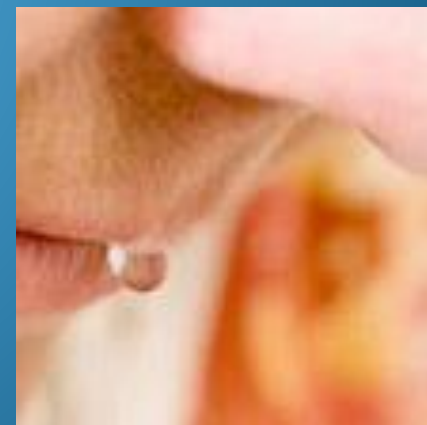


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# Diagnosis of CSF Rhinorrhea: an evidence-based review with recommendations

*By: Abdulrahman A. Al-Humaizi*  
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# Objectives

- Introduction
- Materials and methods
- Results
- Discussion
- Algorithm
- Conclusion

# Introduction

- Risk of meningitis, which has been reported to range from 10% to 37% during conservative management
- In a study of 160 traumatic CSF leak patients, this risk of intracranial infection has been reported to break down to:
  - 1.3% per day for the first 2 weeks after injury
  - 7.4% per week for the first month
  - 8.1% per month for the first 6 months
  - 8.4% per year

# Introduction

- Modalities for confirmation
  1. Ring sign
  2. Glucose testing
  3. Beta-2 transferrin
  4. Beta trace protein
  5. Radionuclide cisternography

# Introduction

- Modalities for localization
  1. High resolution computed tomography (HRCT)
  2. Magnetic resonance cisternography (MRC)
  3. CT cisternography (CTC)
  4. Intrathecal fluorescein (IF)

## Diagnosis of cerebrospinal fluid rhinorrhea: an evidence-based review with recommendations

Gretchen M. Oakley, MD<sup>1</sup>, Jeremiah A. Alt, MD, PhD<sup>1</sup>, Rodney J. Schlosser, MD<sup>2</sup>, Richard J. Harvey, MD<sup>3,4</sup>  
and Richard R. Orlandi, MD<sup>1</sup>

**Background:** Diagnostic strategies employed for cases of cerebrospinal fluid (CSF) rhinorrhea vary widely due to limited evidence-based guidance.

**Methods:** A systematic review of the literature was performed using PubMed, EMBASE, and Cochrane databases from January 1990 through September 2014, to examine 9 diagnostic and localization modalities for CSF rhinorrhea. Benefit-harm assessments, value judgments and recommendations were made based on the available evidence. Study exclusion criteria were language other than English, pre-1990 studies, case reports, and nonrhinologic leak. All authors agreed on recommendations through an iterative process.

**Results:** We reviewed 68 studies examining 9 practices pertinent to the diagnosis of CSF rhinorrhea, with a highest aggregate grade of evidence of C. The literature does not support the use of the ring sign, glucose testing, radionuclide cisternography (RNC), or computed tomography cisternography (CTC) for identification of CSF leak. Beta-2 transferrin is the most reliable confirmatory test for CSF leak. High-resolution CT (HRCT) is then recommended as

the first-line study for localization. Magnetic resonance cisternography (MRC) should be used for CSF leak identification as a second line for each of these if beta-2 transferrin is not available or if HRCT is ambiguous. Intrathecal fluorescein (IF) may also be of benefit in certain clinical scenarios.

**Conclusion:** Despite relatively low levels of evidence, recommendations for the diagnosis and management of CSF rhinorrhea can be made based on the current literature. Higher-level studies are needed to better determine optimal diagnostic and clinical management approaches.  
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### Key Words:

cerebrospinal fluid; CSF leak; CSF rhinorrhea; diagnosis; localization; diagnostic algorithm

