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ORIGINAL RESEARCH

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Multimodal diagnosis of cerebrospinal fluid rhinorrhea: State of the art review and emerging concepts

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Abstract

Objective: Currently, diagnosis of cerebrospinal fluid (CSF) rhinorrhea relies on a multimodal approach, increasing costs and ultimately delaying diagnosis. In the United States and internationally, the crux of such a diagnosis relies on confirmation testing (via biomarkers) and localization (e.g., imaging). Biomarker testing may require analysis at an outside facility, resulting in delays diagnosis and treatment. In addition, specialized imaging may be nonspecific and often requires an active leak for diagnosis. There remains a clear need for innovative new technology.

Methods: A comprehensive review was conducted on both foundational and innovative scholarly articles regarding current and emerging diagnosis modalities for CSF.

Results: Current modalities in CSF rhinorrhea diagnosis and localization include laboratory tests (namely, B2T immunofixation), imaging (CT and/or MRI) with or without intrathecal administration, and surgical exploration. Each of these modalities carry flaws, risks, and benefits, ultimately contributing to delays in diagnosis and morbidity. Promising emerging technologies include lateral flow immunoassays (LFI) and biologically functionalized field-effect transistors (BioFET). Nevertheless, these carry some drawbacks of their own, and require further validation.

Conclusion: CSF rhinorrhea remains a challenging diagnosis, requiring a multimodal approach to differentiate from nonpathologic causes of rhinorrhea. Current methods in diagnosis are imperfect, as the ideal test would be a readily accessible, inexpensive, rapid, highly accurate point-of-care test without the need for excess fluid or specialized processing. Critical work is being done to develop promising, new, improved tests, though a clear successor has not yet emerged.

Level of Evidence: N/A

KEYWORDS

beta-2-tranferrin, CSF leak, CSF rhinorrhea, emerging technologies

1 | INTRODUCTION

An aberrant conduit between the intracranial space (specifically, subarachnoid) and nasal cavity or paranasal sinuses can lead to cerebrospinal fluid (CSF) rhinorrhea. Though generally rare, there are many causes for CSF rhinorrhea, such as traumatic fractures, idiopathic intracranial hypertension (IIH), congenital defects or lesions, iatrogenic injury in sinus, orbital, or cranial surgery, and deliberate opening in skull base approaches.[1] Diagnosing CSF rhinorrhea can be relatively straightforward in certain cases, such as those cases following craniofacial trauma (Figure 1A), involving large sinonasal masses (Figure 1B), and postsurgical scenarios (Figure 1C). However, CSF rhinorrhea is often a challenging diagnosis to make, even for the clinicians and surgeons trained to diagnose and treat the condition.[2]

The condition can be subtle because rhinorrhea is incredibly common in the general population. Moreover, symptoms such as headaches may be nonspecific and are of limited diagnostic value.[3] The diagnosis may be missed entirely and confused with common conditions, such as allergic rhinitis. Even when CSF leak is on the differential, the fluid can be present alongside blood or mucus, complicating physical exam and contributing to false negatives on laboratory testing.[4] These challenges may be compounded in low resource settings. Ultimately, diagnosis is currently imperfect, and often relies not only on clinical judgment, but also upon multiple different modalities to confirm and localize CSF rhinorrhea.[4] Misdiagnosis can lead to significant morbidity, such a meningitis, brain abscess, pneumocephalus, and death.[5]

This review aims to detail current methods for CSF rhinorrhea diagnosis, as well as their pitfalls, and exploring emerging, cutting-edge technologies that may improve upon current paradigms.

2 | METHODS

A focused query of PubMed and Google Scholar for relevant literature between January 1, 2000 and February 1, 2024 was performed utilizing various iterations of the search phrase "Diagnosis of Cerebrospinal Fluid Rhinorrhea." To ensure all articles regarding a particular technology were captured, further searches on the databases were carried out. Reference lists of selected articles were also evaluated for relevant literature. The focus was on current and emerging modalities (Table 1) in diagnosis.

