus are ongoing and hold significant promise for potential future therapies.

**Diagnosis and Evaluation**

When considering the evaluation of a patient with globus, it is prudent to remember that the differential diagnosis can range from benign (conversion disorder, reflux, and others) to serious (esophageal malignancy) conditions, although the vast majority of patients with globus fall into the former category. There is no universal consensus or evidence-based medicine recommendation for the workup of a patient with globus. Indeed, expert recommendations have ranged from a minimalist approach involving only fiberoptic laryngoscopy to a comprehensive workup including esophago-gastroduodenoscopy and barium esophagogram on every patient. Our current recommendations and clinical practice lie somewhat in the middle.
Belafsky recently published an excellent editorial summarizing the wide range of pathologies that can be associated with globus pharyngeus. A summary of the differential diagnosis for patients with globus sensation includes: gastroesophageal reflux, extra-esophageal reflux, conversion disorder, heterotopic gastric mucosa, esophageal dysmotility, cervical osteophytes, aerodigestive tract malignancy, cricopharyngeal muscle spasm or hypertrophy, esophageal candidiasis, Zenker’s diverticulum, thyroid nodule or thyromegaly, lingual tonsillar hypertrophy, Eagle’s syndrome, and vallecular cyst.

It is quite important to differentiate globus from dysphagia or odynophagia; in fact, to arrive at a diagnosis of globus, these latter symptoms should not be present. Several independent studies have shown that globus patients can be reliably distinguished from patients with dysphagia and/or odynophagia. The diagnostic workup for globus patients will differ significantly from patients with the more sinister symptoms of true dysphagia / odynophagia. Several authors have demonstrated that the presence of these symptoms is much more commonly associated with upper aerodigestive tract malignancy.

Diagnosis of globus is made primarily on the basis of clinical symptoms. The most recent consensus guidelines (Rome III criteria) are presence of all of the following: 1. Nonpainful sensation of a lump or foreign body in the throat (persistent or intermittent). 2. Occurrence of the sensation between meals. 3. Absence of odynophagia and dysphagia. 4. Absence of evidence that GERD is the cause of the symptom. 5. Absence of esophageal motility disorders. These symptoms must be present for at least 12 (consecutive or non-consecutive) weeks out of the last six months.

A complete head and neck physical examination is performed, including laryngoscopy (either transnasal flexible, or trans-oral rigid). Following this, most patients then are scheduled for TNE. This procedure is performed without sedation and is well tolerated by the vast majority of patients. While several well respected authors have recommended against routine esophagoscopy in the workup of globus patients, these are primarily based on either flexible esophagoscopy in a sedated patient, or even rigid esophagoscopy under general anesthesia. These both carry a much higher degree of risk, and cost compared to unsedated TNE (reviewed in ). Therefore, we (and others) consider the risk/benefit ratio to now strongly favor routine TNE for patients with globus sensation. This should be tempered by the understanding that while TNE is rapidly advancing as a standard endoscopy modality, it may not be available at all centers. While it is true that the chance of finding an esophageal malignancy in a patient with isolated globus (no dysphagia or odynophagia) is quite low, other more common esophageal conditions such as Barrett’s metaplasia are routinely diagnosed to the patient’s benefit. Some of these findings are presented in Table 1.

### Table 1. Common findings on TNE in globus patients (not in order)

| Normal exam (most common finding) |
| Heterotopic gastric mucosa (“Inlet patch”) |
| Pill esophagitis |
| Cervical osteophytes |
| Esophageal candidiasis |
| Esophageal malignancy (rare) |
| Eosinophilic esophagitis findings (including trachealization of the esophagus) |
| Erosive reflux esophagitis, including pseudodiverticuli |
| Non-esophageal pathologies (seen during approach to the esophagus), including lingual tonsil hypertrophy, vallecular cyst, laryngeal malignancy, laryngopharyngeal-reflux |

In contrast to the role for TNE in globus patients, it is widely accepted that routine Barium Esophagography (“barium swallow study”) is of little value in the workup of globus patients.

### Management and Prognosis

If treatable abnormalities are identified, such as candidiasis, these should certainly be addressed. One area of controversy is what to do with the globus patient who does have an inlet patch which does not respond readily to proton inhibitor therapy. There is a single randomized controlled trial by Bajbouji et al. which demonstrated improvement in globus symptoms after Argon Plasma Coagulation (APC) ablation, compared to sham surgery. A definitive etiology for this response has not been identified, however, and APC ablation is not without risks. At present this therapy is not considered part of the standard of care and should be considered only for select patients and with considerable pre-operative discussion.

Assuming that no abnormalities are identified on laryngoscopy or TNE, the initial management of globus patients should center on reassurance. In our experience, the majority of patients require only an explanation that this symptom is common, and that no concerning findings were seen on in-office endoscopy. It is important for patients to know that their symptoms are likely to persist for several years, so that they may form reasonable expectations. Studies have demonstrated that globus...
symptoms are likely to persist in some patients for 3-8 years, although most patients experience at least some degree of improvement during this time. For patients whose symptoms are more bothersome or poorly tolerated, given the plausible role of reflux in globus etiology, a trial of oral proton pump inhibitor (PPI) therapy is reasonable. This should be tempered by the fact that the single randomized controlled trial of PPI therapy for the treatment of globus patients failed to demonstrate benefit compared to placebo. To date there have not been any controlled trials of twice-daily PPI therapy for globus, which some experts believe is essential for adequate treatment of EER, and may similarly be of benefit in globus. Patients should be cautioned about the potential risks of PPI therapy, including osteoporosis and medication interactions. To this end, our current practice is to attempt PPI weaning as soon as response is achieved (usually 3-6 months). Patients are instructed to taper their PPI dosing to once daily, then once every other day and then discontinue use. If symptoms return they are escalated back up on their PPI dosing.

Manometry is only offered to those who symptoms trouble them to the point that they would consider cricopharyngeal botox or endoscopic myotomy in the event that a significant problem was found with the cricopharyngeus upon manometry. Future treatment directions may lie in attempts to modulate the visceral afferent hypersensitivity that may underlie globus. To date, there has been a single small open label trial using paroxetine (a selective serotonin reuptake inhibitor) for globus treatment. They found paroxetine superior to esomeprazole, but the study had such a short follow-up period (3 weeks) as to make it useless for clinical decision making. Certainly it is hoped that in the near future, well designed larger trials will be performed to investigate neuromodulators in globus treatment.

In summary, globus pharyngeus is common, and usually of benign etiology. Some globe may be due to reflux, and a minority may be linked in some way to inlet patch. Altered visceral afferent sensation likely plays a significant role in globus, but is still poorly understood. Treatment is aimed primarily at reassurance, although a trial of oral PPI therapy is reasonable.

Reference:
2. J. P. A Treatise of Vapours or Hysterick Fits. 2nd ed. London: Edward Place; 1707.
Gaviscon Advance Aniseed Suspension Prescribing Information

**Active Ingredients:** Sodium alginate 1000mg and Potassium bicarbonate 200mg per 10ml dose. Also contains methyl and propyl hydroxybenzoates.

**Indications:** Treatment of symptoms resulting from the reflux of acid, bile and pepsin into the oesophagus such as acid regurgitation, heartburn, indigestion (occurring due to the reflux of stomach contents), for instance, after gastric surgery, as a result of hiatus hernia, during pregnancy, accompanying reflux esophagitis, including symptoms of laryngopharyngeal reflux such as hoarseness and other voice disorders, sore throats and cough. Can also be used to treat the symptoms of gastro-oesophageal reflux during concomitant treatment with or following withdrawal of acid suppressing therapy.

**Dosage Instructions:**
- **Adults and children 12 years and over:** 5-10ml after meals and at bedtime.
- **Children under 12 years:** Should be given only on medical advice.

**Contraindications:**
- Hypersensitivity to the active substances or to any of the excipients, including the esters of hydroxybenzoates (parabens).

**Precautions & Warnings:**
- Each 10 ml dose has a sodium content of 106 mg (4.6 mmol) and a potassium content of 78 mg (2.0 mmol). This should be taken into account when a highly restricted salt diet is recommended, e.g. in some cases of congestive cardiac failure and renal impairment or when taking drugs which can increase plasma potassium levels. Each 10 ml contains 200 mg (2.0 mmol) of calcium carbonate. Care needs to be taken in treating patients with hypercalcaemia, nephrocalcinosis and recurrent calcium containing renal calculi. These medicinal products contain Methyl hydroxybenzoate and Propyl hydroxybenzoate, which may cause allergic reactions (possibly delayed). There is a possibility of reduced efficacy in patients with very low levels of gastric acid. If symptoms do not improve after seven days, the clinical situation should be reviewed. Treatment of children younger than 12 years of age is not generally recommended, except on medical advice.

**Side-Effects:**
Very rarely (<1/10,000) patients sensitive to the ingredients may develop allergic manifestations such as urticaria or bronchospasm, anaphylactic or anaphylactoid reactions. There is a possibility of reduced efficacy in patients with very low levels of gastric acid.

**Basic NHS Price:**
- **(excl VAT):**
  - 250ml - £2.27
  - 500ml - £4.54

**Marketing Authorisation:**
- **Gaviscon Advance Aniseed Suspension** - PL 00063/0108

**Supply Classification:**
Through registered pharmacies only.

**Holder of Marketing Authorisation:**
- Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull, HU8 7DS.

**Date of Preparation:**
- September 2011

**Gaviscon, Gaviscon Advance and the sword and circle symbol are trademarks.**
Exercise induced laryngeal obstruction (EILO): Diagnosis and Management

John-Helge Heimdal MD. PhD.; Thomas Halvorsen MD. PhD.; Robert Christiaan Maat MD.;
Ola D. Reksund MSci. and Jan Olofsson MD. PhD.