### How to Cite this Article:

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Rhinorrhea is a common complaint in any rhinology practice, but the significance of this symptom is en-

tirely different when it is a manifestation of a cerebrospinal fluid (CSF) leak. CSF rhinorrhea is the result of an abnormal communication between the subarachnoid space and the sinonasal tract. It can occur following skull-base trauma, endoscopic sinus surgery, neurosurgical procedures, or have a spontaneous etiology. The latter was traditionally considered an idiopathic cause, but more recently has been shown to be associated with elevated intracranial pressures.<sup>1,2</sup>

Persistent CSF rhinorrhea necessitates surgical intervention because of the risk of meningitis, which has been reported to range from 10% to 37% during conservative management.<sup>3-7</sup> In a study of 160 traumatic CSF leak patients, this risk of intracranial infection has been reported to break down to 1.3% per day for the first 2 weeks after injury, 7.4% per week for the first month, 8.1% per month for the first 6 months, and 8.4% per year from then onward.<sup>4</sup> Although intracranial approaches were historically used for leak repairs, endonasal endoscopic

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Additional supporting information including summary tables can be found in the online version of this article.

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# Materials and Methods

- A systematic review of the literature was performed using PubMed, EMBASE, and Cochrane Review Databases from January 1, 1990 through September 30, 2014



# Results



# Modalities for confirmation

# Ring Sign



# Ring sign



- **Aggregate grade of evidence:** N/A
- **Benefit:** Rapid bedside test
- **Harm:** High potential for misdiagnosis
- **Cost:** None
- **Benefits-harm assessment:** High potential for misdiagnosis outweighs any potential benefit of early information from this test
- **Value judgments:** None
- **Recommendation level:** Recommend Against
- **Intervention:** Avoiding the ring sign in diagnosing a CSF leak.

# Glucose Testing



# Glucose Testing



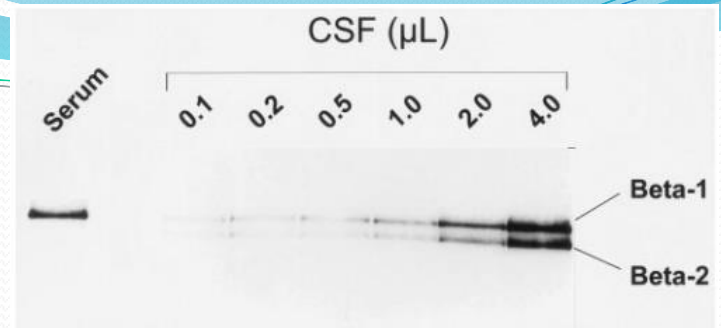
- Philips et al. assessed the glucose content in the airway secretions of:
  - 19 healthy volunteers ~ undetectable
  - 20 patients with acute viral rhinitis ~ detected in 50%
  - 24 patients with DM ~ in 90%
  - 60 ventilated intensive care unit (ICU) patients ~ in 52%.
- Wood et al. evaluated if airway glucose detection could be elicited in 30 healthy volunteers, and at what blood glucose threshold. Subjects with normal glucose tolerance were made hyperglycemic with either a 20% dextrose intravenous (IV) or 75 g per os (PO) glucose load. They found that glucose was detectable in nasal secretions at blood glucose levels of 6.7 to 9.7 mmol/L

# Glucose Testing



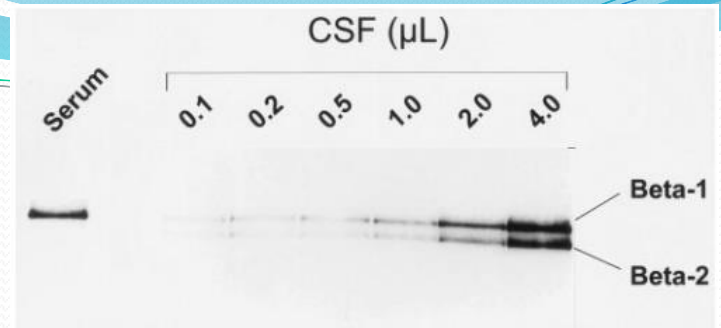
- **Aggregate grade of evidence:** C
- **Benefit:** Noninvasive, quick test
- **Harm:** High potential for misdiagnosis due to low specificity and sensitivity, with subsequent unnecessary interventions due to false positives
- **Cost:** Low
- **Benefits-harm assessment:** Potential harm outweighs benefits
- **Value judgments:** None
- **Recommendation level:** Recommendation Against
- **Intervention:** Avoiding glucose testing in diagnosing a CSF leak.