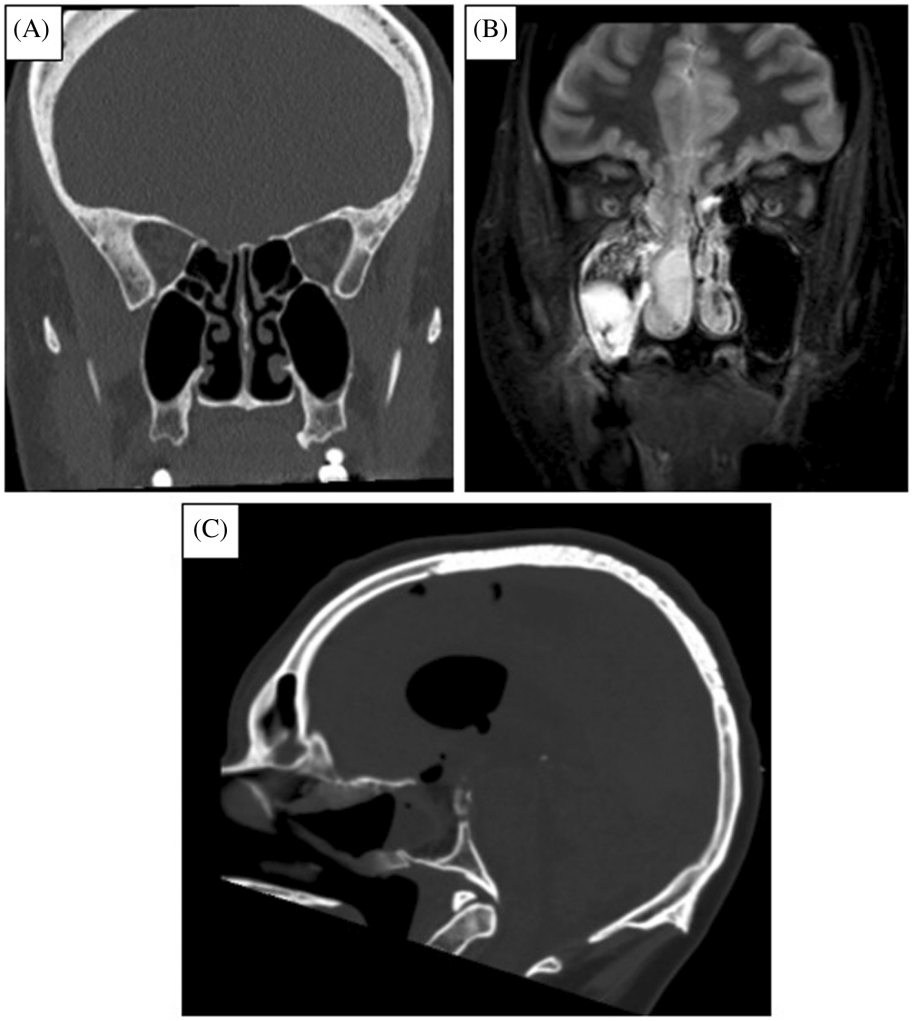

FIGURE 1 Illustrative cases of different etiologies of cerebrospinal fluid (CSF) rhinorrhea. (A) Coronal view of CT of the sinuses demonstrating right posterior ethmoid skull base defect with delayed, active CSF rhinorrhea. (B) T2-weighted images of coronal view of magnetic resonance imaging of the brain demonstrating large right ethmoid skull base encephalocele (hypointense to isointense, similar signal characteristics as native brain) with meningocele extending to floor of nose (hyperintense). (C) Sagittal view of CT of the brain of a delayed CSF leak and pneumocephalus/pneumoventricle following endoscopic skull base surgery.

TABLE 1 Current and emerging modalities in CSF rhinorrhea detection.

