Emerging Technologies for the Diagnosis of Otitis Media

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Abstract

Objective. To review new experimental techniques for the diagnosis of otitis media (OM).

Data Sources. Literature search in English in the following databases: MEDLINE (via PubMed), Ovid Medline, Google Scholar, and Clinical Evidence (BMJ Publishing) between January 1, 2005, and April 30, 2018. Subsequently, articles were reviewed and included only if relevant.

Review Methods. MeSH terms: ["diagnosis"] AND [all forms of OM] AND ["human"] AND ["ear"] and ["tympanic membrane"]). The retrieved innovative diagnostic techniques rely on and take advantage of the physical properties of the tympanomastoid cavity components: tympanic membrane (TM) thickness, its translucency and compliance; middle ear fluid characteristics; biofilm presence; increased tissue metabolic activity in OM states; and fluid presence in the mastoid cavity. These parameters are taken into account to establish OM diagnosis objectively. We review spectral gradient acoustic reflectometry, digital otoscopy, TM image analysis, multicolor reflectance imaging, anticonfocal middle ear assessment, optical coherence tomography, quantitative pneumatic otoscopy, transmastoid ultrasound, wideband measurements, TM thickness mapping, shortwave infrared imaging, and wideband acoustic transfer functions.

Conclusions. New experimental techniques are gradually introduced to overcome the limitations of standard otoscopy. The aforementioned techniques are still under investigation and are pending widespread clinical use. The implementation of these techniques in the market is dependent on their success in clinical trials, as well as on their future cost.

Implications for Practice. New techniques for the diagnosis of OM can objectively evaluate the morphology of the TM, determine the presence of middle ear fluid and evaluate its content, and thus potentially replace standard otoscopy.

Keywords

otitis media, diagnosis, otoscopy, tympanic membrane, middle ear

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Otitis media (OM) is a common infectious disease in children.¹,² For decades, the standard tool for OM diagnosis has been the otoscope. Traditionally, many efforts are invested teaching medical staff to first identify normal anatomy of the tympanic membrane (TM) with its typical landmarks: the malleus handle, the pars tensa and pars flaccida, the fine overlying blood vessels, the position of the TM, and the middle ear structures reflected behind the TM. This allows the examiner to accurately diagnose acute otitis media (AOM) with greater certainty, when otoscopy findings, including TM bulging and hyperemia, loss of normal TM translucency, and presence of fluid behind the TM, are present in the context of typical constitutional signs and symptoms (fever, ear tugging or pulling, otorrhea, restlessness, etc). The otoscopic findings are crucial for correct diagnosis, as detailed in many diagnosis and management guidelines, such as the latest American Academy of Pediatrics (AAP) guideline (2013) and other similar guidelines worldwide.³,⁴

Despite continuing medical education, it has been shown that medical students who received formal guidance in standard otoscopy initially demonstrated significant gains in pediatric otoscopy skills compared to students with only routine immersion learning exposure. However, such learning abilities diminish over time, emphasizing the need for continued “hands-on” exposure to reinforce the otoscopist’s skills.⁵ Besides AOM, appropriate diagnosis of more chronic ear diseases, such as otitis media with effusion (OME) and its sequelae is of clinical importance.⁶

Diagnosis of OM using the standard otoscope has remained unchanged for over half a century and is largely

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dependent on the physician’s experience, using white-light or light-emitting diode (LED) illumination. The addition of pneumatic otoscopy may be helpful in difficult-to-diagnose cases, as recommended by the AAP guideline.\textsuperscript{3,7}

In general, otoscopy may be a challenging task, especially in infants and toddlers, and requires repeated training before some proficiency is achieved. Difficulties include obstructing cerumen, a noncooperative child, anxious parents, visualizing the external ear canal walls instead of the TM, misinterpretation of otoscopic findings, and insufficient illumination.

In several countries worldwide, in-office tympanometry is available and in use for OM diagnosis. Its use also adds supporting data on middle ear status to the clinical judgment of whether middle ear effusion (MEE) is present or not: the 226-Hz tympanometer is designed for children aged >6 months and the 1000-Hz tympanometer for infants aged <6 months.\textsuperscript{8,9} In addition, the existence of middle ear fluid (MEF) in chronic cases is important for therapeutic decision making, given that myringotomy without the prospect of treatment is not accepted for diagnostic purposes.