# Beta-2 transferrin



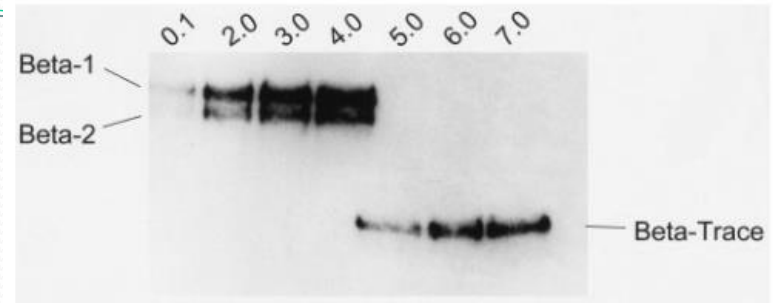
- Sensitivity: 87% to 100%
- Specificity: 71% to 100%
- Bleier et al. assessed the reliability of the beta-2 transferrin assay in CSF samples from 6 patients stored in the refrigerator or at room temperature over 7 days. There were no adverse effects on the accuracy of the test regardless of storage temperature
- Amount?

# Beta-2 transferrin



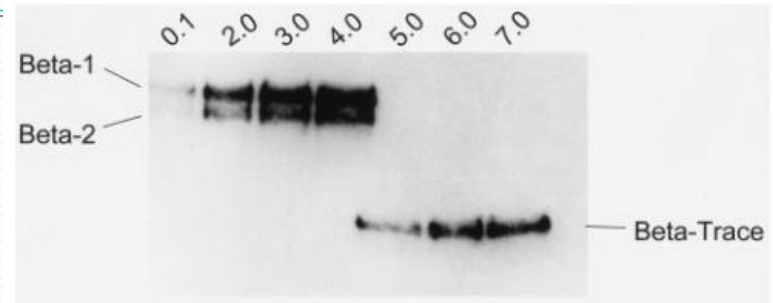
- **Aggregate grade of evidence:** C
- **Benefit:** Noninvasive, highly accurate test
- **Harm:** Delay in diagnosis due to the need to perform the test in a specialty laboratory
- **Cost:** \$37.90
- **Benefits-harm assessment:** Preponderance of benefit over harm
- **Value judgments:** Preference for high accuracy in diagnosis prior to further intervention.
- **Recommendation level:** Recommendation for
- **Intervention:** Using beta-2 transferrin testing for diagnosing CSF leaks

# Beta trace protein



- Sensitivity: 91% to 100%
- Specificity: 86% to 100%
- Because beta trace protein is present in both the blood and CSF, only at vastly different concentrations, blood levels can affect CSF levels
- ↑ with Renal insufficiency
- ↓ with Bacterial meningitis

# Beta trace protein



- **Aggregate grade of evidence:** C
- **Benefit:** Noninvasive, highly accurate test
- **Harm:** Delay in diagnosis due to the need to perform the test in a specialty laboratory; limited availability in the United States
- **Cost:** Low (20\$)
- **Benefits-harm assessment:** Preponderance of benefit over harm
- **Value judgments:** Highly reliable test for the confirmation of CSF leak is important prior to further intervention
- **Recommendation level:** Recommendation for
- **Intervention:** Using beta trace protein testing for diagnosing CSF leaks.

