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Management of Anterior Skull Base Cerebrospinal Fluid Leaks

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Abstract

Cerebrospinal fluid (CSF) leak occurs from traumatic, iatrogenic, and idiopathic etiologies. Its timely diagnosis requires clinical, radiographic, and laboratory testing. Medical and surgical management can mitigate the risk of life-threatening infection and morbidity. This article outlines the pathophysiology, diagnosis, and management or CSF leak of the anterior skull base.

Keywords
- trauma
- skull base
- cerebrospinal fluid leak

Introduction

Cerebrospinal fluid (CSF) rhinorrhea results from a fistulous tract between the intracranial and nasal cavities. The most common etiologies include craniofacial trauma, iatrogenic injury, and neoplasia. Making a diagnosis based on physical examination can be challenging, however, current radiologic and biomarker technology has greatly improved diagnostic accuracy. Patients with untreated CSF rhinorrhea run a significant risk for meningitis, necessitating a timely diagnosis and treatment plan. The decision between conservative versus surgical management is based on the etiology, timing, and severity of the leak. This article will review the pathophysiology, epidemiology, as well as diagnostic and therapeutic options for management of CSF rhinorrhea.

CSF Physiology

CSF is a plasma ultrafiltrate which contains electrolytes, glucose, and proteins. It serves to physically support and buffer both the brain and spinal cord. CSF is formed by the choroid plexus at a rate of 0.35 mL/minute (350–500 mL/day). It circulates throughout the meninges and is reabsorbed by the arachnoid villa into the venous system. The average adult CSF volume is 140 mL; with the total volume being turned over approximately three times per day. Normal pulsations are noted in CSF pressure which are related to fluctuations in cerebral blood flow and proximity to the major branches of the circle of Willis.[1]

Epidemiology

Trauma

A total of 80% CSF leaks result from craniofacial trauma.[2] Traumatic CSF leaks have been reported to occur in 12 to 39% of skull base fractures.[3,4] Greater than 50% of these will present within the first 48 hours, 70% within 7 days, and almost all within 3 months.[3] Delayed presentations (i.e., weeks to months) could be attributed to wound contraction, tissue necrosis, resolution of edema, or increase in intracranial pressure. Leaks most commonly occur in the sphenoid sinus (30%), frontal sinus (30%), and cribriform plate/fovea ethmoidalis (23%). The firm adherence of the dura along the anterior skull base is felt to predispose this region to injury.

Iatrogenic Injury

A total of 16% CSF leaks result from an iatrogenic injury. The most common site of injury during endoscopic sinus surgery is the cribriform plate/fovea ethmoidalis (80%), followed by the frontal sinus (8%) and sphenoid sinus (4%). The most common site of injury during neurosurgical procedures is the sphenoid sinus (67%). This is directly related to the recent advances in and frequency of transnasal endoscopic approaches to pituitary tumors.[5]

Other Etiologies

The remaining 4% of CSF leaks have varied etiologies. Approximately 50% are related to CSF outflow obstruction; with 80% of these being secondary to tumors.[6] The remaining leaks generally result from hydrocephalus or benign intracranial hypertension.

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Classification

CSF Rhinorrhea

Classification systems for CSF rhinorrhea are generally based on etiology, anatomical location, or extent/size of bony defect. Most systems first separate patients into traumatic or nontraumatic etiologies. The traumatic group can be divided into craniofacial or iatrogenic trauma. The craniofacial trauma group can again be divided into acute and delayed leaks; with the acute group being further subdivided into closed head injury or penetrating injury. The iatrogenic group can be subdivided into extracranial and intracranial procedures (see ►**Fig. 1**).[7,8]