J-H. Heimdal (✉) J. Olofsson
Department of Otolaryngology-Head and Neck Surgery, Haukeland University Hospital, 5021 Bergen, Norway
e-mail: john.heimdal@helse-bergen.no Tel: +47 55972670, Fax: +47 55974956

O.D. Reksund and T. Halvorsen
Department of Pediatrics, Haukeland University Hospital, Bergen, Norway

R.C. Maat
Department of Otolaryngology, Röpcke-Zweers Hospital, Hardenberg, the Netherlands

Abstract
In the majority of patients complaining of exercise induced inspiratory stridor (EIIS), laryngeal obstruction can be observed if continuous laryngoscopy throughout a maximal exercise session is performed. Although obstruction may be limited to the vocal cords, it usually begins and involves supraglottic structures. Glottic and supraglottic exercise induced laryngeal obstruction (EILO) may be interrelated or separate disease entities. In previous literature, a number of terms have been applied and focus has been on the vocal cords and a psychological etiology. Proper diagnostic evaluation requires exercise laryngoscopy. Presence of EIIS without EILO requires search for alternative central airway obstruction. The evidence base for treatment of EILO is weak and randomised controlled trials required. Information and advice seems to help, and various forms of speech therapy, psychotherapy, and inspiratory muscle training have been suggested. Severe supraglottic EILO have been surgically treated with positive effects. Treatment should be individualized and based on laryngoscopic findings.

Key words:
Exercise induced laryngeal obstruction; Stridor; Vocal cord dysfunction

Introduction
The term exercise induced laryngeal obstruction (EILO) is used in this paper to describe airflow obstruction at the laryngeal level during exercise in patients with no obvious laryngeal pathology at rest. Obstruction may occur by anteromedial collapse of supraglottic structures (supraglottic EILO) or by inappropriate adduction of the vocal cords (glottic EILO) or by a combination of the two1-4. A number of terms have been applied on this condition in previous literature, often without objective documentation5. Patients generally present with symptoms of exercise induced inspiratory stridor (EIIS). The prevalence of EILO is basically unknown as only a few population based studies have been performed. However, a Danish community study suggests prevalence figures as high as 7.5%6. The pathophysiology of EILO has not been determined since research so far has been hampered by lack of diagnostic tools7-9. Supraglottic EILO has some morphologic characteristics resembling congenital laryngomalacia. However, the two conditions are probably separate entities since EILO most often presents in adolescents with no history of childhood laryngomalacia. Regarding pathophysiology, one may speculate that heavy breathing during exercise generates suction forces at the laryngeal inlet, inducing an inward rotation of the supraglottic part of a larynx that somehow lacks proper
support. Alternatively, stimulation of afferent fibres of the superior laryngeal nerve could potentially activate the laryngeal adductor reflex or lower the laryngeal threshold for protective responses\textsuperscript{10-12}. Psychological mechanisms also seem to play a role, e.g. when athletes subconsciously convert performance anxiety into laryngeal closure and experience choking during sport\textsuperscript{13,14}. If supraglottic and glottic EIO share a common pathophysiology is not known.

**Diagnosis of EIO**

**Symptoms:**
EIO typically presents with prolonged inspiration, inspiratory dyspnoea, shortness of breath, and “noisy breathing” during ongoing exercise. The sound produced may have the character of high-pitched inspiratory noise and symptoms are therefore sometimes labeled exercise induced inspiratory stridor (EIIS). However, the sound picture is sometimes confusing and one should not only expect to hear stridor in the strict sense of the word. In most patients, the onset of stridor is an endpoint of symptom development, increasing from prolonged inspiration via noisy breathing to obvious stridor. EIIS typically worsens with increasing intensity exercise and usually peaks towards the end of an exercise session and during the first 2-3 minutes of recovery. In each patient, symptoms tend to begin at approximately the same level of exercise intensity. However, symptoms may start at an earlier stage and severity may be increased if airborne irritants, low temperatures or psychological stressors are present. Respiratory symptoms are not infrequently accompanied by chest pain, anxiety, hyperventilation attacks and even panic reactions. Unless panic reactions have developed, symptoms usually resolve spontaneously within a few minutes after exercise has stopped. EIO most frequently occurs in physically active and otherwise healthy young subjects, and more often in females than males\textsuperscript{15}. The pattern of symptoms contrasts exercise induced asthma (EIA), where symptoms are mainly expiratory and typically peak 3 -15 minutes after exercise has stopped and may last for hours unless properly treated. Although symptoms related to EIO and EIA are distinctly different, these conditions are still often confused\textsuperscript{16-18}. However, one should be aware that EIO and EIA may co-exist in the same patient\textsuperscript{15,19}.

**Patient history:**
The history of a patient with EIO may at first sight be remarkably similar to that of EIA, explaining some of the confusion between the two conditions. Also, co-existence of both in some patients contributes to the diagnostic difficulties. The typical patient with EIO reports shortness of breath, wheezing and cough when performing exercise or when exposed to irritants or cold air. Often, awareness of inspiratory versus expiratory symptoms as well as the timing of onset in relation to the exercise session may be quite unclear to the patient at first interview, even if specifically asked. One way of solving these uncertainties is to inform of the two patterns of symptoms and their associated diagnostic possibilities and to reschedule the patient after a period of self assessment.

**Lung function tests**
EIO generally does not produce a typical spirometric pattern. Flattened inspiratory and/or expiratory limbs of flow volume loops have sometimes been reported in relation to EIIS, but in our opinion this is more likely to be related to structural pathology than to EIO. Exercise tidal flow volume loops may reveal flattened or notched inspiratory limbs during heavy breathing. At this stage, spirometry cannot be used to diagnose EIO with certainty.

**ENT examination**
Physical examination or laryngoscopy at rest does normally not reveal pathology in the upper airways. However, one should look carefully for aberrant anatomy at the laryngeal inlet, i.e. the cuneiform tubercles, the ary-epiglottic cords and the epiglottic area. In some patients, findings of redundant mucosa, enlarged cuneiform tubercles or retroflection of the epiglottis may point to a possibly closure of the supraglottic part of the larynx during exercise.

Treole and co-workers reported subtle laryngeal abnormality by endoscopy and stroboscopy in subjects with symptoms that the authors related to paradoxical vocal cord dysfunction\textsuperscript{20}. Nevertheless, laryngoscopy during ongoing symptoms is by most authors considered the gold standard for the examination and diagnosing of EIO\textsuperscript{21}.

**Continuous Laryngoscopy Exercise test (CLE-test)**
A set-up combining continuous flexible laryngoscopy with a cardiopulmonary exercise unit has been proposed (Fig.1). Treadmill exercise was preferred since children often do not exercise beyond their anaerobic threshold when using other exercise modalities such as bicycle. The laryngoscope is secured by a specially devised head set and a modified facemask. The cardiopulmonary exercise unit is connected to the patient through the flow-sensor and the facemask. A camera at the tip of the laryngoscope ensures high quality video recordings throughout the exercise session. Respiratory sounds are recorded via a microphone. A film of the external upper part of the body is recorded by an external video camera for documentation.
of associated respiratory distress. All inputs are finally fused into one image and stored as one file for later assessment and documentation.

**CLE-test evaluation**
Continuous video recordings from the CLE test allows for precise evaluation of laryngeal motion at supraglottic and glottic levels throughout a full exercise session. Movements of supraglottic structures and of the vocal cords should be evaluated in all phases of each respiratory cycle at preset stages of the exercise session. A system for grading and classification of observations has been established and assessed in relation to symptoms of EIIS and found to be valid and reliable\(^2^2\). The use of this system improves the objectivity of observations from the CLE-test. Clinical symptoms and breath sounds may be reviewed and scored separately by assessment of the sound and the external film recordings.

**Management of EILO**
Treatment of EILO has so far been based on relatively weak evidence. To our knowledge, no randomized controlled trials utilizing objective outcome measures have been performed. Thus, Level I evidence does not exist for any of the suggested treatment options. Awaiting future prospective randomized studies, we have based our strategy on available literature and our own clinical experience and followed the algorithm presented in Figure 2 (Flow chart). Triggers and contributing factors should be identified, removed or treated, if possible.

Management of EILO must include the exclusion of extralaryngeal pathology causing respiratory distress during exercise. In a study assessing a large group of patients presenting to our clinic with symptoms of EIIS, approximately 10% had structural pathology in the proximal airways, e.g. laryngeal abnormalities evident at rest, subglottic stenosis, tracheobronchomalacia, aberrant vascular structures in the mediastinum or paralysis of the left recurrent laryngeal nerve\(^4,2^3\). While EILO seems to be a functional disorder characterized by an apparently normal larynx at rest and therefore most often also by a normal spirometry, most of the structural abnormalities seen in patients with EIIS had abnormal spirometry at rest.

---

**Figure 1:** (A) illustrates the continuous laryngoscopy exercise (CLE) test performance. While the test subjects run to exhaustion on a treadmill, metabolic ergo-spirometry is performed with continuous recording of parameters of gas exchange, exercise flow volume loops and breath sounds. The flexible laryngoscope is fixed in correct position via a special constructed head band (B) and the connection to a video camera allows continuous recording of laryngeal movements during the test.

(From: Heimdal et al., The Laryngoscope, 2006, publication has been granted by the publisher)
Patients with EIIS with no findings in the larynx while reproducing symptoms should therefore be carefully assessed for other diseases and abnormalities, in particular if resting spirometry is abnormal. Asthma had been excluded or properly treated before inclusion to this study, but the majority of patients had been treated with asthma medication with little effect.

One must also be aware that post-traumatic stress disorders or other types of psychological or psychiatric disorders may induce the glottic type of EILO. Also, overly focus on high performance in athletes may trigger or aggravate symptoms of EILO. Therefore supportive counselling is important, and referral to a psychiatrist or psychologist should be considered if conversion or panic disorders are suspected. In such cases, psychotherapy, speech therapy and relaxation therapy are the recommended treatment options.