# Radionuclide Cisternography

- Sensitivity: 76% to 100%
- specificity of 100%
- Because of its high cost, the fact that it has a lower sensitivity than beta-2 transferrin, and that it is invasive, they recommend beta-2 transferrin be repeated if necessary prior to proceeding with RNC for CSF leak confirmation

# Radionuclide Cisternography

- **Aggregate grade of evidence:** C
- **Benefit:** Moderately accurate for confirmation; localization limited to side of skull base that is leaking
- **Harm:** Invasive study–potential risk of lumbar puncture and intrathecal contrast injection
- **Cost:** High (\$693.64 to \$705.08)
- **Benefits-harm assessment:** Limited benefit with moderate potential harm and significant costs
- **Value judgments:** Low level of evidence; less accurate, more invasive, and more expensive than other available tests
- **Recommendation level:** Recommendation Against
- **Intervention:** Avoiding the routine use of RNC for confirmation of CSF leak.



# Modalities for localization

# HRCT



- Sensitivity: 44% to 100%
- Specificity: 45% to 100%
- Manes et al. looked specifically at 15 patients with spontaneous CSF rhinorrhea and negative HRCT findings. They found that all 15 spontaneous CSF leak patients with no identifiable bony defect had an olfactory cleft opacification that marked the leak site with 100% accuracy (confirmed intraoperatively)

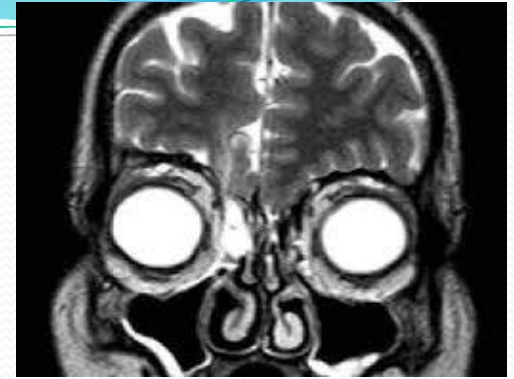
# HRCT



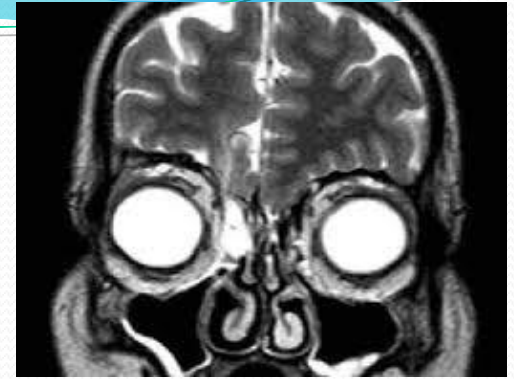
- **Aggregate grade of evidence:** C
- **Benefit:** Noninvasive, high accuracy
- **Harm:** Low risk associated with radiation
- **Cost:** Moderate (\$280.32)
- **Benefits-harm assessment:** Preponderance of benefit over harm
- **Value judgments:** Highly accurate test for knowledge of sinus anatomy and localization of a CSF leak is important for operative planning in nearly all cases
- **Recommendation level:** Recommendation for
- **Intervention:** Using HRCT for localizing CSF leaks.

# MR Cisternography

- Sensitivity: 56% to 94%
- Specificity: 57% to 100%
  
- Intrathecal gadolinium-enhanced MRC (CE-MRC)?

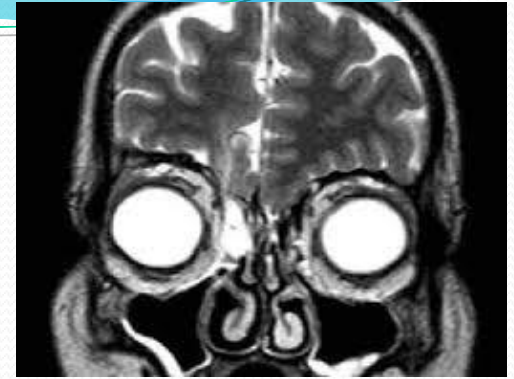


# MR Cisternography



- Aggregate grade of evidence: C
- **Benefit:** Noninvasive (unless combined with intrathecal contrast) with good accuracy.
- **Harm:** None (unless combined with intrathecal contrast).
- **Cost:** \$807.34
- **Benefits-harm assessment:** Preponderance of benefit over harm when diagnosis or site of leak is in doubt.