Diagnosis

Clinical Presentation

The most common clinical presentation of CSF rhinorrhea is intermittent, unilateral, clear, watery drainage. It is classically positional in nature and exacerbated by dependent head positioning (i.e., "reservoir sign"). Patients may note salty or sweet tasting postnasal drainage. Posttraumatic leaks may be more readily recognized due to associated findings such as epistaxis, periorbital ecchymosis, visual changes, anosmia, cranial nerve deficits, and pneumocephalus. Clear drainage suspicious for CSF can be grossly tested for a "halo sign." The bloody nasal drainage is allowed to drip onto filter paper. If CSF is present, it will diffuse faster than blood and result in a clear halo around the blood. Chronic CSF leaks are typically more difficult to diagnose. There are often no associated findings, and the drainage may be confused with other sinonasal disorders such as allergic, vasomotor, and nonallergic rhinitis. A low index of suspicion and delay in diagnosis can increase the risk of meningitis or brain abscess.[4]

Diagnostic Testing

Glucose oxidase: The CSF glucose concentration typically exceeds serum concentration by 50%.[9] Analysis of glucose concentration in nasal secretions suspicious for CSF has therefore been used since the late 1800s. However, high false-positive and negative rates occur for many reasons including hyperglycemia, bacterial contamination, and even excessive assay sensitivity.[5] Glucose oxidase testing is currently of historical value only.

β2 Transferrin: The β2 transferrin assay was first introduced by Meurman et al in 1979.[10] β2 transferrin is a highly specific chemical found primarily in the CSF. Extremely high sensitivity (99%) and specificity (97%) has made this test the gold standard for diagnosis of suspected CSF rhinorrhea.[11] Despite its high sensitivity and specificity, the β2 transferrin assay has several disadvantages: a requirement of 2 to 3 mL of fluid for testing, it is expensive and labor intensive to perform, and it is as "send out" test for most institutions with a 5 to 7 day turnaround time.[12]

β Trace protein (β-TP): β-TP is another diagnostic marker that has been used as a low cost, noninvasive, test for CSF rhinorrhea. β-TP is one of the most abundant proteins in CSF, and is present in other body fluids at a much lower concentration. The assay requires a small sample size (200 µL) and results can be obtained within 20 minutes.[13] It has similar sensitivity and specific to β2 transferrin assays. However this technique is still designated for research purposes only. Additionally, it is unreliable in the setting of