**Patient information:**

The laryngeal video recordings should be presented and explained to the patients and their parents (if relevant). Information on normal laryngeal function and possible causes for laryngeal obstruction should be highlighted. We usually stress that the condition is not dangerous as most patients are afraid it might be. We also emphasize that we believe that their condition are caused by an organic abnormality and that psychological factors are usually secondary, but nevertheless may trigger or aggravate attacks. Finally, we instruct patients to learn their own “thresholds” if present, and to focus on a rapid expiration and not on the inspiration. If symptoms appear, patients should reduce the intensity slightly, inhale through the nose (sniff) or through a mouth with closed teeth and try to avoid panicking. This information alone seems to reduce anxiety and ease the problems for many patients, and further treatment is therefore often not necessary. Biofeedback techniques based on real time video recording of the larynx have been suggested by some to be beneficial.

**Speech therapy:**

Highly motivated patients may benefit from guidance by speech therapists, but unfortunately most studies do not reveal the treatment protocols in detail, nor the criteria for patient inclusion. There are however some protocols describing pitch change, diaphragmatic breathing and reduction of extrinsic muscle tension. Patients are instructed to focus their attention away from the larynx and inspiration and instead to concentrate on active expiration using the anterior abdominal muscles, and to relax the oropharyngeal, intercostal, neck, and shoulder girdle muscles. This technique appears to have its strengths in the glottic type of EILO and requires high

---

*Figure 2: Proposed flow chart for treatment of EILO, based on the clinical experience until now. Prospective studies are required to establish evidence-based treatment algorithms for patients with EILO (From: Maat et al., Eur Arch ORL, 2011, publication has been granted by the publisher)*
motivation. Having said this, speech therapy does not represent a fully developed concept and much research is required in relation to its content and position in the treatment algorithms.

**Pharmacotherapy**

Weinberger reported that an anticholinergic aerosol (ipratropium bromide) applied before exercise could prevent what he called exercise induced paradoxical vocal cord adduction. Pharmacological agents have otherwise been used to decrease the impact from triggers of paradoxical vocal cord motion.

**Inspiratory muscle training (IMST)**

This treatment option has been reported effective in case reports. The theory is that the diaphragm and the posterior cricoarytenoid muscle (the only abductor of the larynx) are closely related, and that inspiratory muscle training activates both, opening for a more effective laryngeal abduction.

**Surgery**

For supraglottic EILO, a surgical procedure similar to the technique used for congenital laryngomalacia has been proposed by some authors, i.e. laser supraglottoplasty. Smith demonstrated that removal of the corniculate cartilages by laser epiglottoplasty in patients with a supraglottic collapse of tissue during exercise was associated with improvement in endurance and physical fitness. Positive effects from supraglottoplasty or epiglottopexy have been demonstrated in selected cases with the supraglottic EILO.

We have used similar techniques as described by Smith and co-workers in patients with severe and disabling supraglottic EILO. Pre- and postoperative CLE-tests have demonstrated significantly less supraglottic adduction after surgery. In a later study we found that this effect lasted for several years, and that operated patients reported less symptoms than comparable patient who had not been operated.

**CONCLUSION**

In the majority of patients presenting with EIIS, exercise laryngoscopy will relieve laryngeal obstruction. Although the obstruction may be limited to the vocal cords, it usually begins and involves supraglottic structures. Glottic and supraglottic exercise induced laryngeal obstruction (EILO) may be interrelated or separate disease entities. Proper diagnostic evaluation requires exercise laryngoscopy. The presence of EIIS without EILO requires further examination, searching for alternative central airway obstruction. The evidence base for treatment of EILO is weak and randomised controlled trials required. Information and advice seems to help, and various forms of speech therapy, psychotherapy and inspiratory muscle training have been suggested. Severe disabling supraglottic EILO have been surgically treated with positive effects. Surgical treatment has to be further evaluated and especially the selection of whom that should be treated. Treatment should be individualised and based on laryngoscopic findings.

**Reference List**

5. Morris MJ. Diagnostic criteria for the classification of vocal cord dysfunction. 2010 Nov.


ENT Manifestations of HIV in Clinical Practice

Oskar Edkins MBChB, FCORL (SA), MMed (ORL), Tashneem Harris MBChB, FCORL (SA), Johannes J. Fagan MBChB, FCS (SA), MMed (Otol)
Division of Otorhinolaryngology, University of Cape Town

Abstract
Almost every patient infected with the Human immunodeficiency virus (HIV) will at some point present with an otolaryngological or head and neck manifestation of their disease. Awareness of these manifestations will lead to accurate diagnosis, management and on occasion making the initial diagnosis of HIV infection. This article serves to outline the ENT manifestations of HIV and their management.

Introduction
Up to 100% of patients infected with the Human Immunodeficiency Virus (HIV) will develop a head and neck manifestation of their disease. In 2002 5.3 million South Africans were living with HIV; in 2009, 33.4 million [31.1 million–35.8 million] had HIV globally. One can therefore appreciate the frequency with which these patients will present to general practitioners and ENT services with oral, nasal, otological and head and neck manifestations of HIV. Recognition of these clinical presentations may facilitate diagnosis of HIV in patients who may otherwise have been unaware of their status. Table 1 outlines the more common ENT manifestations of HIV infection. A brief description and management of the commoner and more challenging conditions follows.

<table>
<thead>
<tr>
<th>Oral</th>
<th>Sinonasal</th>
<th>Otological &amp; Neurotological</th>
<th>Head &amp; Neck</th>
</tr>
</thead>
<tbody>
<tr>
<td>− Recurrent aphthous ulcers</td>
<td>− Adenoidal hypertrophy</td>
<td>− Otitis media &amp; externa</td>
<td>− Generalized lymphadenopathy</td>
</tr>
<tr>
<td>− Candidiasis</td>
<td>− Sinusitis: acute &amp; chronic</td>
<td>− Malignant Otitis Externa</td>
<td>− Lymphoepithelial cysts of the parotid gland</td>
</tr>
<tr>
<td>− Herpes simplex</td>
<td>− Herpes simplex</td>
<td>− Otitis media with effusion (OME)</td>
<td>− Neck mass</td>
</tr>
<tr>
<td>− Gingivitis</td>
<td>− Herpes zoster</td>
<td>− Eustachian tube dysfunction</td>
<td>− Neoplasia</td>
</tr>
<tr>
<td>− Stomatitis</td>
<td>− Seborrheic dermatitis</td>
<td>− Sensorineural hearing loss (SNHL)</td>
<td></td>
</tr>
<tr>
<td>− Periodontitis</td>
<td>− Neoplasia:</td>
<td>− Bell’s palsy</td>
<td></td>
</tr>
<tr>
<td>− Xerostomia</td>
<td>Kaposi’s sarcoma</td>
<td>− Ramsay Hunt syndrome</td>
<td></td>
</tr>
<tr>
<td>− Condylomata</td>
<td>NHL</td>
<td>− Neoplasia:</td>
<td></td>
</tr>
<tr>
<td>− Hairy leukoplakia</td>
<td></td>
<td>Kaposi’s sarcoma</td>
<td></td>
</tr>
<tr>
<td>− Neoplasia:</td>
<td>NHL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma (NHL)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Oral Manifestations
Oral candidiasis is the commonest, and often the earliest oral manifestation. The classic form of this is pseudomembranous candidiasis but other types include hyperplastic or atrophic forms. Treatment is with topical antifungal agents. Systemic treatment may be indicated in severe or resistant cases or with worsening immune status.

Recurrent aphthous ulcers are common and may cause significant discomfort. They may be single or multiple and vary in size. Treatment is symptomatic with topical anaesthetics, steroids, antibacterials or combination thereof. If lesions fail to respond to treatment biopsy is indicated.

Oral Hairy Leukoplakia, often asymptomatic, is a white, raised, corrugated or filiform lesion on the lateral border of the tongue, and is almost pathognomonic for HIV. It may also arise from other sites in the oral cavity. It is thought to be related to Epstein-Barr virus (EBV). Biopsy is diagnostic if the clinical diagnosis is in doubt. It responds to antiretroviral (ARV) therapy or topical retinoic acid.

Xerostomia occurs as a result of chronic inflammation of major and minor salivary glands. This may lead to dental caries and periodontal disease. Treatment is symptomatic.

Sinonasal Manifestations
Adenoidal hypertrophy may result in upper airway obstruction and otitis media with effusion (OME). Adults with adenoidal hypertrophy should be investigated for HIV. Treatment includes topical steroid sprays and antibiotics, adenoidectomy being reserved for severe or refractory cases. Biopsy may be warranted to rule out malignancy such as NHL.

Sinusitis, acute and chronic, in HIV infected individuals presents with similar symptoms and bacteriological aetiology to non-HIV infected patients. Atypical organisms such as Pseudomonas aeruginosa, should be suspected in patients with low CD4 counts who present with sinusitis. Invasive fungal sinusitis may present in these patients and most commonly is as a result of infection with inter alia, Aspergillus. Mucomycosis is uncommon with HIV unless patients become severely immunocompromised and neutropaenic. Management of sinusitis remains the same with clinical, endoscopic and radiological evaluation; treatment with antibiotic, or antifungal therapy; and surgical intervention in selected cases.

Otological and Neurotological Manifestations
Lower motor neuron (LMN) facial palsy may appear as the first manifestation of HIV in early asymptomatic stages or as part of the seroconversion illness, usually with a good prognosis. The facial nerve palsy may actually precede seroconversion by 4 to 6 weeks. Therefore HIV testing should be repeated after several weeks if clinically indicated and prior testing is negative.

The prevalence of Bell’s palsy in a HIV infected population appears to be higher than in the general population and bilateral palsies in association with various stages of HIV, have also been described (thus far 20 cases in the literature). Bilateral LMN facial palsies generally result from systemic disease. Rigorous assessment and workup is warranted and should consist of a detailed neurological examination, blood count, CMV, HSV, herpes zoster, EBV, Borrelia burgdorferi, HIV serology, a VDRL test, and testing of the angiotensin-converting enzyme level. To rule out central nervous system lesions, a CSF examination as well as brain magnetic resonance imaging (MRI) with gadolinium enhancement is useful.