# MR Cisternography



- **Value judgments:** Highly accurate test for the localization of CSF leak is important for operative planning; patients may prefer a test that does not involve radiation; nearly 3 times more expensive than HRCT.
- **Recommendation level:** Recommendation for cases where cheaper or less invasive studies have failed to diagnose or localize the site of a leak.
- **Intervention:** Using MRC for localizing CSF leaks.

# CT Cisternography

- Sensitivity: 33% to 100%
- Specificity ~ 94%



# CT Cisternography

- **Aggregate grade of evidence:** C
- **Benefit:** Relatively lower accuracy than other available modalities.
- **Harm:** Invasive study–potential risk of lumbar puncture and intrathecal contrast injection.
- **Cost:** \$542.76
- **Benefits-harm assessment:** Potential harm
- **Value judgments:** Low level of evidence; lower cost compared to MRC; lower sensitivity and accuracy compared to other modalities and similar if not higher risks due to intrathecal injection.
- **Recommendation level:** Recommendation Against.
- **Intervention:** Avoid routine use of CTC for localization of CSF leaks.

# Intrathecal Fluorescein

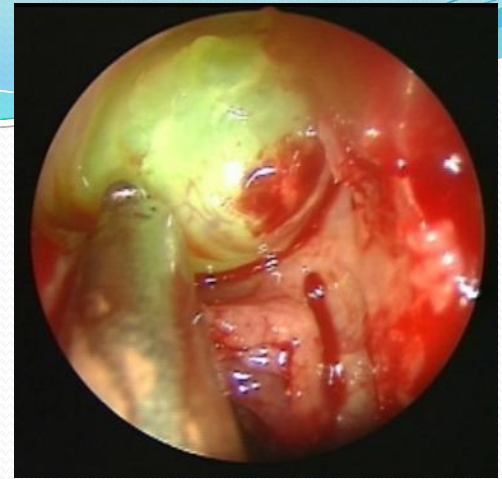


- off-label
- 15 relevant studies reported that IF identified the CSF leak site in 46% to 100% of cases.
- Seth et al. noted that whether or not IF was used intraoperatively did not have a statistically significant effect on the CSF leak recurrence rates.
- Moseley et al. surveyed 1111 members of the American Association of Neurological Surgeons, who reported ranges of 0.1 to 5 mL of 5% fluorescein diluted in 0 to 10 mL of the patient's CSF before intrathecal injection.