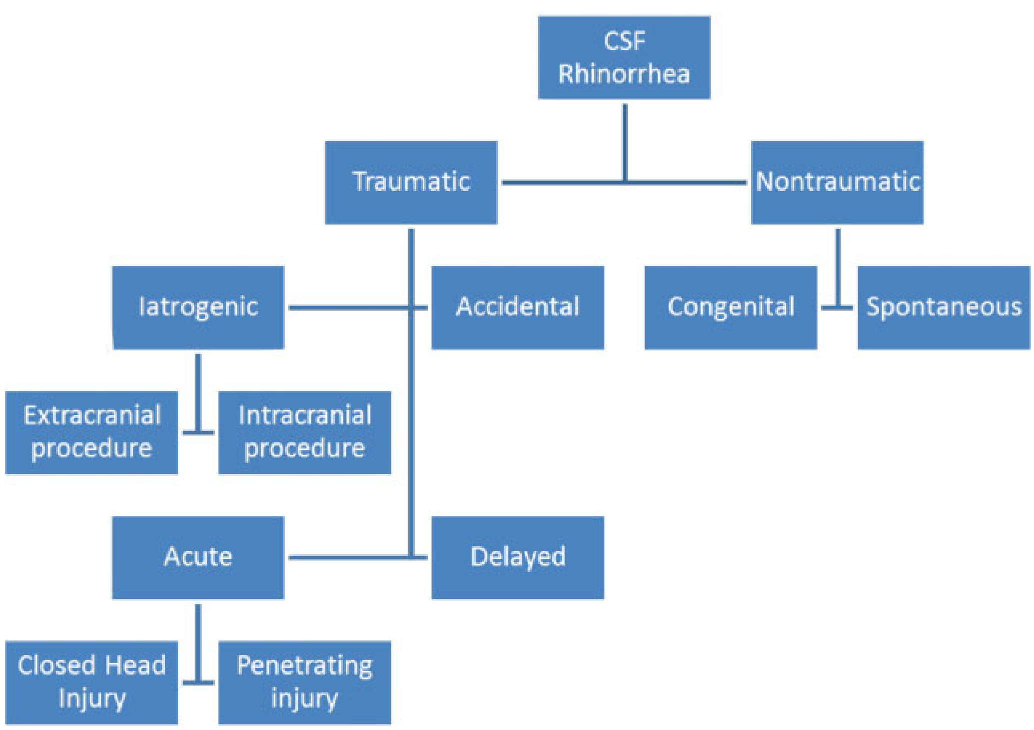

Fig. 1 Classification of cerebrospinal fluid leaks. (Adapted from Ziu et al.[7])

Table 1 Diagnosis of cerebrospinal fluid rhinorrhea

Type	Test	Notes
Clinical	Reservoir sign	Nonspecific and may be difficult to reproduce
	Halo sign	
Laboratory	Glucose oxidase	False positives and negatives; historical value only; limited by hyperglycemia and bacterial contamination
	B2 transferrin	Highly specific; long turnaround time as send out test; requires 2–3 mL of fluid
	Beta trace protein	Small sample size required but largely relegated to research purposes

renal disease and meningitis.[12] (See ►**Table 1** for summary of diagnostic testing of CSF rhinorrhea.)

Anatomic Localization

Nasal endoscopy: After confirmation of CSF rhinorrhea with diagnostic testing, localization of the dural defect should be attempted. Nasal endoscopy is rapid, cheap, and can be used to localize the side or general location of the leak. Unfortunately, in clinical practice, visualization of the actual fistula site is often challenging or impossible.

High-resolution computed tomography (CT) scan: High-resolution, thin cut ($\leq$ 1–1.5 mm) CT scanning with coronal and sagittal reconstructions is currently the gold standard for radiographic localization of anterior skull base defects/rhinorrhea. It is rapid, requires no contrast material, is relatively inexpensive, and has a sensitivity of approximately 87% for identification of CSF fistulas.[14] Coronal images are used for identification of sphenoethmoid defects, while axial and sagittal images are more accurate for identification of posterior table, frontal sinus defects (see ►**Fig. 2**).[2]

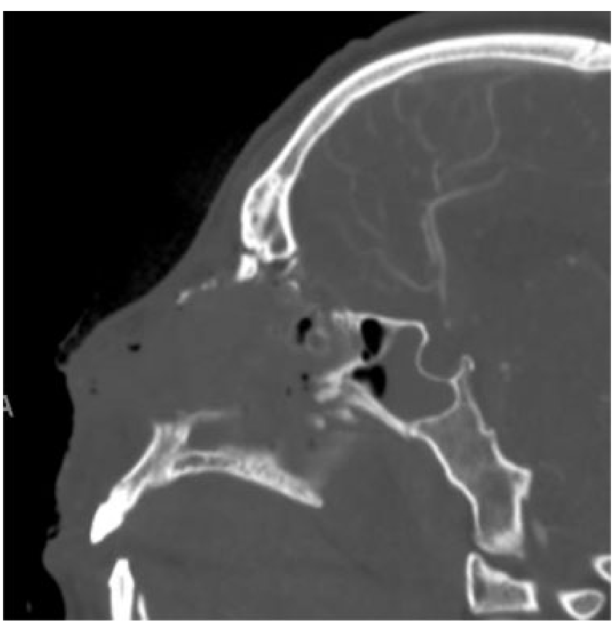

Fig. 2 High-resolution sagittal CT in trauma patient shows defect along posterior wall of frontal sinus which manifested as CSF rhinorrhea. CT, computed tomography; CSF, cerebrospinal fluid.