The management of LMN facial palsy in HIV is similar to that of Bell’s palsy, consisting of antiviral therapy, famciclovir or acyclovir. However the use of steroids is controversial, especially in the setting of an immunocompromised host. The role of antiretroviral drugs in the management of LMN facial palsy is still unknown.

Table 2: Causes of facial nerve paralysis in HIV positive patients

<table>
<thead>
<tr>
<th>Cause</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>Bells’s palsy</td>
</tr>
<tr>
<td>Infectious</td>
<td>Human Immunodeficiency Virus (HIV)</td>
</tr>
<tr>
<td></td>
<td>Herpes zoster (HZV)</td>
</tr>
<tr>
<td></td>
<td>Herpes simplex (HSV)</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus (CMV)</td>
</tr>
<tr>
<td></td>
<td>Epstein Barr Virus (EBV)</td>
</tr>
<tr>
<td></td>
<td>Syphilis (treponema pallidum)</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td></td>
<td>NHL</td>
</tr>
</tbody>
</table>

Malignant otitis externa (MOE) in HIV differs slightly in that fungal infection, commonly Aspergillus, makes up a significantly higher proportion of infections. This tends to occur in advanced HIV disease, when CD4 counts reach 50/mm³, and is invasive in nature. Management of the affected areas, middle ear and mastoid, involve surgical debridement and antifungal therapy like amphotericin B.
compromised patients, as it combats resistance and a combination of ciprofloxacin and either an aminoglycoside or third generation cephalosporin is suggested. Comparable cure rates have also been achieved with addition of rifampicin. At least 4-8 weeks of antibiotic treatment is recommended; this may be changed to oral therapy after a 2 week course of combined intravenous therapy if good clinical response is achieved.

**Pneumocystis Carinii** infection may present as otitis externa, otitis media or mastoiditis and may extend to the middle cranial fossa. Bilateral ear involvement has also been reported. The diagnosis is made histologically using a Gomori methenamine silver stain and immunohistochemistry with monoclonal antibody to P. Carinii may be helpful. Management includes a combination of intravenous and oral antiprotozoal agents such as trimethoprim, sulfamethoxazole and dapsone and mastoid exploration may be avoided.

Tuberculosis goes hand in hand with HIV. Tuberculous otitis has been classically described as painless otorrhoea with multiple tympanic membrane perforations, exuberant granulations, severe hearing loss and bone necrosis. However, clinical manifestations of tuberculous otitis media do not always comply with this classical description. Patients who present with otorrhoea refractory to standard antibiotic treatment or chronic middle ear infection associated with facial nerve palsy should raise suspicion of tuberculous otitis media. Thirty per cent of tuberculous otitis media patients present with acute infection or superinfection and mastoid involvement and concomitant pulmonary tuberculosis may or may not be present.

Otoscopy examination in tuberculosis otitis media may reveal necrotic components with abundant pale granulation tissue and diagnosis is by culture of tissue specimens or ear discharge as Ziehl-Nielsen staining is often unreliable. Polymerase chain reaction is an unreliable diagnostic method to enable the definite diagnosis of extrapulmonary tuberculosis infection. Antituberculous medication is required for at least six months, except in cases of disseminated tuberculosis and tuberculous meningitis which require 9-12 months of treatment. The role of surgery in tuberculous otitis media remains controversial. Singh reported healing time to be equivalent for surgery or medical therapy with questionable results for facial nerve palsy. Surgery may be indicated for removal of sequestrum. However the presence of sequestrum may prove difficult to establish preoperatively. More recently, Cho et al reported in a series of 52 patients with tuberculous otitis media, that those who underwent chemotherapy after surgery appeared to achieve a dry ear earlier than those without surgery.

Sensorineural hearing loss (SNHL) ranges between 21% to 49% of HIV-positive patients. The hearing loss is typically a high-frequency SNHL with a pattern similar to that seen with presbyacusis. Aetiology includes opportunistic infections of the central nervous system, malignancy, and ototoxic medication. While highly active antiretroviral therapy (HAART) has significantly improved the lifespan of patients with HIV, multiple toxic effects including SNHL, have been associated with its use. Due to its neurotropic nature the HIV virus itself can cause SNHL from viral spread to the cochlear nerve and semicircular canals. Roland et al in a retrospective case series and temporal bone analysis of deceased HIV-positive patients demonstrated the presence of HIV-like virus particles in the cochlea suggesting that the HIV virus may be directly cochleotoxic. There are only two articles available in the literature addressing the issue of cochlear implantation in HIV infected patients. In both these articles the authors maintain that HIV infected patients with profound hearing loss benefit from cochlear implantation without increased surgical risk provided that the general health of the patient is taken into consideration.

**Head and Neck Manifestations**

Neck masses are common presentations of HIV and may be due to lymphadenopathy, parotid disease, neoplasia and infections (Table 3). Investigation starts with a thorough history and ENT and systemic examination, followed by FNAC and imaging when indicated.

**Table 3: Differential diagnosis of a neck mass particular to HIV infection**

<table>
<thead>
<tr>
<th>HIV lymphadenopathy</th>
<th>Parotid</th>
<th>Lymphoepithelial cyst</th>
<th>Lymphoepithelial lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasia</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Hodgkin’s disease</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Infectious</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td><em>Mycobacterium avium</em></td>
<td><em>Pneumocystis carinii</em></td>
</tr>
<tr>
<td></td>
<td><em>Toxoplasma gondii</em></td>
<td><em>Cryptococcus neoformans</em></td>
<td></td>
</tr>
</tbody>
</table>

**Generalised lymphadenopathy** is common in HIV and can present early in the disease after seroconversion. It is defined as lymphadenopathy > 1cm, of unexplained aetiology, involving >2 extra-inguinal sites, and lasting >3 months. FNA cytology or biopsy may be indicated for a single lymph node > 3cm, constitutional symptoms, elevated erythrocyte sedimentation rate (ESR), cytopenia...
or lymphadenopathy that is rapidly enlarging, unilateral or localized\(^1,2,32\).

**Lymphoepithelial parotid cysts** are almost diagnostic of HIV1. They are usually asymptomatic, multiple (90%) and bilateral (80%), and occur during the chronic or latent phase of HIV infection\(^33,34\). FNAC yields clear proteinaceous fluid with epithelial and lymphoid cells. Ultrasound confirms multiloculated, thin walled parotid or periparotid cysts\(^34\). Management is directed at the cosmetic deformity. Cysts generally resolve with ARVs\(^34\). For patients who do not meet the criteria for ARV therapy, sclerotherapy with 95% alcohol, sodium morrhuate, doxycycline or tetracycline has been described with variable success rates\(^34-38\).

### Malignancies in HIV

HIV-infected individuals have a higher incidence of certain malignancies such as Kaposi’s sarcoma (KS), Non-Hodgkin’s lymphoma (NHL), Hodgkin’s Disease (HD), squamous cell carcinoma (SCC), plasmacytoma and leiomyosarcoma in children\(^19\) and conjunctival SCC. Tumours arise due to lack of immune response or reactivation of causative agents such as viruses that are associated with malignancy (Table 4)\(^39\). Although ARV medication has led to a reduction of these malignancies, HIV related malignancy remains a significant problem in developing countries due to poor access to ARVs.

**KS** is an AIDS defining illness. It may present as cervical lymphadenopathy or as mucosal lesions of the oral cavity, oropharynx, nose or ear\(^1,2,39\). Otologically it may involve the external auditory canal (EAC), tympanic membrane (TM) and also has been documented in the inner ear and eighth nerve within the internal auditory canal\(^17\). Diagnosis is usually clinical but can be confirmed by biopsy or FNAC in the case of cervical nodes\(^1,2\). They may bleed due to their vascularity\(^2\). KS is almost diagnostic of AIDS which may mimic KS is bacillary angiomatosis\(^42\). It is important to differentiate between the two as the management differs. Bacillary angiomatosis (caused by Bartonella bacilliformis) can be treated successfully with a macrodile and tetracycline antibiotic\(^42\).

**NHL** and **HD** tend to be more aggressive, can be difficult to manage and have a poorer outcome with HIV\(^1,39\). Extranodal presentations of NHL are more common in HIV negative patients, and HD presents more frequently with disseminated disease\(^1\). NHL has been reported to involve the pinna, EAC, TM and temporal bone with associated facial palsy\(^43-47\). Combined chemotheraphy and ARV therapy seem to be superior to chemotherapy alone\(^39\).

### Conclusion

With the vast range of conditions that HIV-positive patients may present with to an ENT service, it is clear that both knowledge of these manifestations and a high index of suspicion are needed for the accurate assessment of these patients. Furthermore, a number of these individuals may be unaware of their HIV status when presenting with HIV defining illnesses, which when recognised, will assist in appropriate diagnosis and referral for these patients.

In the developing world, the management of the conditions associated with HIV infection remains a challenge due to the relative lack of access to ARVs.