Target	Mechanism of detection	Time without preprocessing	Sample volume	Detection or cut-off limits	Preprocessing required?	Requires extensively trained individual?	Quantitative or qualitative	Sensitivity and specificity
Beta-2-Transferrin	Immunofixation electrophoresis (gold standard)	In-house: >2.5 h Send out: 3–5 days	200–500 µL	Detection: 2 µg/mL	Yes	Yes	Qualitative	Sensitivity: 87%–100% Specificity: 71%–94%
	Lateral Flow Immunoassay by Oh et al.	Not Stated	Not Stated	Not Evaluated	Yes	No	Semi-Quantitative	Sensitivity: 96.2% Specificity: 97.1%
	BioFET by Carey et al.	Seconds	Not Stated	7 ng/mL	No	No	Quantitative	Not Evaluated
	BioFET by Shao et al.	Seconds	Not Stated	0.01 fg/mL	Yes	No	Quantitative	Not Evaluated
Beta-trace protein	Nephelometry	15 min (not available in US)	5 µL	N/A given also present in serum	Yes	No	Quantitative with CSF/serum ratios	Sensitivity: 78%–100% Specificity 86%–100%
	Lateral flow immunoassay by Kita et al.	20 min	Swab	Cut off: 0.7 mg/L for gray zone, >1.3 mg/L for positive	Yes	No	Semiquantitative	Sensitivity: 87.5% Specificity: 100%
	Lateral flow immunoassay by Chou et al.	15 min	2 µL	Cut off: 4 µg/mL	Yes	No	Semiquantitative	Sensitivity: 90% Specificity: 97%
Dickkopf-related protein 3 (DRP3)	Immunofixation electrophoresis	>1.5 h	0.5 µL of pure CSF	Detection: 0.5 µL of pure CSF	Yes	Yes	Qualitative	Not evaluated
Tau protein	Immunofixation electrophoresis	Not stated, but presumably >1.5 h	400 µL	Cut off: 87 ng/mL	Yes	Yes	Qualitative	Not evaluated

3 | CURRENT METHODS IN DIAGNOSIS

3.1 | Clinical signs and symptoms

3.1.1 | History

Naturally, history and physical are paramount, and will often set off the cascade of tests that will lead to the diagnosis. These patients will often present with unilateral, dependent, positional rhinorrhea. The rhinorrhea should, in cases of pure CSF, be clear and of low viscosity ("watery"). They may often also endorse a salty or metallic taste. It is important to elucidate factors that may point to a potential etiology of CSF rhinorrhea, such as prior trauma, sinus surgery, or neurological surgery. Symptoms such as headaches, obesity, and pulsatile tinnitus may point to idiopathic IIH. Oftentimes, when these patients present to specialists, they will have already been trialed on and failed traditional rhinitis medications. These patients may also have been previously treated for a prior spontaneous meningitis episode or, in some cases, multiple episodes.[4,6,7]

Though some of these elucidated details may more clearly point to CSF rhinorrhea (e.g., recent head trauma), history is often nonspecific. The classic description of "clear, unilateral rhinorrhea" is of limited value, because only 30% of patients with these classic symptoms who were referred to a tertiary center rhinologist (presumably after being seen by one [or more] other physician) were actually confirmed to have CSF rhinorrhea.[8] In another study, 38% of patients undergoing endoscopic skull base reconstruction reported rhinorrhea in the postoperative setting. Of those, only 7% had an actual CSF leak, with an

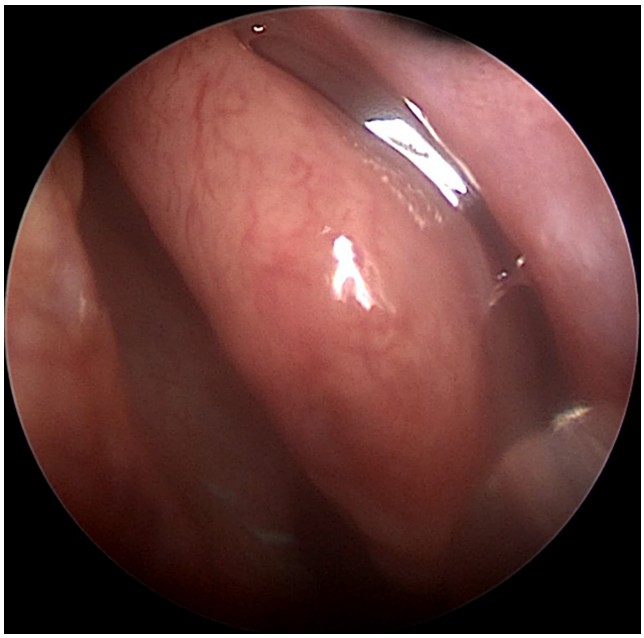

FIGURE 2 Cerebrospinal fluid rhinorrhea seen on nasal endoscopy with a "meniscus" at the left middle meatus due to a frontal sinus leak, illustrating the "meniscus sign."

overall positive predictive value of 7.6%.[3] Therefore, history alone is generally not a reliable indicator for CSF rhinorrhea and is usually combined with other diagnostic modalities to clench the diagnosis.