CT cisternography: CT cisternography can be used to increase the sensitivity of high-resolution CT for active CSF drainage. CT cisternography uses an intrathecal injection of radiopaque contrast material (metrizamide, iopamidol, or iohexol), followed by thin cut CT imaging. Sensitivity of CT cisternography is reported to be 80 to 95%.[12,15] It is most useful in frontal or sphenoid sinus leaks, because these sinuses act as reservoirs to collect the contrast material. Cribriform and ethmoid leaks are more challenging to identify with cisternography because the contrast material can drain more readily into the nasopharynx.[16] Disadvantages of CT cisternography include the need for a lumbar puncture with its associated risks (bleeding, infection, spinal headache, neurologic injury, and reaction to intrathecal contrast material) and the need for active CSF flow to identify a leak (see ►**Fig. 3**).[17]

- Magnetic resonance imaging (MRI): MRI is an effective imaging modality for localizing CSF fistulas. CSF is hyperintense on T2-weighted imaging and can be readily identified within the nasal cavity.[15] MRI also provides higher soft tissue resolution for identification of brain/dural herniations. Current imaging modalities can achieve a sensitivity of 85 to 92% and specificity of nearly 100%.[16] MRI is however more time consuming, costly, and physically more difficult to obtain (due to gantry size and patient tolerance). Therefore, MRI is most commonly obtained when more clinical information is required after acquisition of a high-resolution CT.

Fig. 3 CT cisternogram, coronal view, demonstrates extravasation of radio-opaque tracer through left cribriform defect into left ethmoid region.

- Magnetic resonance cisternogram: Magnetic resonance cisternography is similar to CT cisternography and is performed with an intrathecal injection of gadolinium contrast material via lumbar puncture. This can enhance the detection of CSF within the nasal cavity. The risk of neurological changes or seizure activity with the use of gadolinium is extremely low.[13] The sensitivity of this image modality for detection of CSF leak is approximately 85 to 92% and specificity of 100%.[16] Magnetic resonance cisternography is again more time consuming, costly, and physically more difficult to obtain (due to gantry size and patient tolerance) than high-resolution CT. It also requires a lumbar puncture with its associated risks (bleeding, infection, spinal headache, neurologic injury) as well as the need for active CSF flow to identify the leak. Given these limitations, both MRI and magnetic resonance cisternography are generally reserved for patients who have already undergone high-resolution CT and the presence of location of a CSF leak still remains in question. Other anatomic abnormalities such as an encephalocele or meningocele would also warrant MRI. It should be noted, however, that gadolinium is not approved for intrathecal use in the United States.[18]

Radionucleotide cisternogram: Radionucleotide cisternography is of historical significance and mentioned here for completeness. This technique involves intrathecal injection of a radioactive isotope via lumbar puncture (with all the associated risks noted under CT cisternography above). After a period of time for diffusion of the isotope, an endoscope is used to place pledgets within the nasal cavity for a period of 12 to 24 hours to absorb any radioisotope that leaks into the nose. The pledgets are then removed and analyzed for presence of the radioisotope. There are many limitations to this technique including the fact that the leak must be active and significant enough to diffuse onto the pledgets, the patient must tolerate pledgets within the nasal cavity for 12 to 24 hours, and the fact that the technique (when positive) only localizes the leak to one side of the nose of the other. The sensitivity of the test is only 62 to 76%.[19]

Intrathecal fluorescein: Intrathecal fluorescein is used almost exclusively for localization of CSF leaks in the intraoperative setting. Please see the “Surgical Management” section for discussion of this technique. (See ►**Table 2** for anatomic localization summary of CSF leaks).

Medical Management

Nonsurgical management of CSF rhinorrhea consists of bed rest with maintenance of strict precautions to reduce or eliminate increases in intracranial pressure. These include the following: Elevation of the head of bed $\geq$ 30 degrees, routine use of stool softeners, and avoidance of straining/Valsalva maneuver (i.e., nose blowing, sneezing, straining at stool, incentive spirometry, etc.). Most posttraumatic CSF fistulas will resolve with medical management, particularly after surgical fracture reduction. Bell et al reviewed 34 cases of traumatic skull base CSF fistulas treated medical management and found resolution of CSF leak in 85% of the patients.[20] Mincy found that 68% of the posttraumatic CSF fistulas closed spontaneously within 48 hours and 85% closed within 7 days of initial injury.[21] Persistent CSF rhinorrhea after conservative management can be successfully treated with CSF diversion for 7 to 10 days.[2,20] A lumbar drain is the most common technique; however, an external ventriculostomy can be used for patients with traumatic brain injury, low Glasgow coma scale scores, or a requirement for intracranial pressure monitoring.[7,8] Optimal CSF drainage (~10 mL/hour) should reduce pressure on the fistula without resulting in CSF hypovolemia.[22] CSF hypovolemia can result in severe headache, pneumocephalus (from retrograde airflow through the fistula), or even brainstem herniation. The addition of CSF diversion to nonsurgical treatment raises the success rate to approximately 90%.[20] Some surgeons also use CSF diversion as part of routine postoperative management after repair of skull base defects.