### References


### Table 4: Viral aetiological agents in HIV associated tumours

<table>
<thead>
<tr>
<th>Virus</th>
<th>Tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td></td>
<td>Hodgkin’s disease</td>
</tr>
<tr>
<td></td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Kaposi’s sarcoma associated herpesvirus (KSHV) or Human herpesvirus-8 (HHV-8)</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Human papilloma virus (HPV)</td>
<td>Squamous cell carcinoma</td>
</tr>
</tbody>
</table>
Management of Metastatic Cutaneous Squamous Cell Carcinoma of the Head Neck; State of the Art Review

Faruque Riffat, Michael J. Veness, Carsten E Palme
Department of Otolaryngology Head & Neck Surgery, Head & Neck Service, Westmead Cancer Care Centre, Westmead Hospital, University of Sydney

Corresponding Author:
Carsten E Palme FRACS
PO Box 533, Westmead NSW 2145, Australia
P: + 61 2 9845 6025 F: + 61 2 8089 1025
E: carsten_palme@wsahs.nsw.gov.au

Introduction
Non-melanoma skin cancer (NMSC) is the most common malignancy worldwide and is managed by a diverse group of clinicians. It is a heterogeneous group of malignancies encompassing many different histological sub-types all requiring different management and with widely varying prognosis. These malignancies range from very common lesions foremost basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) to relatively uncommon lesions including Merkel cell carcinoma (MCC). The most common NMSC is overwhelmingly basal cell carcinoma (BCC) which comprises 70-75%, followed by squamous cell carcinoma (SCC) (20-25%) and the rarer merkel cell carcinoma is responsible for less than 5%. The majority of lesions are cured with simple surgical excision, but a small but significant proportion is locally aggressive and can metastasize. Treatment is complex and associated with significant morbidity and mortality. Best outcomes are achieved with a multidisciplinary approach.

Epidemiology and rising incidence
NMSC is at epidemic rates in regions such as Australia which has the highest incidence of skin cancer in the world. Notably, there are widely differing rates of NMSC in various populations and in most regions the incidence is increasing. In Australia, North America and Europe the incidences have increased by 3-8% per year since the 1960s. de Vries et al predicted that the incidence of NMSC in the Netherlands will increase over the next 10 years to 80%

Metastatic Cutaneous SCC
Studies suggest that the risk of developing nodal metastatic disease in patients with low risk SCC is 3-5%. When considering the population at risk of developing NMSC a number of factors are important. These include patient factors such as increasing age, male gender, caucasian background, chronic sun exposure, outdoor occupation, immunosuppression and certain systemic diseases including, epidermolysis bullosa, oculocutaneous albinism and xeroderma pigmentosum. Environmental exposure to UV radiation and the presence of immunosuppression are the major and most important aetiologic factors that can lead to the development of NMSC. Additional factors such as proximity to the equator, ozone layer depletion and both occupational and recreational exposure significantly increases this risk.

Various factors have been suggested as potential reasons for the rise in incidence of NMSC throughout the world over time. Firstly, the increase in the number of people at risk with both an aging population and increasing numbers of immunosuppressed patients (eg. renal transplant, HIV). SCC in this setting often behaves more aggressively with increased rates of both local recurrence and metastatic disease compared to the general population. The rates for developing nodal metastases were increased and between 10-18%. Secondly, it has been proposed that there has been an increased exposure to more intense UV radiation both due to ozone layer depletion and increased exposure to sunlight through increased leisure time, fashion and social trends. Lastly, increased awareness has led to a greater submission of skin lesions for histopathological verification.

Typically NMSC develops in older (>60 years old) caucasian males with a history of chronic sun exposure over their life time. The majority of lesions arise within the sun exposed regions of the head and neck.
The risk of developing metastases among patients who present to tertiary head and neck cancer centers many with high risk primary lesions. The parotid gland is the most frequent site for developing metastatic disease in patients with head and neck primaries with other regional basins such as the axilla or groin rarely involved.

The risks for developing metastasis can be divided into patient, tumour and treatment factors. Patient factors that have shown to predict the development of metastatic disease include male gender, immunosuppression and delayed presentation. Tumor factors include tumor size, depth/thickness of the primary (>2-4 mm), invasion of adjacent tissue, location, the presence of perineural/lymphovascular invasion, tumor grade and growth rate. Horizontal tumor size is acknowledged as a risk factor for developing metastatic nodal disease although it is probably a weak independent predictor. Veness et al reported a series of 266 patients with metastatic nodal disease where 70% of lesions were < 2cm in size16. In this study tumor thickness was > 4mm in the majority of patients with T1 lesions, all of whom had nodal disease. There was a significant correlation between increasing tumor thickness and lesion size, suggesting these tumors had a propensity for both vertical and horizontal growth. The authors noted that not all large SCCs will metastasize, and it is possible that lesions which are horizontally large (2-3cm), but not thick (i.e. 2-3mm), may lack the propensity to metastasize.

Tumor thickness (4-5mm) has also been associated with increased risk for the development of metastatic disease by others. Kraus et al demonstrated that while only one third of patients with SCC have lesions >4mm thick these accounted for >80% of lesions which develop metastatic nodal disease17.

Recurrent lesions are associated with a marked increase in the risk of developing metastases18. Patients with inadequately excised lesions are at risk of both local recurrence and the development of nodal disease. Grover et al noted that the risk of nodal metastasis was 15% in patients with recurrent lip SCC compared with 2% in those with de novo lesions19.

Poorly differentiated SCC is more likely to be associated with the development of regional metastases. Breuninger and colleagues reported a significant difference in the rate of nodal metastasis between high and low grade SCC (17% vs. 4%)20.

Although the presence of perineural invasion in SCC is relatively uncommon it leads to an increased risk of both local recurrence and metastatic disease. Goepfert reported a 47% local recurrence rate and a metastatic rate of 34.8% in patients with perineural invasion treated surgically21. Lymphovascular invasion, at least in one study, has also been reported to increase the risk of developing nodal metastatic disease. Moore and colleagues documented lymphovascular invasion as an independent risk factor with 40% of patients with nodal metastasis having lymphovascular invasion compared with only 8% of node negative subjects22.

Specific anatomical subsites have been identified as having an increased risk. Patients with lesions draining to the parotid (e.g. lateral scalp, temple, forehead, ear or cheek) should be considered as high risk. In considering the pattern of metastatic spread in the neck from primary SCC it has been described that nearly 40% where from the anterior part of the face, 15% were from the external ear and 22% were from the posterior region of the head and neck with around 25% of primary sites not identified23.

Treatment factors which are important include inadequate primary treatment including incomplete resection and failure to consider re-excision or adjuvant external beam radiotherapy with subsequent persistent disease or development of local recurrence. Patients developing local recurrence are at a much higher risk of developing nodal metastases14,16. Over 70% of metastatic nodal disease presents within 1 year of treatment of the primary lesion while few patients present with nodal metastatic disease after 5 years.

**Clinical Presentation**

The most common presentation of a patient with metastatic cutaneous SCC of the head and neck is with a hard mass located within the parotid gland or upper cervical lymph node levels including the external jugular and occipital nodal groups. At advanced stages there may be associated fixation of the mass to underlying structures, facial nerve palsy, skin involvement, invasion of the temporal bone, maxilla and / or mandible. An index lesion can be identified on history in approximately 70 % of patients presenting with metastatic disease. Presentation of lymph node metastases concomitant with a primary head and neck lesion is uncommon.

Patients with metastatic cutaneous SCC are best managed within the setting of a multidisciplinary team. Routine investigations performed include a fine needle aspiration biopsy as well as appropriate imaging including Orthopontogram, contrast computed tomography and magnetic resonance scanning of the head, neck and chest. Increasingly PET Scans are being used to stage distant...
metastasis. Audiograms are an important consideration when contemplating temporal bone resection.

**Controversies and evolution of staging**

The American Joint Committee on Cancer, Cancer Staging Manual (AJCC) tumor, node metastasis (TNM) system is widely utilized in staging of patients with SCC.

Previous editions of the AJCC TNM classification did not differentiate on account of subtype of NMSC. Only horizontal size of the primary lesion was considered important when differentiating T stage (i.e. T1- T3). Nodal disease was simply classified as either N0 or N1 to indicate either the absence or presence of regional involvement17. This system did not usefully separate patients into prognostic groups. This has stimulated significant debate and research by a variety of different institutions and research groups. An alternative staging was proposed by O’Brien and others. (Ref This aimed at separating nodal disease based on size and number occurring within the parotid gland (P) and or cervical lymph node groups (N) (Table 3). Palme et al subsequently tested this new P and N staging system on a separate group of patients from the Head and Neck Service, Westmead Hospital, Sydney24. 126 patients with SCC metastatic to the parotid and/or neck were retrospectively restaged and the results demonstrated that increasing P stage was associated with a reduction in local control and increased treatment failure within the parotid bed. Immunosuppression, single modality therapy and increasing P stage were all found on multivariate analysis to be significantly associated with decreased survival, however, unlike O’Brien’s original paper increasing N stage was not found to be significant.

The results from these studies prompted a multi institutional international trial involving 6 institutions – 3 from Australia and 3 from North America and a total of 322 patients with metastatic cutaneous SCC of the head and neck involving the parotid gland and or neck lymph nodes. The vast majority were treated with surgical resection, 90%, with 236 receiving adjuvant external beam radiotherapy. The remainder was treated with radiotherapy only. Disease recurred in 105 cases (33%) with 42 occurring within the parotid bed, 33 within neck nodes and 30 at distant sites. Advanced P stage did not affect local control but there was a trend toward worse survival. When considering nodal disease in the neck there was a statistically significant survival difference favoring patients staged N030. The results from these studies have led to significant changes and improvement of the staging of NMSC the majority of which have been adopted in the revised 7th edition of the AJCC manual. (Table 1).

<table>
<thead>
<tr>
<th>Table 1 High Risk features for primary tumor (T) staging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depth/invasion</strong></td>
</tr>
<tr>
<td>Clark level &gt;= IV</td>
</tr>
<tr>
<td><strong>Anatomic Location</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Differentiation</strong></td>
</tr>
</tbody>
</table>

The current T classification differentiates early lesions (T1 or T2) based on size and advanced lesions (T3, T4) based on the degree of invasion into surrounding tissues (Table 2).

**Treatment Options**

Current state of the art therapy in patients who develop nodal metastases includes combined modality treatment involving surgical resection when possible and adjuvant external beam radiotherapy. Surgery or radiotherapy alone is associated with a significantly lower chance of achieving local control and disease specific survival. Based on the current literature the recurrence rates with single vs. multimodality therapy are approximately 20% vs. 50% respectively25.