3.1.2 | Physical Exam and Endoscopy

On physical exam, patients may exhibit the clear, low viscosity, unilateral rhinorrhea, particularly when provoked by tilting the patient forward (known as the "tilt test"), though the overall level of evidence for this remains low.[9] Nasal endoscopy may also reveal pooling of fluid, though rarely will the actual defect be seen unless they are large in size or coming from a visible meningocele. Examiners may evaluate for a "meniscus" sign (Figure 2),[10] though, ultimately, the fluid can be difficult to distinguish from normal nasal secretions. Some providers opt to place topical fluorescein pledgets throughout the nasal cavity after drying the cavity. Fluorescein changes to a green color upon contact with CSF, and having the patient perform a Valsalva maneuver may lead to confirmation and localization.[11] A systematic review of seven studies found this to have a diagnostic accuracy rate of >96%,[12] though another systematic review astutely pointed out that only three studies before 2021 were utilized as pre-operative diagnostic tools (as opposed to intraoperative), and all located already confirmed leaks.[13] Nevertheless, patients may not be actively leaking during the time of examination, which may be due to concurrent inflammation or a ball-valve effect with intracranial contents during periods of low intracranial pressure.[4,6,7]

Classically, the "halo sign"—a ring appearing on a piece of fabric or paper after being exposed to CSF—was widely taught as a predictor for CSF rhinorrhea.[6,14] However, it has become outdated and lacks utility as it is unreliable and most fluids, when mixed with blood, can develop a halo.[15] Recently, Nulty et al. published a prospective on the utilization of an ipratropium bromide "challenge" for patients with unilateral clear thin rhinorrhea—nonresponse had a 96% sensitivity and 100% specificity for predicting CSF rhinorrhea.[16] Another component of a physical exam in patients with suspected CSF leaks is a fundoscopic exam by an ophthalmologist. The identification of papilledema may suggest IIH, raising the likelihood of spontaneous CSF rhinorrhea in certain patients, although this is also not specific.[17]

Ultimately, many of these findings may not be present during initial examination and may require subsequent visits with the same provider or other specialists prior to diagnosis. Relying on history and physical alone may lead to delays in diagnosis, which can lead to unnecessary morbidity.

3.2 | Confirmation and localization

With the "story" (history and physical) suggesting CSF rhinorrhea, focus turns toward confirmation and localization.

3.2.1 | Confirmation: Glucose testing

Quantitative glucose level analysis was one of the earliest tests developed to confirm CSF rhinorrhea.[18] Classically, CSF glucose content is thought to be about 60%–70% of that found within serum. However, various pathologies (i.e., infection) can affect the glucose content of CSF, potentially leading to false negatives. Similarly, nasal secretion glucose content can be elevated for a variety of reasons, such as in intubated patients, patients with a generalized hyperglycemic state (i.e., diabetic patients), or in those with acute viral rhinitis, leading to false positives. Overall, sensitivity may be as high as 100% but specificity is low at 45% (as determined by a small study of 19 patients).[19] Though some may use the analysis as a "rule out" test, a positive result is not diagnostic, and, as such, the test has largely fallen out of favor due to its lack of utility.[4,14] Another historical target is transthyretin, though it has also fallen out of favor due to poor accuracy.[14]

3.2.2 | Confirmation: Beta-2-transferrin (B2T) and beta-trace protein (BTP) assay

The current gold standard in laboratory analyses is detection of B2T, which was developed in 1979 as a test for CSF rhinorrhea[20] as it is a specific variant of the transferrin protein found only in CSF, perilymph, aqueous humor, and vitreous humor.[4,14] This test is not perfect; the presence of B2T in the blood can be modulated in rare cases by liver and metabolic disorders, which may lead to the presence of B2T in the sinonasal tract (false positives), while certain intracranial infections can decrease B2T within CSF (false negatives).[21] Even so,

sensitivity and specificity reportedly range from 87%–100% to 71%–94%, respectively.[4,14,22]