Prophylactic Antibiotics

Meningitis is the most common major complication associated with posttraumatic CSF rhinorrhea. Eljamel and Foy found a 0.62% chance of meningitis in the first 24 hours, 9.12% after 1 week, and 18.82% after 2 weeks.[23] Despite these findings, the most recent Cochrane database review from 2011 does not

Table 2 Anatomic localization of cerebrospinal fluid leak

Test	Notes
Nasal endoscopy	Difficult in acute trauma setting
High resolution CT scan	Gold standard; rapid; highly sensitive (over 85%)
CT cisternography	Requires lumbar puncture and active leakage; reported sensitivity 80–95%; most useful in frontal and sphenoid leaks as these reservoirs collect fluid
MRI	Highly sensitive (up to 85–92%) but more time-consuming than CT scanning; may yield additional information if encephalocele is suspected
MR cisternography	Requires lumbar puncture; intrathecal gadolinium is off-label in the United States
Radionucleotide cisternography	Mainly historical use; difficult for patients to tolerate pledgets for 12–24 h
Intrathecal fluorescein	Requires lumbar puncture; off-label use for intraoperative localization; reported complications of lower extremity weakness, numbness, seizures, opisthotonos, cranial nerve deficit

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

support the use of routine prophylactic antibiotics in patients with skull base fractures to reduce the risk of meningitis.[24]

Surgical Management

Surgical treatment is considered first-line therapy for patients with chronic CSF rhinorrhea (i.e., idiopathic, nontraumatic, etc.). Posttraumatic patients are generally considered surgical candidates after failure of medical management for 3 to 7 days.[2,25,26] Earlier surgical intervention is recommended for patients with significant intracranial pathology (i.e., intraparenchymal hemorrhage and midline shift, severe skull base fractures, or tension pneumocephalus).[2,4,8]

Transcranial Approach

The transcranial approach for repair of CSF rhinorrhea was first described by Dandy in 1926 when he used a bifrontal craniotomy for access and repair of a dural defect with fascia lata. A frontal craniotomy provides access to the cribriform plate and fovea ethmoidalis. The sphenoid sinus can be accessed through an extended craniotomy and skull base dissection. Multiple reconstructive options have been described with this approach including free grafts (e.g., fascia lata, acellular dermis, fat grafts, muscle plugs) and vascularized grafts (e.g., galea aponeurosis or pericranial flap). Such grafts can be held in place with tissue glue, sutures, or a combination of both. While this technique does provide direct access to the defect (or defects), there are multiple disadvantages including the need for a craniotomy, relatively high failure rates (up to 27%), and the need for brain retraction which can result in intraparenchymal hematoma, seizure, anosmia, and direct brain injury.[27] Newer endoscopic extracranial techniques are now advocated in most situations, reserving transcranial approaches for patients requiring a craniotomy and skull base exposure for associated intracranial pathology (see ►**Fig. 4**).[22]