In management of the primary NMSC within the head and neck a wide local excision with at least a 5mm margin is pursued. The unique anatomical challenges presented by the head and neck region mean that this is not often possible without sacrifice of functionally important structures or bony resection of the temporal bone or maxilla.

The ablative procedures are reconstructed with a reconstructive ladder no different to what is applied in mucosal SCC. Where possible local flaps (eg. Cervicofacial, temporalis fascia) are utilized but increasingly as microvascular expertise is available free flap reconstructions achieve superior cosmetic and functional outcomes. There has been a move away from prosthetic reconstruction in

<table>
<thead>
<tr>
<th>Table 3 O’Brien et al system for clinical staging of metastatic cutaneous SCC involving the parotid gland +/- neck</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parotid</strong></td>
</tr>
<tr>
<td>P1 Metastatic node up to 3cm diameter.</td>
</tr>
<tr>
<td>P2 Metastatic node more than 3 cm up to 6cm in diameter or multiple parotid nodes.</td>
</tr>
</tbody>
</table>
recent times but for certain anatomical areas (eg, pinna, external nose) these remain excellent alternatives to more complex surgical options.

Management of metastasis to the parotid is managed with a facial nerve sparing parotidectomy (with or without overlying skin) or in cases where there is pre-operative paralysis with nerve resection. The management of the N+ neck is with a comprehensive neck dissection while the patient with parotid gland only disease should undergo a selective neck dissection. This is based on the knowledge that the occult nodal rate in this group is in excess of 25%. All patients require adjuvant external beam radiotherapy.

Primary radiotherapy alone can be considered for patients unfit for surgery bearing in mind the higher local recurrence rates but is often recommended for palliation.

Currently there is a randomized controlled trial being undertaken in Australia and New Zealand considering the benefit of adding platin based chemotherapy as an adjuvant therapy in high risk patients (POST Trial).

Prognosis and Future Developments
The Westmead Hospital Group has recently published a 4 factor prognostic scoring system, the ITEM score, which considers Immunosuppression, Treatment, Extracapsular spread and Margins Status most significant in determining prognosis in patients with metastatic cutaneous scc of the head and neck. In this study a cohort of 250 patients was examined to identify relevant patient, tumor and treatment factors that are prognostic in patients with metastatic SCC of the head and neck. In this study 28% of patients developed recurrence. Those treated with combined modality had a lower recurrence rate than those patients treated with either surgery or radiotherapy alone (17% vs. 48% respectively). Regional recurrence was the first site of recurrence in 73% of patients while distant metastatic disease as the first presentation of recurrence was uncommon and occurred in only 9 (13%) cases. Patients failing treatment did so with a median time of 8 months and 73% died of their disease demonstrating the importance of achieving nodal control. Multivariate regression analysis confirmed that the presence of immunosuppression, extent of treatment – single modality vs. multimodality, extracapsular spread and margin status were the most important prognostic factors in patients with metastatic cutaneous SCC of the head and neck. Using the coefficients of the ITEM variables as weights, risk scores were able to be calculated for each patient. This is a simple and easy system that can be used clinically to prognosticate and it may also allow the precise identification of patients at significant risk of a poor outcome and therefore may prove useful when allocating and testing new and more targeted therapeutic regimes.

Molecular markers such as epidermal growth factor receptor (EGFR) are emerging as potential biomarkers for aggressive SCC. Ch’ng et al reported overexpression of EGFR present in 79% of primary lesions which

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Nodes</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Nx</td>
<td>M0</td>
</tr>
<tr>
<td>T0</td>
<td>N0</td>
<td>M1</td>
</tr>
<tr>
<td>Tis</td>
<td>N1</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>N2a</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>N2b</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>N2c</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>N3</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Staging for Cutaneous SCC – 7th Edition of AJCC staging manual

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Nodes</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Nx</td>
<td>M0</td>
</tr>
<tr>
<td>T0</td>
<td>N0</td>
<td>M1</td>
</tr>
<tr>
<td>Tis</td>
<td>N1</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>N2a</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>N2b</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>N2c</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>N3</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Staging for Cutaneous SCC – 7th Edition of AJCC staging manual
subsequently developed nodal metastasis. However, Ch’ng noted that only 47% of metastatic deposits expressed EGFR. An Australian study reported that EGFR was expressed in only a minority of tumors and that it was not always activated. These findings along with a Phase II trial of an EGFR inhibitor, which did not find an objective response, suggest that while EGFR may be a marker of aggressive disease, further prospective research is required to establish its full significance in predicting the development of regional spread in patients with SCC.

**Summary**

NMSC is the most common malignancy worldwide with an ever increasing incidence. The sun exposed regions of the head and neck are at risk and the most common site involved. The majority of lesions are managed and cured by simple excision. There is a small but increasing subset of lesions that behave aggressively with local tissue destruction and both regional and distant metastasis. Current best practice management requires a multidisciplinary approach in a center with significant resources and experience at treating this complex and challenging group of patients. The future lies within prevention and developing selective targeted adjuvant therapy that improve survival and reduce morbidity from this debilitating disease.

**References**

2. A.Buettner PG Raasch BA Incidence of skin cancer in Townsville Australia Int J Cancer 1990; 78:587-593
4. Talman YP Problems in the Current TNM Staging of nonmelanoma skin cancer of the head and neck and Head Neck 29:525-527 2007
6. Marks, R Rennie, G Malignant Transformation of Solar Keratoses to Squamous Cell Carcinoma The Lancet 1988, 1:795-797
30. Andrucho J.L. et al Implications for clinical staging of metastatic cutaneous squamous carcinoma of the head and neck based on a multicentre study of treatment outcomes Cancer 2006;106:1078-83
Presentation, Diagnosis and Treatment Options for TMJ Dysfunction

Andrew J Sidebottom BDS, FDSRCS, MBChB, FRCS, FRCS (OMFS)  
Consultant Oral and Maxillofacial Surgeon  
Queens Medical Centre, Nottingham, UK

Abstract
TMJ disorders commonly present to ENT with “ear” and “facial” pain. This article presents a simple technique for examination, investigation and diagnosis of TMJ disease and subsequent overview of management under the care of the maxillofacial team.

Introduction
Temporomandibular joint problems commonly present to ENT with “earache” or “facial” pain. Around 30% of the population have TMJ symptoms at some stage during their life, with around 10% having active symptoms or signs. The following provides a guide to TMJ diagnosis and primary management for the ENT surgeon, with advice on when referral for maxillofacial advice is appropriate.

History of TMJ Disease

Primary symptoms include:
1. Pain
2. Joint noises
3. Locking
4. Restriction of mouth opening
5. Other joint disorders particularly rheumatological and hypermobility

Pain
History and examination aim to distinguish between TMJ and myofascial pain and other causes of facial pain.

Pain localised in front of the tragus is likely to be TMJ pain. It is often precipitated by function (eating and yawning), and may radiate to surrounding structures.

Poorly localised pain, “numbness” and aching on the side of the face, may be myofascial pain. This may be worse in the mornings, due to clenching or grinding the teeth at night, or during “stressful” life situations.

Joint Noises
Joint noises are common and require reassurance. Clicking follows relocation of an anterolateral displacement of the disc (ADD). It will soften with time and does not predispose to “arthritis of the joint”. Crepitus does not warrant treatment but suggests “scarring” within the joint.

Locking
Locking is the inability to either fully open or fully close the joint. Locking may be overcome following massage with resolution of full opening. Causes include disc displacement with reduction (ADDR), acute muscle spasm and lubricant related problems. Inability to fully close over a period of time is due to a joint effusion (synovial fluid) or blood (haemarthrosis). This may be secondary to trauma although the former may be secondary to acute synovitis.

Restriction of Opening
Adult range of mouth opening is above 35mm inter-incisal distance. Opening greater than 55mm suggests hypermobility.

Muscle spasm and disc displacement can cause restriction. Opening less than 25mm in a young adult suggests anchored disc phenomenon, due to loss of joint lubrication. Urgent management by a maxillofacial specialist with early arthrocentesis (joint washout under pressure) is usually curative. Significant delay may lead to a permanent restriction.

Acute restriction may also be caused by a dental abscess with soft tissue space involvement and urgent referral for maxillofacial advice is essential as rapid deterioration with loss of airway can occur.

Other Joint Disorders
The TMJ can be affected by rheumatoid joint diseases and hypermobility. Rheumatoid disease often presents with pain and ultimately can lead to joint collapse with a disturbance in the way the teeth bite together (occlusion). Ankylosing spondylitis may lead to joint ankylosis with pain and restriction of opening. Psoriatic arthropathy also may cause pain, restriction and occasionally joint collapse.
Hypermobility predisposes to joint dislocation where the mandibular condyle is displaced anterior and superior to the articular eminence. Reduction is achieved by firm downward pressure with the thumbs lateral to the molar teeth, with upward finger pressure under the chin whilst standing behind the patient with their head against the doctors’ abdomen. It occurs in two age groups – young adults with hypermobility and the elderly who have loose ligaments and overclosure of the jaw due to lack of teeth.

Clinical Examination
Clinical examination should determine the sites of tenderness and the degree of disorder present.

1. Joint palpation for tenderness and noises/crepitus, closed and open, lateral and posterior
2. Palpation of the masseter and temporalis muscles for tenderness and muscle spasm
3. Measurement of inter-incisal mouth opening
4. Observation of the mandibular opening path
5. Interdigitation of the teeth (Dental occlusion)

Palpation of the Joint
The TMJ is palpated just in front of the tragus of the ear. Rotation occurs in the lower joint space and glide from the upper joint space over the articular eminence. Tenderness may be elicited over the lateral aspect of the joint whilst stationary or in motion. The posterior joint can be palpated in wide opening between the back of the joint and the tragal cartilage. Joint tenderness implies inflammation in the joint related structures of capsule, synovium and bone.

Noises may be palpated and heard such as click or crepitus (crunching). Often the patient will complain of noises which are either intermittent or cannot be detected by the examiner. Tinnitus is not a symptom of TMJ disease, although the patient may describe the clicking as “tinnitus”.