# Intrathecal Fluorescein

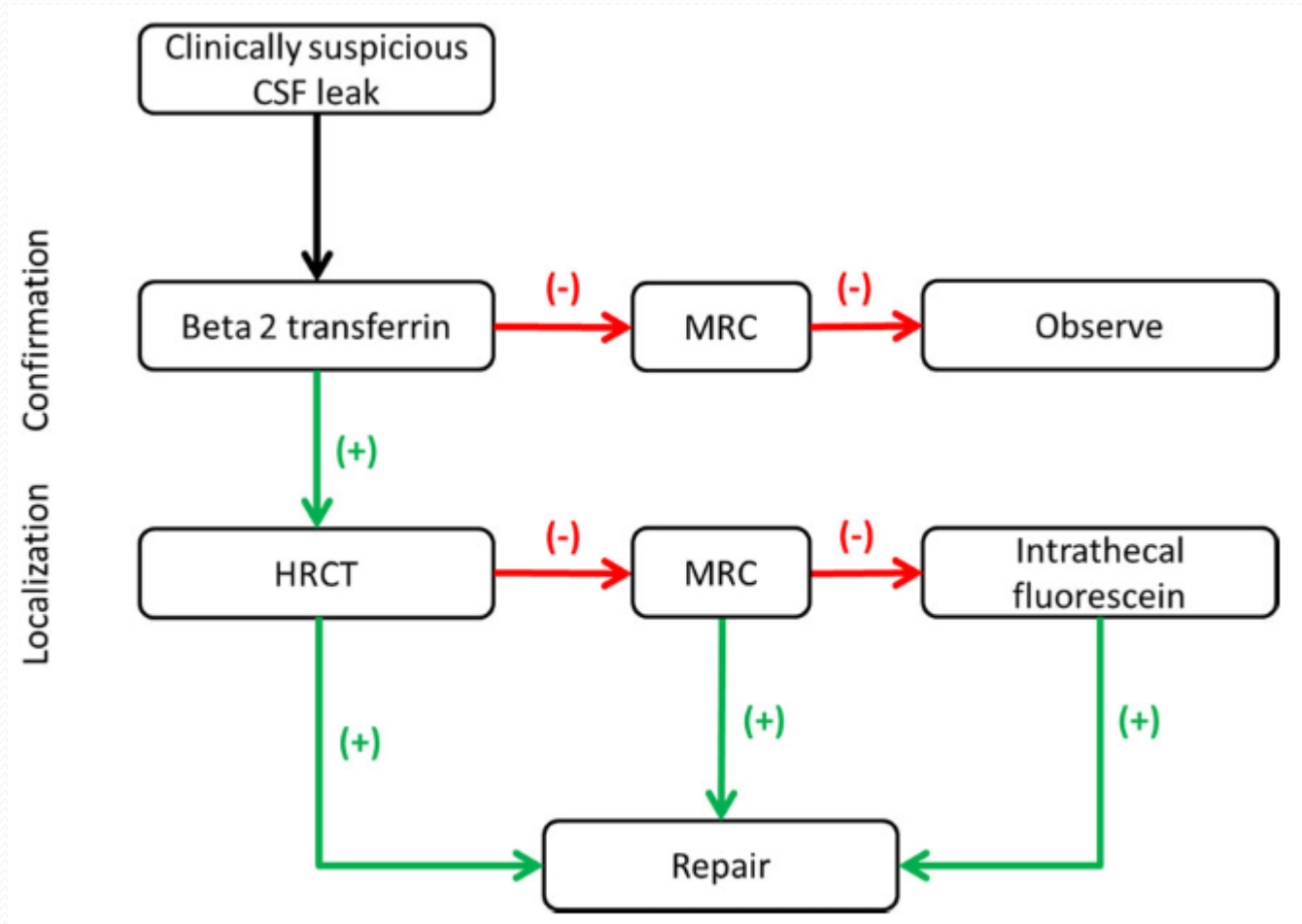
- This literature search also revealed 3 studies that addressed the use of topical fluorescein for diagnosis. In this case the fluorescein is placed topically in the nasal cavity, and when mixed with CSF, changes colour to identify the leak. These studies reported an accuracy of 100%. Controlled studies using other clear fluids, such as nasal mucus or saline, have not been conducted, so it is unclear if there is the potential for false positives with topical application of fluorescein, such as those seen in the halo test.

# Intrathecal Fluorescein



- Aggregate grade of evidence: C
- Benefit: Real-time confirmation and localization;
- Harm: Invasive study–potential risk to lumbar puncture and intrathecal injection of a neuro-irritative agent.
- Cost: \$524.88
- Benefits-harm assessment: Balance of benefit and harm;
- Value judgments: Low evidence level
- Recommendation level: Option
- Intervention: Using IF for localization of CSF leaks

# Evidence-based algorithm



# Conclusion

- This evidence-based review demonstrates that the best test for confirming the clinical suspicion of a CSF leak is a beta2 transferrin test.
- Once the leak is confirmed, it is best localized with a HRCT scan.
- MRC may be helpful if these other tests are not available or if the results are ambiguous.
- In a few cases, IF injection may be necessary to localize the leak.
- The overall level of evidence on this topic is relatively poor.
- Additional higher-level research is needed to better understand the best diagnostic method for CSF leaks.

**Thank You**