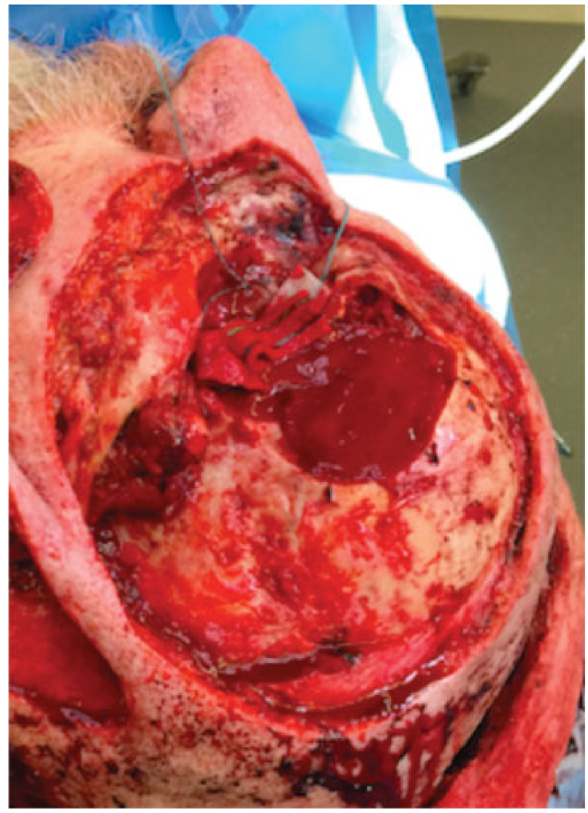

Fig. 4 Transcranial repair after tumor ablation. Primary dural repair has been augmented by a patch of collagen scaffold before definitive cover with vascularized free tissue flap.

Naso-Orbital Approach

In 1948 Dohman described the first extracranial approach to a CSF leak repair via a naso-orbital incision. Success rates for this approach range from 86 to 97%.[28,29] Advantages of this approach include avoidance of brain retraction (with its associated risks), while providing improved exposure to the anterior cranial fossa (i.e., frontal sinus, cribriform plate, fovea ethmoidalis, ethmoid labyrinth, sphenoid sinus, and parasellar region). Disadvantages include a facial scar, and the potential for paresthesias as well as orbital injury.

Transnasal Approach

In 1952 Hirsch described a transnasal approach to the sphenoid sinus.[30] Vrabec and Hallberg later applied this approach to repair of a cribriform defect.[31] While the transnasal approach avoids an external incision, visualization is more difficult, there is limited exposure of the lateral and superior sphenoid sinus, and there is risk of septal perforation.

Endoscopic Endonasal Approach

In 1981 Wigand described an endoscopic transnasal approach for repair of an anterior skull base defect.[32] In 1989 Papay et al expanded on this approach, describing the first endoscopic endonasal repair of a CSF fistula.[33] Kennedy and coworkers have since shown this to be a highly effective and minimally invasive technique for repair of CSF rhinorrhea.[34,35] The endoscopic endonasal approach is currently the preferred method for repair of anterior skull base defects/rhinorrhea.[4]

Traditional endoscopic sinus surgery techniques are used to identify and expose and the fistula. The endoscope offers excellent visualization of the entire anterior skull base from the sphenoid sinus to the frontal sinus. Visualization of the lateral sphenoid sinus can be achieved with the use of angled endoscopes or a direct dissection through the pterygomaxillary space.[36,37] Access to the frontal sinus itself can be achieved via a modified Lothrop procedure, however, far lateral defects can still be challenging to access endoscopically.[36,37]

Intrathecal Fluorescein

The use of intrathecal fluorescein was first described by Messerklinger in 1972 and it is still commonly used for intraoperative identification of difficult skull base defects. Fluorescein is administered via a lumbar puncture, allowing 30 to 60 minutes for diffusion throughout the CSF. Intraoperatively, fluorescein is seen as a bright green/yellow material draining from the skull base defect. Intrathecal fluorescein at high concentrations has been associated with seizures, coma, and death.[38] However, in a study of 420 patients, Keerl et al found that low-dose administration of