In recent years, innovative technologies have been gradually introduced to overcome some of the limitations of standard otoscopy. The advantages of these methods include ease of performance, simple interpretation, rapid results, and high reliability. In this article, we review these techniques, as we anticipate that some of them will be implemented in clinical practice over the next several years.

**Methods**

We searched for the following keywords: [“otitis media” (OM) or “acute otitis media” (AOM) or “serous otitis media” (SOM) or “middle ear with effusion” (MEE) or “otitis media with effusion” (OME) or “middle ear fluid” (MEF) or “chronic otitis media” (COM), ie, chronic perforation without drainage, or “chronic suppurative otitis media” (CSOM), ie, chronic drainage with perforation] AND “diagnosis” AND [“tympanic membrane” (TM) or “eardrum” or “drum” or “middle ear”] AND “human” AND “ear” AND “tympanic membrane” in various electronic databases: MEDLINE (via PubMed), Ovid Medline, Google Scholar, and Clinical Evidence (BMJ Publishing). These databases were searched from January 1, 2005, through April 30, 2018, for manuscripts in the English language. All 4 authors reviewed the retrieved manuscripts and chose to present the relevant emerging techniques in the context of OM, specifically among the pediatric population. The theme of this review is narrative, and no meta-analysis could be performed due to the heterogeneity of the techniques and their different stages of development.

**Results**

Initial search revealed 549 publications, which were then reduced to 47 publications reporting on 12 new techniques for OM diagnosis, after removing duplications, irrelevant articles, and studies in animal models. Supplemental Table S1 (available in the online version of the article) summarizes novel techniques for OM diagnosis in different stages of development and research. We herein provide details on the mechanism and clinical utility of each technique.

**Spectral Gradient Acoustic Reflectometry**

Acoustic reflectometry measures the level of sound transmitted and reflected from the middle ear to a microphone located in a probe tip placed against the ear canal and directed toward the TM. The first reports on its utility in OM diagnosis appeared in the 1980s.\textsuperscript{10} Yet, several publications in the years after did not recommend it, due to its high cost without clear benefit for the individual patient, inability to differentiate between AOM and MEE, and inability to allow for identification of subpopulations with good or poor progression.\textsuperscript{11,12}

Spectral gradient acoustic reflectometry does not require an airtight fit in the external ear canal (unlike tympanometry or the previous acoustic reflectometry devices), can be successfully performed even with a struggling child, and releases a chirping sound that most children find pleasurable (Figure 1). Several recent studies showed the clinical utility and simplicity of this improved method to detect MEE, even when the examination is performed by parents who had received a short training.\textsuperscript{13-15} Yet, it could not distinguish AOM from MEE\textsuperscript{16} and did not correlate with the severity of hearing loss associated with MEE presence, as observed in otoscopy and qualitatively measured with tympanometry.\textsuperscript{14}

![Figure 1. Cumulative proportions of the acoustic reflectometry angle values in relation to 5 otoscopic diagnoses.](image-url)
Digital Otoscopy

Digital otoscopy has been in use for a decade, but only recently has telemedicine enabled remote review and analysis of these images. In a study by Moberly et al., high-definition still images of the TM were taken by digital handheld smartphone-enabled video otoscopy, which were then separately reviewed by 12 neurotologists, using an online diagnostic assessment tool (Figure 2). Responders were asked to give their diagnosis, based on images previously obtained from 7 common middle ear/TM diseases, which served as “reference” images for those images that were obtained from “real” patients. Their answers were compared to the gold-standard clinical otomicroscopy, coupled with pneumatic otoscopy when needed, along with the diagnostic data from audiometry and tympanometry. Participants rated their degree of confidence for each diagnosis. While the average percentage correct score for normal TM images was medium to high (72%), the overall accuracy of diagnosis for middle ear pathologies ranged from low, 48% (TM perforation), to very high, 100% (tympanostomy tube [TT] in place). Some pathologies were specifically more difficult to diagnose (ie, OME) and had even lower scores. This technique possibly enables the nonexperienced otoscopist to consult with a specialist when deemed necessary.

**Tympanic Membrane Image Analysis**

This technique relies on automated software analysis of standard otoscopy images obtained from a commercial video-otoscope (Figure 3). Of 562 images obtained from children living in a rural South Africa area and were available for analysis by the automated software device, 489 were analyzed by image-processing software techniques. Of them, 80% were used to train the software system, and the other 20% were used to validate and test the system. For the purpose of algorithm formation for the diagnostic decision of the otoscopic images, 2 experienced otologists validated and categorized otoscopic images as (1) obstructing cerumen or foreign body in the external ear canal, (2) normal TM, (3) AOM, (4) OME, and (5) COM. This bank of images was the standard reference to which the other images could be compared.