Palpation of the Masseter and Temporalis
The masseter muscles lie over the vertical ramus of the mandible up to the base of the zygomatic arch. The temporalis lies above the zygomatic arch, behind and above the ear and onto the forehead below the hairline. Muscle tenderness during clenching or the palpation of tight muscle bands indicate myofascial pain. The other muscles of mastication are difficult to palpate and this is un-necessary in non-specialist practice. Headaches may be a symptom of TMJ disorder when there is associated muscle or joint tenderness.

Measurement of Inter-incisal Opening
The distance between the upper and lower incisors during maximal mouth opening gives a reliable and reproducible measure of loss of function and outcome. Mouth opening is greater than 35mm in 97% of the population. Some patients with opening greater than 35mm have subjective restriction and in others less opening is normal. Improvement in opening following treatment gives a good measure of outcome.

Observation of Opening Path
Mouth opening tends to deviate towards the side of pathology. The early phase is rotation of the condyle against the disc in the lower joint space. From 25mm glide occurs between the disc-condyle complex and the glenoid fossa of the temporal bone in the upper joint space deviating away from that side. Joint pathology causing restriction is often related to upper joint space problems, muscle spasm or joint pain restricting movement. This aids confirmation of the side of the problem.

Interdigitation of the Teeth (Dental Occlusion)
The way the teeth bite together can be altered by joint collapse. Collapse causes the fulcrum on that side to move.
superiorly with premature contact of the posterior teeth and centreline deviation towards that side. Bilateral collapse causes the front teeth not to meet (anterior open bite). Increased joint space (from effusion or haemarthrosis) lowers the fulcrum, preventing the posterior teeth on that side from meeting.

Radiographs are seldom useful other than to exclude dental pathology.

Initial Management
Initial management of most TMJ disorders is reassurance that there is unlikely to be a significant underlying condition, arthritis is unlikely and most patients can be managed non-surgically. Psychological changes are not uncommon and the reassurance will go some way to improving symptoms. The placebo effect should facilitate a “cure” in around 40%.

Explanation of the disease process as a joint “sprain” with consequent joint pain due to inflammation and muscle spasm empowers the patient and reduces the risk of following internet mis-advice. Rest with avoidance of chewy and tough foods, particularly chewing gum, and restriction of wide mouth opening (the pain may have been induced by a dental visit or tonsillectomy) will improve symptoms. Topical non-steroidal anti-inflammatory gels applied to the joint 4 times daily for 4 weeks gives additional benefit in terms of pain relief and reduction of joint inflammation. Paracetamol may be used as a simple analgesic.

The patient’s dentist should provide a lower soft full occlusal coverage splint to wear at night. This reduces muscle and joint load overnight, particularly in patients with a clenching habit and helps to eliminate the habit. It may take a few weeks for symptoms to improve. There is no benefit in adjusting the way the teeth bite together (tooth grinding or occlusal adjustment). A Cochrane study has shown that doing nothing is just as effective and is much less harmful.

Physiotherapy may have short-term benefit but there is no evidence of long-term efficacy. Steroid injections should be avoided as they may cause joint collapse.

Following a 2 month trial of these treatments, if there has been no significant improvement, or if there is acute severe restriction in opening then referral to a maxillofacial specialist, preferably with an interest in TMJ disorders should be considered. (Table 1)

Maxillofacial Management
Maxillofacial surgeons will reiterate the advice of rest, reassurance, NSAIDs and a bite splint. For those patients in whom there has been some initial improvement persistence may continue for up to 6 months.
Earlier intervention with therapeutic arthroscopy (examination and washout of the joint) or arthrocentesis (joint washout under pressure) is indicated in patients with restricted opening who fail to improve or in those with persistent locking. Around 80% will improve with this procedure. Additionally arthroscopy under GA gives a good idea of whether restriction is due to muscle spasm and pain and the degree of intra-articular damage (opening improves with the muscle relaxation of general anaesthesia.

Where arthroscopy is unsuccessful, the joint was normal and mouth opening improved during anaesthesia myofascial pain is likely and muscle relaxant medication may be suggested. Commonly a low dose tricyclic is used starting at 10mg and potentially rising to 75mg titrated to symptoms and side effects. These take around three weeks to become effective and doses should be increased monthly until full analgesia is achieved or side-effects prevent a further increase in dose. The analgesic dose is maintained for 6 months and then the patient weaned off, according to recurrence of symptoms, over the next few weeks. Alternative therapy under investigation is the injection of Botulinum toxin into the areas of muscle spasm, which is effective in around 70% of patients.

Where arthroscopy has shown intra-articular problems open joint surgery may be used if symptoms do not improve. A variety of techniques have been used along orthopaedic principles with ultimately joint replacement as the final option. The latter is not to be considered lightly and in the UK less than 100 total joints replacements are carried out each year by less than 10 recognised joint replacement surgeons. National guidelines have suggested when these may be indicated.

**Conclusion**

TMJ disorders are commonly seen in ENT practice. History and examination of the joint is a simple addition to the routine ENT examination and should be included for any patient with facial pain. Simple conservative management can usually deal with most TMJ problems and it is rare that open surgery will be required. Arthroscopy is increasingly used with good success rates by a suitably trained surgeon.

**Further Reading**

AJ Sidebottom
Leading Article. Current thinking in TMJ management
BJOMS 47: 91-94; 2009

Ohnishi M.
Arthroscopy of the temporomandibular joint.
J Jpn Stomatol 1975: 42: 207-212

Nitzan DW, Dolwick MF, Heft MW.
Arthroscopic lavage and lysis of the temporomandibular joint: a change in perspective.

Dimitroulis G.

Dimitroulis G.
The role of surgery in the management of disorder of the temporomandibular joint: a critical review of the literature. Part 2.

AJ Sidebottom.
Guidelines for the replacement of the TMJ in the UK.
BJOMS 46: 146-147; 2008

**Table 1**

<table>
<thead>
<tr>
<th>When to Refer for Maxillofacial Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute severe restriction of opening</td>
</tr>
<tr>
<td>Failure of simple conservative measures in conjunction with dentist over 2 months</td>
</tr>
<tr>
<td>Associated rheumatological disease</td>
</tr>
<tr>
<td>Recurrent dislocation of the joint</td>
</tr>
<tr>
<td>Disturbance of the dental occlusion</td>
</tr>
</tbody>
</table>

**Figure 6:** TMJ Concepts total joint replacement in situ.

Towards Safer Practice in Otology: A Report on 15 Years of Clinical Negligence Claims

Mr Rajeev Mathew, Dr Eleni Asimacopoulos, Mr Peter Valentine
Presenting Author: Mr Rajeev Mathew, SpR Otolaryngology, Royal Surrey County Hospital, Guildford, Surrey, GU2 7XX.
E mail: rgmathew@hotmail.com

Background
The National Health Service Litigation Authority (NHSLA) was created in 1995 to manage negligence claims and improve patient safety. The aim of this study is to present the claims in Otology over the last 15 years.

Methods
Under the Freedom of Information Act all claims relating to Otolaryngology between 1995 and 2010 were obtained from the NHSLA database. Claims were categorised by subspecialty, cause of injury and type of injury.

Results
Over 15 years there were 139 claims in Otology, representing 26% of all the claims in Otorhinolaryngology. Of these, 119 have been closed and 85% of all closed claims resulted in payment. The average cost to the NHS per claim was £61,000.

Of the 101 successful claims, 61 were related to post operative complications, with mastoid surgery being the most common procedure resulting in injury. The commonest post operative injuries were hearing loss (41%), facial paralysis (24%) and dizziness/imbalance (9.8%). There was 1 fatality following a dural tear during mastoid surgery. There were also 6 cases of wrong side/site surgery, and 5 cases of morbidity due to delayed surgery.

Other successful claims included 14 cases of failed/delayed diagnosis, 10 cases related to outpatient procedures, and 5 claims of medical mismanagement including 3 cases of ototoxicity due to ear drops.

Conclusion
This paper examines key aspects of the law in medical negligence claims. By looking at individual cases over the last 15 years, we highlight ways in which otologists can make their practice safer and reduce litigation.

Outcome following elective ventilation tube removal in children

Presenting author: Mr. Chee Yean Eng, Specialist Registrar, Study site: Sheffield Children's Hospital (SCH).
Email address: cyeng@doctors.org.uk

Objective:
To determine the rate of residual tympanic membrane perforation following removal of ventilation tube; and whether performing additional procedures at the time of ventilation tube removal reduces the risk of residual perforation.

Introduction:
Ventilation tube insertion remains the primary surgical intervention in persistent otitis media with effusion following a period of observation as recommended by NICE. Around 7% of patients with ventilation tube in-situ will require elective removal for various reasons.

Methods:
Retrospective case notes review over an eight year period was performed.

Results:
One hundred and thirteen patients were included in this study. The average age at grommet insertion and removal was 5.8 years old and 8.3 years old respectively. The average duration of grommet in-situ prior to removal was 29.33 months. The most common indication for removal was chronic infection and discharge (81%). Eighty two percent were Shah grommets. Average duration of follow-up after grommet removal was 15.63 months. Majority of
patients (80%) had intact tympanic membrane following ventilation tube removal without additional procedures such as fat plug or insertion of overlay absorbable material. Shah and Shepherd grommets have significantly lower residual tympanic membrane perforation rate compared to T- Tube or Titanium grommet.

**Discussion and Conclusion:**
It was shown in our series that Shah and Shepherd grommets are least likely to cause a residual perforation following elective ventilation tube removal. The tympanic membrane tends to heal spontaneously without intervention.