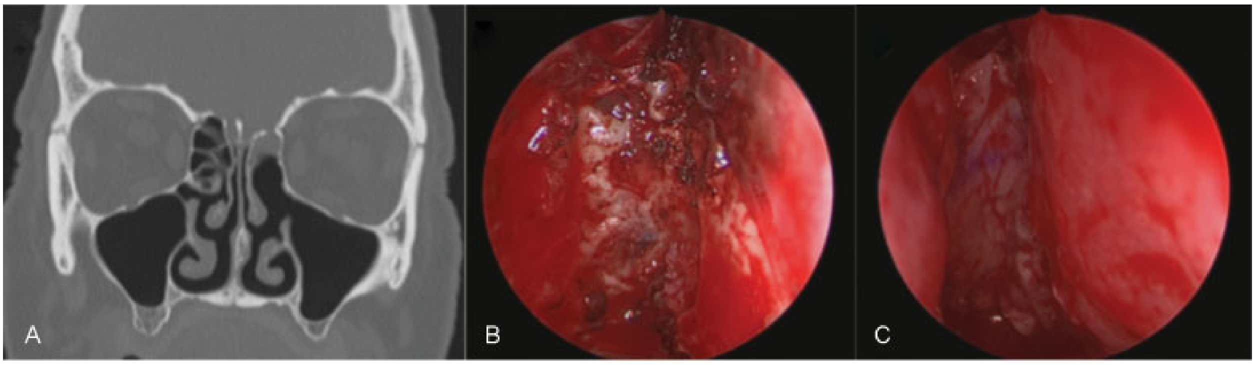

Fig. 5 Patient with history of head trauma presenting with left-sided CSF rhinorrhea. (A) Coronal CT scan showing a left ethmoid skull base defect. (B) Intraoperative image of left skull base defect (5 mm). (C) Repair of skull base defect with pedicled nasoseptal flap. CT, computed tomography; CSF, cerebrospinal fluid.

intrathecal fluorescein (less than 50 mg) could assist in localizing CSF fistulas without complications.[39] The current recommended protocol is dilution of 0.1 mL of 10% intravenous fluorescein in 10 mL of the patient's own CSF. This is slowly reinfused over 30 minutes. However, intrathecal fluorescein is an off label use, and patients must counseled about the potential risks before the procedure.

Once the skull base defect is identified, the surrounding sinus mucosa must be denuded to circumferentially expose the defect. Many grafting techniques and materials have been described. Small defects can be repaired with a simple only technique using any number of materials (e.g., temporalis fascia, fascia lata, nasal/septal mucosa, etc.).[22,36,37] Fat or muscle plugs placed in a "dumbbell" fashion (both intra and extracranially) have also been successfully described.[21,35,36] Hegazy et al published a meta-analysis revealing that graft material type does not affect success rates when good surgical technique is employed.[40] There is some controversy regarding the need for a rigid, layered repair for larger ($\geq$ 1.5–2 cm) skull base defects. Septal bone and cartilage can be used in combination with layered only mucosal grafts. However, many surgeons feel that even very large defects can be adequately repaired with vascularized mucosal flaps.[22] With recent advances in extended endonasal approaches to skull base tumors, the pedicled nasoseptal flap (see ►**Fig. 5**) has become the workhorse of reconstruction for even very large skull base defects extending from the sphenoid to frontal sinuses.[41,42] Cartilage or bone grafts are generally not used in such situations. Other vascularized flaps that have gained less popularity due to