From a practical standpoint, the test has a series of issues related to its use. First, it conventionally requires about a half milliliter (mL) of fluid for analysis, which may be challenging for low-flow or intermittent leaks.[14] In such cases, patient may be given a specimen cup and told to collect at home and return the specimen. After collection, the specimen commonly needs to be sent to an outside facility, because the test—often an immunofixation assay—is not widely available and requires a trained technician and lab to perform (there are very few centers with in-house B2T testing).[23] This can lead to a multiday interval between collection and test result, which raises concerns about the time interval that the fluid can accurately be tested after collection, especially in cases where the specimen is collected and returned on the patient's own time. Though originally thought to be 7 days,[24] recent analysis suggests the fluid may be stable up to 14 days after collection at room temperature.[25] Assuming the fluid is tested within this time frame, the results relies on a qualitative analysis and interpretation of the presence of bands that may suggest B2T. That lack of quantitative testing can lead to human error. Moreover, even if a facility were to invest in the training and infrastructure needed to perform this test in-house, the assay itself requires pre-processing (dilutions) prior followed by 3–6 h to perform the gel electrophoresis and subsequent immunoassay, precluding its use in time-sensitive situations.[14,26] Finally, these laboratory tests do not aid in localization of the defect, but merely confirmation that CSF is detected outside of the subarachnoid space.

More recently, BTP has emerged as a potential alternative endpoint for CSF detection. BTP, though present in both serum and CSF, has CSF concentrations 34–35 times that found within plasma and is absent in nasal secretions.[4,14] It has several advantages over B2T. For one, it can be measured via nephelometry, which is an automated immunological technique that uses angled, scattered light to measure protein content. Nephelometry can be performed in under 15 min and is quantitative, though also requires preprocessing.[27] Furthermore, only 5 µL of fluid are required for analysis. Nevertheless, as it is present in blood, many conditions may decrease its sensitivity, such as renal disorders.[4] A 2008 review suggested a 78%–100% sensitivity and a 86%–100% specificity.[28] Several studies comparing the clinical utility of BTP and B2T have concluded that the former is more clinically useful due to cheaper costs ($20 vs. $50 per test), decreased need for human labor, and decreased assay time without sacrificing sensitivity and specificity.[14,26,29–32] Of note, BTP detection has not undergone the U.S. Food and Drug Administration (FDA) approval process, and is not generally available for testing in the USA (though widely used in Europe).[23,33]

3.2.3 | Localization: Imaging

Most patients obtain a computer tomography (CT) scan during workup, primarily for detecting bony skull base defects, fluid accumulation in dependent areas or areas near suspicious skull base thinning/defects, and the presence of pneumocephalus. Nevertheless, CT cannot detect dural defects, so suspicious areas cannot be assumed with certainty to be the site of leak. Ultimately, in those with B2T-confirmed leaks, CT demonstrates a 70% sensitivity in finding the site of leak.[22,34] Although there is low-dose radiation associated with CT, if the patient does end up having a true leak, the scan is commonly used for intraoperative surgical navigation.[22] In cases of postoperative/post-traumatic patients (i.e., after sinus or skull base surgeries or injuries), new or specific patterns of pneumocephalus on CT scan can be suggestive of a CSF leak.[35,36]

In cases where CT fails to determine the site of leak, magnetic resonance imaging (MRI) may be obtained. CSF exhibits T2 signal prolongation, allowing for differentiation from other fluids.[11,22] As CSF appears hyperintense with brain parenchyma appearing hypointense, heavily T2-weighted sequences, such as constructive interference in steady state, can differentiate CSF; CSF leaks can be localized while also determining whether encephaloceles are present.[11] MR cisternography (MRC) is a modification of MRI techniques which utilizes high-resolution scanners, commonly with patients in the prone position to provoke leaks. However, this modality depends on an active leak to confirm and localize CSF rhinorrhea, thus carrying a 56%–94% sensitivity and a 57%–100% specificity.[22] When CT/MRI fails and there is a high suspicion or laboratory confirmation of a leak, or if there are multiple candidate defects, a CT cisternogram or contrast-enhanced MRC with intrathecal contrast injection can be pursued for localization. Iodine contrast for CT is FDA approved for injection, though gadolinium injection for MRI is off label.[11,22] Nevertheless, contrast injection carries the risks of neurotoxicity and risks associated with lumbar puncture. Furthermore, this modality requires an active leak for diagnosis and localization; this can be somewhat mitigated by MRI, which can be done up to 24 h after injection, and thus can be delayed until the patient manifests a clinical leak.[22]