**Correlation between radiological and pathological staging in cervical nodal disease in head and neck squamous cell carcinoma**

Prasai A, Salvage D, Jose J, Stafford N  
Presenting Author: Mr A Prasai, Specialist Registrar  
Study Site: Departments of Head and Neck Surgery and Radiology, Hull and East Yorkshire Hospitals NHS Trust.  
Email address: amitprasai@yahoo.co.uk

**Aim**
To evaluate the accuracy of magnetic resonance imaging (MRI) and computerised tomography (CT) scanning in the staging of cervical nodal disease in head and neck squamous cell carcinoma (HNSCC).

**Method**
This is a retrospective study of patients who underwent neck dissection for HNSCC between 2008-2009. All the patients were evaluated through the regional head and neck multi-disciplinary team (MDT) meeting. American joint committee on cancer (AJCC) TNM classification (2006) was used to stage HNSCC in both radiological and histopathological assessment. The histopathological staging was used as the gold standard when compared to radiological evaluation. The data collected included patient demographics, TNM staging, surgery performed and radiological and histopathological staging of cervical nodal disease in HNSCC.

**Results**
Total of 36 patients who underwent neck dissection were included in the study. 25 patients were evaluated with MRI, 11 with CT and 1 patient was evaluated with both CT and MRI scanning. Of the 12 patients evaluated with CT scanning, 4 (33%) were correctly staged when compared to the histopathological staging. CT scanning upstaged the neck disease in 2 (17%) patients and downstaged 6 (50%) patients. Total of 26 patients underwent MRI scans. MRI scanning correctly staged the neck disease in 16 (62%) of patients, upstaged 5 patients (19%), and downstaged 5 (19%) patients.

**Overall**
MRI and CT scanning only correctly staged the neck disease in 54% of the patients and downstaged the disease in 30% of the patients.

**Conclusion**
MRI appears to better than CT at evaluating cervical nodal status in metastatic HNSCC, however up to 30% of patients are downstaged on CT and MRI evaluation when compared to histopathological staging of neck disease. We need to bear this in mind when deciding management options in HNSCC.

**‘Sausage Roll Rhinoplasty’**

Claire Hopkins, Ben Hunter, James Earnshaw, David Roberts  
Presenting Author: Ben Hunter, Guys Hospital, Great Maze Pond, London SE1 9RT  
Correspondence: benhunter@doctors.org.uk

**Introduction**
Augmentation of a deficient nasal dorsum can be challenging and a range of both autologous and non-autologous grafts are available. We have previously reported excellent long term results using Permacol™, a sheet of acellular cross-linked porcine dermal collagen and its constituent elastin fibres. We now describe a novel modification of our technique.

**Methods**
A ‘sausage roll’ is created by rolling a sheet of Permacol to the required width and thickness, and securing with PDS sutures. It is trimmed to the correct length, and sited via open or closed rhinoplasty approach. The dorsal heights were measured from pre-operative photographs and compared to the height 1 year after surgery.
Results
We have used the ‘sausage roll’ rhinoplasty technique in 10 patients, with a minimum of 1 year follow-up. Indications include trauma, inflammatory conditions, and revision rhinoplasty. The technique achieved excellent smooth augmentation of the dorsum, with a mean improvement in dorsal height of 30% at one year.

Discussion
Although a porcine based product may not be acceptable to all patients, we have found it provides excellent long-term augmentation of the nasal dorsum, with a low complication rate and high patient satisfaction rates. The results presented should be achievable in the hands of all rhinoplasty surgeons.

Conclusion
We believe this to be the ideal graft material and technique to achieve a significant and lasting augmentation of the nasal dorsum.

Diffusion-weighted MRI for detection of cholesteatoma: a prospective cohort study and qualitative systematic review

Emma Stapleton, SpR Otolaryngology, Emily Stedman, F1 Otolaryngology, Jaydip Ray, Consultant Otolaryngology, Royal Hallamshire Hospital, Sheffield
Presenting Author: Emma Stapleton, Specialist Registrar
Email: emmastapleton@doctors.org.uk

Introduction
A large number of published cohort studies recommend diffusion-weighted magnetic resonance imaging for detecting primary and recurrent cholesteatoma. In this study, the Sheffield cohort is analysed, and a systematic review of literature is carried out.

Participants
30 patients having diffusion-weighted imaging between 12 and 18 months after combined approach surgery for cholesteatoma. 36 prospective cohort studies reporting outcomes following 705 patients having diffusion-weighted imaging and surgery for cholesteatoma.

Main Outcome Measures
Sensitivity, specificity, positive and negative predictive values of diffusion-weighted magnetic resonance imaging in detecting cholesteatoma

Results
In our cohort, 7 patients had recurrent disease on diffusion-weighted imaging. At second-look surgery, 5 patients had recurrent disease. There were no false negative results (sensitivity = 100%) and two false positive results (specificity = 92%). Positive predictive value 71.4%, negative predictive value 100%.

In our systematic review, no level I or II evidence was found to support the use of diffusion-weighted imaging in the detection of cholesteatoma. 36 prospective cohort studies were identified. Amongst 705 cases reported, the overall sensitivity of diffusion-weighted imaging in the detection of cholesteatoma was 79%. Overall specificity 91%. Overall positive predictive value 93%. Overall negative predictive value 74%.

Conclusions
There is no high-level evidence for using diffusion-weighted imaging in the detection of cholesteatoma. Published cohort studies differ in their conclusions regarding the usefulness of diffusion-weighted imaging. There is no evidence that diffusion-weighted imaging contributes more than CT scanning. Systematic review of the literature suggests that diffusion-weighted imaging is not sufficiently accurate to replace second-look surgery.

The Wii habilitation in visual vertigo - Initial experiences

N. Sivaji; J. Ray; P. Bacon; MP Yardley; L. Willers; C. Codina
Presenting Author: N Sivaji, ENT Department, Department of Medical Physics, Academic Department of Ophthalmology, Royal Hallamshire Hospital, Sheffield
Correspondence: benhunter@doctors.org.uk

Introduction:
Visual vertigo (VV) refers to vertigo provoked by moving visual stimulation. Evidence suggests that patient with VV benefit from exercises involving visual vestibular conflict. Wii fit balance game has generated interest in this area. This study investigates the above hypothesis.
Aim:
To determine the feasibility of using wii fit balance games in rehabilitation of visual vertigo.

Material and method:
Site: Royal Hallamshire Hospital, ENT Department

Subjects
20 patients with visual vertigo were recruited. Those with episodic or rotatory vertigo were excluded. The mean age was 49 yrs

Method
Detailed vestibular (VNG, caloric test, Head shake test, Sway Pen posturography) and visual assessment was undertaken in all before and after rehabilitation. Each received detailed instructions on 9 different balance games of gradually increasing complexity on the Wii fit device which they were instructed to use for 30 minutes each day. As their performance improved the system unlocked a newer and more difficult game and kept a log of their score and compliance. They were reassessed at 6 weeks.

Results:
Outcome measures included Situational Characteristics Questionnaire (SCQ) and Vestibular Rehabilitation Benefit Questionnaire (VRBQ). All participant displayed SCQ score of >0.94 (SCQ score>0.94 indicates Visual vertigo). TheVV patients demonstrated significant reduction in the SCQ scores (p=0.002) (average reduction 0.46). 66.6% demonstrated significant reduction in VRBQ symptoms subscales (Dizziness, Anxiety and Motion-provoked dizziness)

Conclusion:
Wii fit provides a low cost, engaging measurable option for balance rehabilitation in carefully selected patients of visual vertigo.

Small lingual carcinomas that metastasize early can be predicting using histological and immunohistochemical parameters

Gibbins N, Hoffman G, Jani P.
Presenting Author: Mr Nicholas Gibbins MRCS SpR, Great Ormond Street Hospital, London. WC1N 3JH
E-mail: nickgibbins@virginmedia.com
Place where the research took place:
Department of Histopathology, Addenbrooke's Hospital, Hills Rd, Cambridge. CB2 0QQ

Background
Oral squamous cell carcinoma is the 10th most common cancer in the 1st World and comprises 2-3% of malignancies diagnosed in the United Kingdom each year. The life expectancy of this disease remains the same as it was 30 years ago and its incidence is rising. 85% of lingual cancers are found on the tongue's lateral border. It is known that 40% of those spread early to regional lymph nodes. All patients receive treatment of the neck so 60% of patients are over-treated. Finding predictive factors within these cancers that predict whether it will spread early would improve diagnosis, treatment and potentially survival.

Method
Clinical records, predisposing factors, histological parameters and 5 extracellular matrix proteins (MMP-1, MMP-3, uPA, TGF-β1 and integrin α3) were examined in a retrospective study. Differences were noted between two homogeneous groups of lingual cancers; 19 of which did not go on to develop cervical metastases and 20 of which that did. The extracellular proteins were examined immunohistochemically techniques using tissue microarrays.

Results
Heavy smoking and drinking predispose to early spread. The tumour invasive front grade correlated to early spread. There was significantly increased expression of MMP-3 (p<0.05) and decreased expression of integrin α3 (p<0.01) in the walls of blood vessels of the metastases positive group.

Conclusion
Small lingual carcinomas that spread early can be predicted using histological and immunohistochemical techniques. This may help individualize patient's treatment and reduce treatment comorbidity caused by overtreatment.
How do you increase efficiency in head and neck procedures?

Precisely.

If you already use HARMONIC® devices for thyroidectomies, then you’re familiar with the efficiency and precision ultrasonic technology offers. But HARMONIC® technology advantages apply to other head and neck procedures.

The same qualities that allow HARMONIC® technology to shorten thyroidectomy times by 30 minutes* without compromising safety can yield important advantages in other head and neck procedures:

• In parotidectomies, reduce intraoperative blood loss and duration of drainage.*

• In parathyroidectomies, improve efficiency while minimizing thermal tissue injury.

• In all procedures, reduce instrument exchanges by enabling you to dissect, cut and coagulate with the same device.

*Save 30 minutes in thyroidectomies vs. clamp, cut and tie. Data on file at Ethicon Endo-Surgery.


For further information please email ukfocus@its.jnj.com

That’s Positive Energy