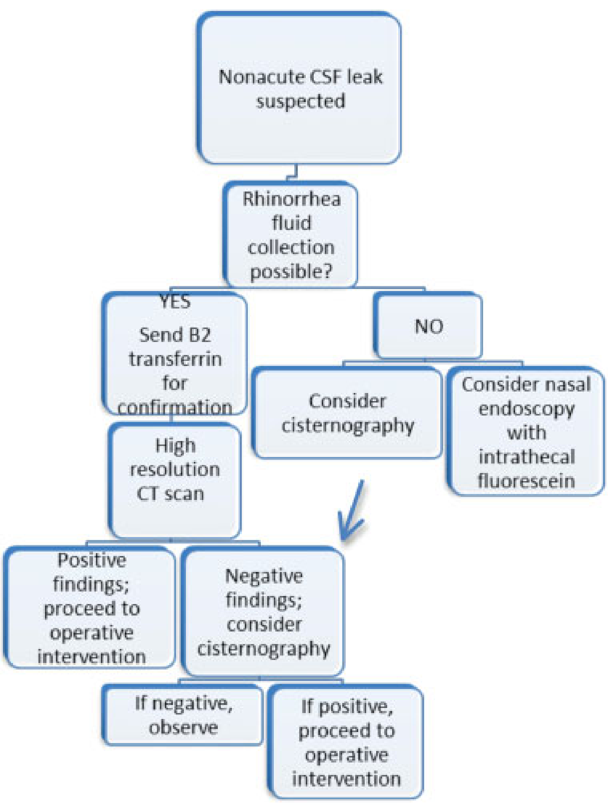

Fig. 6 Nonacute/chronic CSF rhinorrhea algorithm. CSF, cerebrospinal fluid.

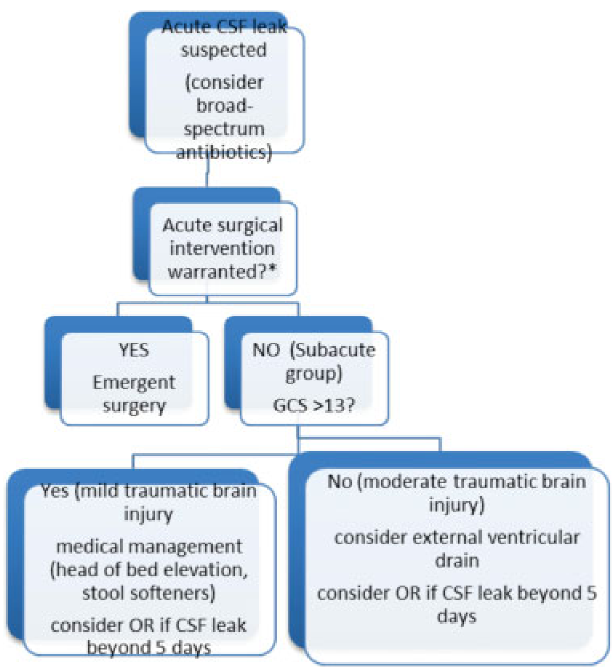

Fig. 7 Acute CSF leak management algorithm. CSF, cerebrospinal fluid. (Adapted from Sherif et al.[8]) *Space-occupying bleed, bone fragment displacement over 1 cm in any plane, intracranial hypertension $>$ 20 cm H_2O, pneumocephalus $>$ 2 mL.

access and size include: middle and inferior turbinate pedicled flaps,[43,44] temporoparietal fascia flap,[45] and palatal flap.[46]

The results from endonasal endoscopic repair of CSF fistulas are exceptional, with published success rates ranging from 94 to 98% in large retrospective reviews.[5,35] Disadvantages of the endonasal endoscopic technique include difficulty with addressing CSF fistulas of the posterior table and lateral walls of the frontal sinus, risks of anosmia, septal perforation, or visual loss.

Obviously, surgeon experience, radiology expertise, and hospital resources vary considerably. We find it easiest to separate CSF rhinorrhea into acute (usually trauma) and chronic categories. A summary of one potential algorithm for management of these categories is illustrated in ►**Figs. 6** and **7**.

Summary

Diagnosis of CSF rhinorrhea should start with a high clinical suspicion, particularly in patients with craniofacial trauma. Common diagnostic modalities include nasal endoscopy, β2 transferrin testing, followed by high-resolution CT. For posttraumatic patients, medical management should be considered for 3 to 7 days if there are no acute indications for surgery. This may include the use of a lumbar drain or external ventricular drain. The use of prophylactic antibiotics is controversial, but meta-analysis failed to show a reduction in the incidence of meningitis. Patients who fail medical management (or who present with a chronic leak) are candidates for surgical repair. Current endoscopic techniques are minimally invasive and have excellent success rates (94–98%). Leaks located in the periphery of the frontal sinus or associated with concurrent intracranial pathology may still require a transcranial approach.

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