Finally, nuclear medicine (radionuclide) cisternography can also be considered, which entails an intrathecal injection of a radiotracer (often technetium-99 or indium-111). Cotton pledgets are then placed in the nasal cavity 24–48 h later to capture extravasation of the radiotracer, and analyzed for radioactivity.[22] However, this is a lengthy and uncomfortable test for patients, with large variability in location of pledget placement based on surgeon skill and patient anatomy; even with consistent and complete placement, mucus will generally mix throughout the nasal cavity, giving little information on location.[37] Ultimately, a meta-analysis of eight radionuclide cisternography cohort studies determined that sensitivity and specificity were 0.90 (0.81–1.00) and 0.50 (0.00–1.00), indicating an unacceptably high false positive rate. The study concluded that, while CT should generally be the first line test, MRI should be second line over a radionuclide study due to improved confirmation and localization accuracy.[38]

3.2.4 | Surgical exploration and intrathecal fluorescein injection

As many leaks need to be repaired primarily, surgical exploration may also be used to confirm and/or localize leaks in equivocal cases, with the possibility of concomitant definitive treatment. If

done for the purposes of diagnosis, providers may opt for intrathecal fluorescein injection, which dyes CSF green and can be further visualized in the nasal cavity with a blue light filter (Figure 3).[4] Two systematic reviews have been published on the topic in the last few years, with results suggesting a >78% success rate in localization, though this varies with fluorescein dose.[39,40] False negatives can be obtained in patients with lumbar stenosis, insufficient dosing, small defects that ball-valve with intracranial content, low CSF volume, and adhesions in prior meningitis patients.[11] It is important to note, however, that intrathecal fluorescein administration is not FDA approved, and requires informed consent for potential side effects that can be as severe as seizures and lower extremity weakness.[4,11] After confirmation and localization, the fluorescein can also be used to confirm watertight closure, and can be administered again to detect suspected postoperative leaks if a lumbar drain were in place postoperatively.[11]

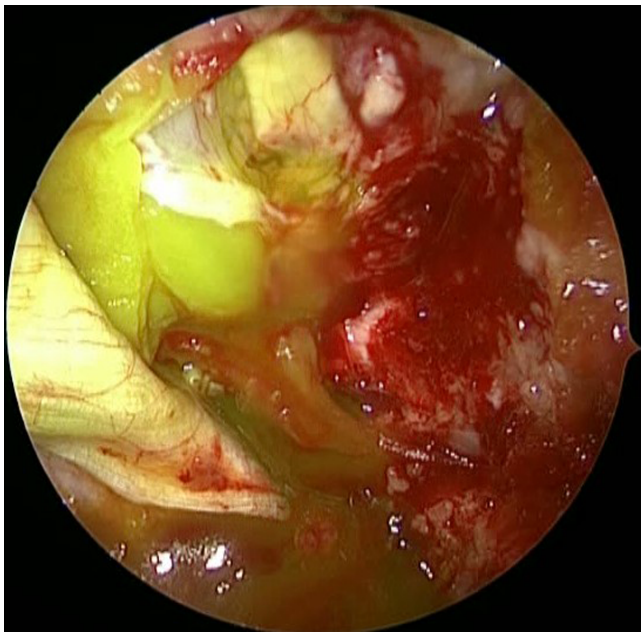

FIGURE 3 Illustrative case of intrathecal fluorescein utilized intraoperatively, which can localize and confirm closure of a cerebrospinal fluid leak. Fluorescein in the image is represented by the yellow/green fluid.

The above highlights the current state of the art for CSF rhinorrhea diagnosis, which largely still depends on a combination of clinical judgment—ascertaining the story, confirmation, and localization—and is prone to both test and human error (Figure 4). Thus, there lies a tremendous opportunity for improving this process.

4 | EMERGING TECHNOLOGIES, MODALITIES, AND METHODOLOGIES IN DIAGNOSIS

4.1 | Automated immunofixation electrophoresis devices

In 2005, Papadea and Schlosser published on a successful automated immunofixation electrophoresis system, which may preclude the need