For the 20% images that were not used to train the software, an accuracy of 80.6% was achieved for the diagnosis of images taken with the commercial video-otoscope, which compares favorably to the average diagnostic accuracy of OM diagnosis using standard otoscopes among pediatricians (~80%), general practitioners (64%-75%), and otolaryngologists (73%). An overall accuracy of 78.7% was calculated for images captured on site with the low-cost custom-made video-otoscope.

**Multicolor Reflectance Imaging**

The addition of multicolor imaging capabilities to the “standard” otoscope enables superior characterization of the middle ear contents by exploiting changes in tissue absorption and light scattering of the TM brought about by pathologic changes (Figure 4). Possible advantages of this technique include an increase in image contrast; clear visualization of middle ear elements; better assessment of TM vascularity (increased absorption in the blue and green regions), which is a hallmark in evaluating several middle ear pathologies; and improved demarcation of critical morphological structures, including the malleus and the promontory. These details cannot be assessed in standard otoscopy.

In a pilot study by Valdez et al., narrowband reflectance image sequences were obtained from healthy volunteers.
(normal TM, served as a reference for other pathologies), from patients scheduled for TT placement, and from patients undergoing congenital cholesteatoma excision. For the pathologic conditions, the captured high-definition images enabled improved outlining of middle ear mucosal structures, thus showing MEE and the presence of keratin (Figure 5). Because the metabolic activity in the middle ear is different in AOM and MEE states, this technique can potentially differentiate between these 2 conditions in an objective manner.

**Anticonfocal Middle Ear Assessment**

This technique relies on the inflammatory state of the middle ear mucosa, which is directly linked to tissue metabolic activity and thus to its blood content. As blood is the main absorber in mucosal tissues, increased metabolism, such as seen in OM cases, would result in a higher absorption coefficient with a concomitant decreased reflection signal. The presence of middle ear fluid (serous or purulent) does not interfere with such measurements.

An anticonfocal system combined with spectroscopic measurements in the visible and near-infrared range was proposed to reject unwanted signals from the TM and measure the blood content within the middle ear cavity. In a study by Jung et al,\textsuperscript{24} the anticonfocal system measured the severity of inflammation in patients with AOM defined by an inflammation index. Results showed effective rejection of signals from the TM while still detecting signals from the middle ear mucosa, thus allowing reliable assessment of the inflammatory state within the middle ear cavity. A remaining problem was the influence of other parameters in the middle ear, such as color and translucency of the TM, which resulted in the distortion of some measurements (Figure 6).

**Optical Coherence Tomography**

Optical coherence tomography (OCT) is a relatively new, noninvasive imaging technique that uses low coherence
interferometry (LCI), first introduced for retinal imaging. Using long wavelengths allows deep tissue penetration, and low coherence of light beams allows interference patterns after reflecting off the tissue of interest and enables high-resolution visualization at the micrometer level. This has become a widely applicable technique used in many fields since the early 1990s and is also currently used for the objective assessment of MEE presence and assessing its viscosity in OM cases.\textsuperscript{25}

A portable, handheld OCT system used in a study by Monroy et al\textsuperscript{26} was developed for clinical use (Figure 7). Patients with COM and in need of surgical placement of TTs were imaged with the experimental handheld OCT. If present, MEEs were first imaged in vivo, and after myringotomy, the MEE was aspirated (ex vivo), observed, and imaged. OCT-based ear imaging showed strong potential also for structural imaging of the middle ear besides the characterization of the viscosity of MEEs noninvasively and in vivo. Subsequent reports from this group using this technology visually demonstrated the content of the middle ear before surgery in different inflammatory states, such as planktonic bacteria, biofilm, and the middle ear fluid itself (Figure 8).\textsuperscript{27,28} It is still unclear if the diagnosis of preoperative planktonic bacteria can justify oral antibiotics before surgery or even defer it.

**Quantitative Pneumatic Otoscopy**

The combination of OCT and pneumatic otoscopy enabled measuring minute deflections of the TM from insufflation pressure stimuli. Shelton et al\textsuperscript{29} performed such a study in various TM locations in 15 otherwise healthy volunteers.
and patients with MEE altogether. They showed that they were able to quantitatively differentiate normal ears from ears with MEE (Figure 9). It has not been shown to be superior to standard otoscopy. This technique can be helpful at times when such a distinction is hard to make and in conjunction with the clinical scenario of subjective hearing loss or delayed language acquisition, as well as with an abnormal audiometric evaluation.