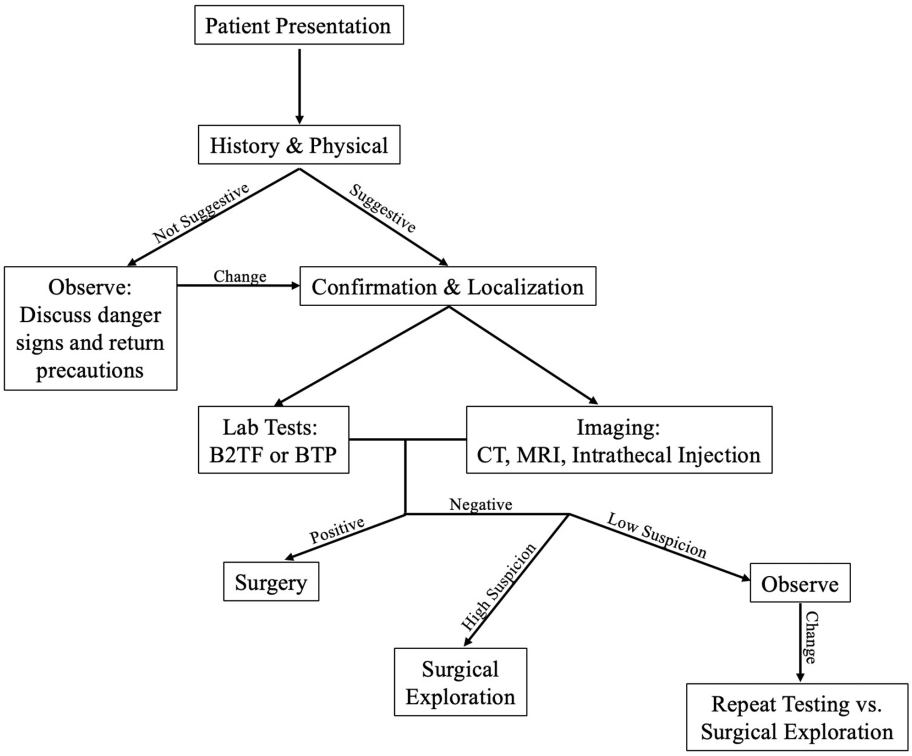

FIGURE 4 Flowchart of current diagnostic algorithm.

for skilled staffing (and thus a send out test) needed for traditional immunofixation techniques.[41] However, this did not gain traction as a widespread method, as it still required a qualitative evaluation for results and still requires hours of testing. In addition, it would require purchasing of the said system.

4.2 | Lateral flow immunoassay (LFI)

At its core, LFI leverages anti-B2T or anti-BTP antibodies to create easy-to-use and, perhaps eventually, cost-effective systems for a relatively more rapid, in-house diagnosis. Essentially, the sample is placed on a strip of paper that is already prepared with the antibodies at certain locations that undergo color change when activated. Kita et al. were the first to publish on this technology in 2018.[42] Their system tests for BTP via a three-stripe approach (i.e., there are three separate stripes of anti-BTP antibodies on a single test strip at varying concentrations), with the idea being that CSF will contain enough BTP to transverse the entire strip and activate all three stripes. They eventually tested the system with human samples,[43] and, though promising, a few challenges have emerged. First, although the entire process can be performed in 20 min, vastly faster than the current standard of care, the test still requires pre-processing (serial dilutions) of the fluid. Second, while their results suggest that only one activated stripe should be considered CSF negative, and three CSF positive, the test created a "gray zone" with two activated stripes. The authors mention these samples tended to be those contaminated with blood, which further limits use in trauma patients or postoperatively. If the "gray zone" is considered a negative test, this system had a maximum sensitivity and specificity at 87.5% and 100%, respectively.

Oh et al. created a similar system, which leverages the lack of a sialic acid residue on the B2T side chain, as opposed to serum transferrin.[44] Their strips initially expose the sample to lectin, a known sialic acid binding substrate, facilitating the capture of serum transferrin. Subsequently, the sample migrates to the second stripe, housing antitransferrin antibody. Assuming the first stripe effectively captured all the serum transferrin, only B2T should be detectable in a genuine CSF sample, thereby triggering activation of the second stripe. In their analysis of CSF, the system demonstrated a 96.2% sensitivity and 97.1% specificity. However, again, the system requires preprocessing by conjugating all transferrin proteins with gold nanoparticles, followed by centrifugation to recover the complexes, to eliminate proteins that can create false negatives and positives.[44] The system also necessitates image analysis to compare the signal intensity to that of the control stripe, which adds time to the procedure.[44]

Finally, Chou et al.'s LFI iteration is much simpler in concept, utilizing a single stripe of anti-BTP antibodies, demonstrating 90% sensitivity and 97% specificity.[45] As discussed, BTP is also present in the serum, although at lower concentrations. As such, image analysis is needed to quantify intensity of signal.[45] Sample preprocessing is also required for this system.[45]