**Transmastoid Ultrasound**

Ultrasound waves have been previously applied in MEE diagnosis via the external ear canal. Although potentially useful, it requires a water medium instilled into the ear canal as a coupling medium and is considered relatively invasive.

An innovative approach suggested probing the mastoid with an ultrasound transducer to characterize the mastoid and thus identify MEE.\(^{30}\) When air cells in the mastoid are filled with air and fluid, a wide range of intensities and amplitudes is seen. Once mastoid air cells are fluid filled, this variance decreases. In a report by Chen et al\(^{30}\) of 20 normal ears, 15 ears with MEE confirmed by otoscopy alone, and 18 ears with MEE confirmed by TT surgery, the authors showed an increase in the Nagakami parameter, a physical parameter for density measurement in the mastoid area, when MEE was present (Figure 10). A receiver operating characteristic analysis revealed an 81% diagnostic accuracy for this technique.

**Wideband Measurements**

Wideband immittance testing was developed to evaluate the external ear canal and middle ear function using wideband frequencies. Wideband immittance (which includes absorbance and acoustic admittance) is measured at the external ear canal and enables analysis of the acoustic transfer functions of the ear canal and middle ear. Wideband acoustic absorbance values range from 0 to 100, where 0 represents the whole energy being reflected back to the microphone and 100 represents the whole energy being absorbed by the middle ear cleft. Advantages of wideband acoustic absorbance include short duration, a continuous broad frequency response between 0.25 and 8 kHz, the option to measure pressurized or ambient responses, and the ability to measure reflectance independent of changes in ear canal pressure.

In a study conducted by Nguyen et al,\(^{31}\) the authors reported on complex broadband measurements performed on 5 TMs containing biofilms, fluid, or both. After visualization and confirmation of biofilm presence using OCT, a sealed probe was inserted in each ear, and complex broadband measurements after stimulus over the frequency range of 0.2 to 6 KHz were recorded. Acoustic reflectance (the ratio between backward pressure wave to forward pressure

\[ \text{Figure 9.} \quad \text{(a) Compliance in a healthy left ear as a function of the tympanic membrane (TM) location; (b) scatterplot of healthy subjects under healthy (green circles) and Valsalva (blue squares) conditions, as well as subjects with middle ear effusion (red diamonds).} \]

\[ \text{Figure 10.} \quad \text{Transmastoid ultrasound system comprises a 2.25-MHz delay-line transducer, portable ultrasound pulser-receiver, and computer. (Republished with permission from Chen CK, Fang J, Wan YL, Tsui PH. Ultrasound characterization of the mastoid for detecting middle ear effusion: a preliminary clinical validation. Sci Rep. 2016;6:27777.)} \]
wave) and impedance (the addition of true and theoretical resistance) were collected for each ear and compared to normal reference ranges. The authors used wideband measurements to assess middle ear fluid characteristics after OME diagnosis had been established.

In their reports, the authors used the acoustic properties of ears with confirmed bacterial biofilms and showed that compared to the known acoustic properties of normal middle ears, each of the ears with a bacterial biofilm had an elevated power reflectance in the 1- to 3-kHz range, corresponding to an abnormally high resistance (Figure 11). Thus, this is a possible tool for assessing the viscosity and content of the MEE in chronic cases when other measurements are not possible (ie, perforated TM) or convincible (tympanometry C measurements in the presence of clinical SOM).

### Tympanic Membrane Thickness Mapping

Low coherence interferometry (LCI) can also use a low coherence light source to accurately measure multiple-layer membranes at the micrometer level, such as the TM. A combined LCI-otoscope system was used to reconstruct a “true” TM image upon which a thickness distribution map was superimposed.

In a study by Pande et al., 6 abnormal human TMs were assessed in vivo to show thickness distributions across different TM regions (Figure 12). TMs were scanned and video recorded at 500 different TM locations, which were later reconstructed using a mosaicking algorithm. The LCI portion of the system enabled the researchers to later superimpose thickness distribution maps comprising the mean of 100 measurements at the same location onto these images. All 6 TMs had similar thickness distributions at distinct TM locations, with only 10% variability (all 4 TM quadrants, pars flaccida alone, and pars tensa alone were compared and analyzed). When OM or COM were present, the thickness of the TM was 100% to 200% that of a normal TM, thus giving the thickness distribution maps with mosaicking visualization a promising future in TM pathology diagnosis, which may indicate pathological middle ear changes.

### Shortwave Infrared Imaging

Shortwave infrared (SWIR) otoscopes use longer wavelengths than near-infrared and visible light. Such wavelengths show less scattering properties, giving enhanced sensitivity to chromophores (water, lipids, collagen). Imaging with this technology enhanced the TM transparency and intensified contrast when fluid was present compared to visible light images, which showed only a miniscule change in contrast. In a study by Carr et al., 18 TMs of 10 adults and one 3-dimensionally printed middle ear model were used to test this method in the
Figure 12. (a) Mosaicked tympanic membrane (TM) image. (b) Thickness distribution map shown as a surface plot (thickness values, \(\mu\)m). (c) Corresponding video-otoscope image of the TM. (d) Thickness distribution map overlaid on the mosaicked image (thickness values, \(\mu\)m).

Figure 13. Outline of the middle ear structures as seen by standard otoscopy and shortwave infrared (SWIR): chorda tympani (ct), malleus (m), incus (i), stapedial tendon (st), cochlear promontory (p), and round window (rw) niche.
differentiation of normal ear (aerated ear with a normal-appearing TM, without MEE) from MEE (Figure 13). The authors showed the anatomical differences between visible light otoscopy and SWIR imaging in healthy ears. The SWIR light otoscopy extended the available evaluation of middle ear pathologies to a regimen in which endogenous contrast of middle ear fluid and anatomy may be assessed more objectively given the inherent properties of these low wavelengths.

**Wideband Acoustic Transfer Functions**

Wideband acoustic transfer functions (WATFs) measure middle-ear function across a broad frequency spectrum, 0.25 to 8 KHz (unlike tympanometry, which uses 1 frequency). WATFs are measured in the external ear canal and provide a spectral analysis and acoustic transfer function of the external ear canal and the middle ear cleft. WATF measurements have been successfully recorded in infants and children, as well as for non-OM indications, but the accuracy and interpretation of the readings were not always consistent with other methods, such as tympanometry or acoustic reflectometry.

In a cross-sectional study by Ellison et al., 53 ears in 44 children with OME scheduled for TT insertion were matched with 59 ears in 44 healthy children with no otologic history or findings. They measured 3 parameters to assess preoperatively MEE in the OME group, later to be confirmed by myringotomy and concomitant TT insertion: acoustic absorbance, measured as the energy reflectance (ratio of reflected to incident energy), admittance phase, and magnitude (inverse of impedance). They showed that the absorbance was reduced in ears with MEE compared to ears from the control group. An index combining the 3 tested parameters was the most accurate to predict MEE presence.

Absorbance varied systematically with TM mobility based on data from pneumatic otoscopy (Figure 14).

**Implication for Practice**

Most technologies described in this review are emerging and cannot be found in widespread use due to many reasons; the first and foremost is that they have not been shown to be statistically superior to otoscopy (standard and pneumatic) in diagnosing OM. To achieve common clinical use beyond the initial discoveries of these diagnostic techniques for OM, future in vivo imaging/measuring devices should be easy to use and easy to teach. They should feature low-cost probes and transducers, have simple designs with fast imaging acquisition modalities, and prove superior diagnostic utilities to standard otoscopy. In our view, the techniques that seem to be most promising are digital otoscopy, optical coherence topography, and SWIR. The achievement of these goals warrants the engagement and close collaboration between engineers and clinicians. Therefore, the appearance of these tools in daily practice is dependent on their success in clinical trials and their future market cost.

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**Author Contributions**

Tal Marom, conceptualized and designed the study, performed statistical analyses, wrote the manuscript, critically reviewed the manuscript, and approved the final manuscript as submitted; Oded Kraus, collected the data, critically reviewed the manuscript, participated in data analysis, and approved the final manuscript as submitted; Nadeem Habashi, critically reviewed the manuscript, participated in data analysis, and approved the final manuscript as submitted; Sharon Ovnat Tamir, conceptualized and designed the study, performed statistical analyses, wrote the manuscript, critically reviewed the manuscript, and approved the final manuscript as submitted.

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**Supplemental Material**

Additional supporting information is available in the online version of the article.

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