4.3 | Digital biosensing platforms

Metal oxide semiconductor field effect transistors (MOSFET) have emerged as powerful techniques for biologic molecule detection. In short, a MOSFET system has three parts: (1) a power source where a current is generated; (2) a gate that the current is modulated through; and (3) a detector that the current reaches after the gate. Biologically functionalized field effect transistor (BioFET) is a subtype of MOSFET that can be used to detect biological molecules by coating the gate with a substrate that interacts with a given molecule, thus modulating the electrical signal in the presence of the molecule.[46] Carey et al. first published on the application to CSF fluid detection in 2019; they reported a BioFET system in which they fashioned the gate into disposable strips coated with B2T antibody. With the system, B2T was detectable at CSF levels as low as 0.1 ng/mL and as high as 100 μg/mL (with actual B2T levels significantly lower) within just 5 min without the need for any pre-processing requirement.[47] When subsequently tested on CSF collected from lumbar drains of nine patients, it was able to detect B2T levels up to five orders of magnitude below the lower limit of traditional immunofixation technique—7 ng/mL.[48] However, this has yet to be evaluated in a standardized fashion to determine sensitivity and specificity.

A second group also published on a similar topic in 2022. Despite achieving the capability to detect B2T levels as low as 0.01 fg/mL, the BioFET device is designed to identify various types of transferrins, necessitating prior isolation of B2T through affinity chromatography. Consequently, this process extends the testing duration to 1 h and requires trained personnel to carry out the isolation step.[49]

4.4 | Optical technologies

Recently, Klein et al. developed a sinuscope that emits and detects a narrow band 1480 nm laser, which is absorbed by CSF, and thus may be used for detection. While it proved successful in detecting CSF in a porcine model, the major shortfall is that water, rhinorrhea, and blood would also absorb this spectrum. This restricts its utility in both confirming and localizing CSF when analyzing contaminated samples.[50]

4.5 | Novel CSF biomarkers

Though most technologies have been focused on detecting B2T or BTP, many are searching for novel and alternative targets that may be more specific to CSF, especially in certain disease states (e.g., renal or liver disease). Two emerging targets currently under investigation include the Dickkopf-related protein 3 (DRP3) and Tau protein. DRP3 is found in CSF, not serum, and is not cleared by the kidneys. It has been shown to be effective in detecting CSF, but currently published detection methodologies are still utilizing immunofixation techniques.[51] Tau protein has been tested in a small sample of humans and found to have 100% sensitivity and specificity, though, again,

entails immunofixation and needs preprocessing, limiting utility in its current form.[52]

5 | CONCLUSION: IN SEARCH OF THE IDEAL TEST AND THE FUTURE

The challenge with CSF rhinorrhea is that it can be difficult to distinguish from physiological rhinorrhea, may not be clinically apparent during all encounters, can present subclinically, and has a variety of causes that can be difficult to discern. Thus, the ideal test is one that is not only accurate, but also rapid without need for preprocessing, can be performed in-house as a point-of-care test, inexpensive, works despite contamination (e.g., blood, mucus), can be easily conducted without specialized training, and readily accessible in all settings. Currently, confirmation and localization of CSF rhinorrhea is reliant on a multimodal approach, including clinical judgment, laboratory testing, imaging, and, occasionally, surgical exploration. The current gold standard laboratory testing is done via immunofixation of B2T, which is time-intensive, requires a relatively large amount of fluid, requires a send out test due to the need for specialized expertise, and may take days to obtain results.

Recognizing the obvious limitations, many have attempted to improve upon the system. Currently, LFI has emerged as a promising published modality for CSF rhinorrhea detection, but not without limitations. LFI is semi-qualitative, given the need to interpret equivocal results, and requires pre-processing, which can limit use when immediate results are needed. BioFET has similarly emerged as a promising modality, but clinical utility (sensitivity and specificity) and accuracy with contamination has still yet to be determined. Ultimately, there still remains a clear need for innovation and improvement to create a true paradigm shift.

CONFLICT OF INTEREST STATEMENT

Edward C. Kuan is a consultant for Stryker and 3-D Matrix, and receives royalties from Springer Books. These disclosures are not relevant to the current research. The other authors declare no relevant conflict of interest.

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