

Management of cerebrospinal fluid leak: the importance of multidisciplinary approach

Trattamento delle fistole rinoliquorali: quando è richiesto un approccio chirurgico multidisciplinare al basicranio?

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SUMMARY

Cerebrospinal fluid (CSF) leak remains a rare condition, characterized by serious complications and potentially fatal. According to different etiologies, CSF leaks may be classified into two main categories: traumatic and spontaneous. Spontaneous fistulas seem to be mainly related to obesity and idiopathic intracranial hypertension. Diagnosis is both clinical and radiological. During the last three decades, surgical treatment has mostly shifted to endonasal endoscopic approach, which widely demonstrated to be more effective than invasive intracranial ones. Post-operative complications, long-term sequelae and hospital stay are strongly reduced thanks to endoscopic approach. The diagnosis and treatment of CSF leaks represent a difficult and challenge task. The main effort seems to be related to the precise localization of the leak. An accurate assessment of both predisposing factors and comorbidities is mandatory in case of spontaneous leaks. However, a clinical multidisciplinary evaluation as well as treatment, is essential to decrease the rate of failure of surgery. The presence of a dedicated instruments, the Skull Base Team, the knowledge of reconstructive materials and techniques represents a decisive result in therapeutical management even if for each patient an effective therapeutic algorithm can be obtained considering the correct leak detection and characteristics. In conclusion the strict teamwork with neurosurgeons, neuroradiologists, ophthalmologists will enable the development also of innovative biomaterials, which could spread and standardize multi-layer techniques, nowadays still related to surgeon preferences.

KEY WORDS: CSF leak, rinoliquorrea, endoscopic skull base surgery

RIASSUNTO

Le fistole rinoliquorali sono una patologia poco comune ma, a causa delle temibili complicanze, potenzialmente fatale. A seconda dell'eziologia, possono essere classificate in traumatiche e spontanee. La diagnosi è sia clinica che radiologica. Negli ultimi tre decenni, il trattamento chirurgico si è molto evoluto, passando da un approccio invasivo intracranico ad un approccio endoscopico endonasale, il quale si è dimostrato maggiormente efficace a fronte di un minore numero di complicanze post-operatorie a breve e lungo termine e della riduzione dei tempi operatori e di ospedalizzazione. La diagnosi ed il trattamento delle fistole rinoliquorali sono da sempre stati alquanto complessi. Le principali problematiche dipendono dalle difficoltà di localizzazione della sede della fistola e, nel caso delle forme spontanee, anche dal corretto inquadramento di eventuali fattori predisponenti e comorbidità. Al fine di ridurre al minimo i rischi di insuccesso del trattamento chirurgico è necessario un approccio gestionale di tipo multidisciplinare. In conclusione, la possibilità di assumere le decisioni terapeutiche nell'ambito di un'équipe multidisciplinare dedicata – Skull Base Team –, che si avvalga della presenza di otorinolaringoiatra e neurochirurgo, così come del neuroradiologo e dell'oculista, è fondamentale per localizzare con precisione la sede e delineare le caratteristiche della fistola in modo da ottenere il successo terapeutico. La stretta collaborazione multidisciplinare potrà inoltre permettere lo sviluppo in futuro di nuovi biomateriali in grado di facilitare e standardizzare le tecniche di riparazione multistrato, oggi in gran parte condizionate dalle preferenze del chirurgo.

PAROLE CHIAVE: fistole rinoliquorali, rinoliquorrea, chirurgia endoscopica, basicranio

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Introduction

Cerebrospinal fluid fistula, also called CSF leak, is an uncommon but severe condition with potentially fatal outcome. CSF leaks can be essentially classified according to two criteria: etiology and location.

Considering etiology, O'Connell's historical classification¹, subsequently revisited by Ommaya² and then by Har-El³, considers two large groups:

- **traumatic**, with generally delayed clinical manifestation, divided into:
 - *iatrogenic*, related to nasal (e.g. functional endoscopic sinus surgery [FESS], endoscopic sinus surgery [ESS]) (Fig.1), or cranial surgery (e.g. craniotomies), which are further divided into accidental and imperfect reconstruction. Patients with extensive pneumatization are most at risk⁴.
 - *non iatrogenic*, linked to blunt or penetrating trauma, which do not always result in an obvious liquor loss, but become evident, sometimes several years later, presenting a complicated clinical picture (e.g. meningitis, encephalocele). CSF leaks occur in 3% of closed head injuries, in 9% of open head injuries, and in 10-30% of skull base fractures⁵. The frequency is higher in males between their thirties and fifties and are quite rare in childhood due to elasticity of cranial bones⁶. In 80% of cases, early symptoms occur within the first two days of the event, and in 95% within the first three months of the traumatic event.
- **non-traumatic**, divided according to CSF pressure into *high-pressure* and *low-pressure*.

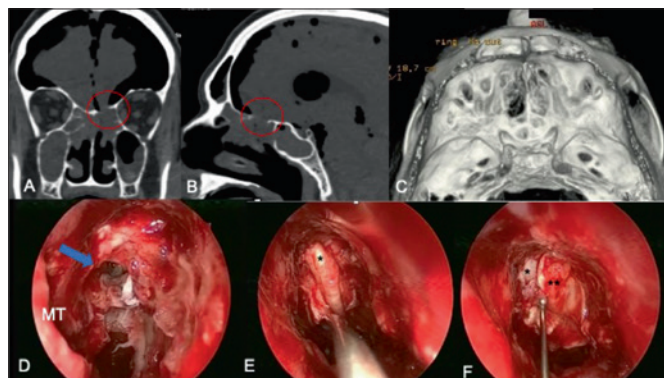


Figure 1. A CT scan in coronal (A) sagittal (B) and 3D reconstruction (C) of posttraumatic (iatrogenic) CSF leak at the level of the left ethmoid sinus occurred during Functional Endoscopic Sinus Surgery (FESS) surgery for nasal polyposis. A massive pneumocephalus occurred due to delayed diagnosis of intraoperative leak. The patient underwent to endoscopic repair of the wide defect (D arrow) using fascia lata graft in a multilayer fashion (E and F): first* underlay layer and second** overlay layer + rotation of middle turbinate (MT).

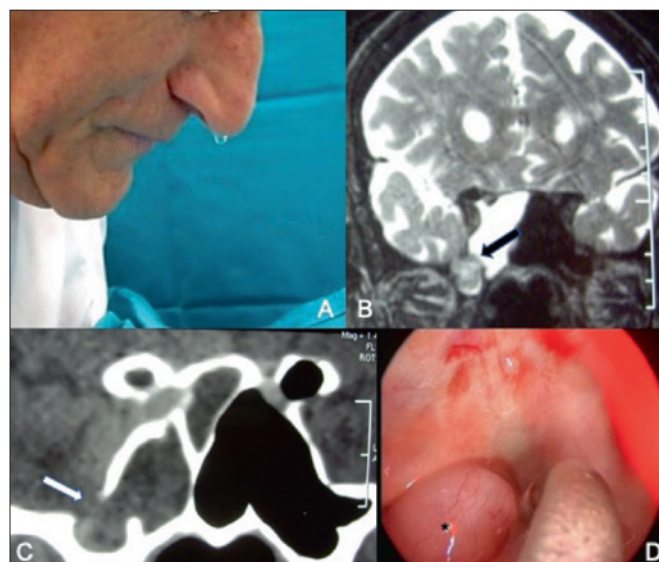


Figure 2. A case of spontaneous right nostril rhinoliquorrhea (A) in a patient with a meningoencephalocele in the right sphenoid sinus as showed in T2 weighted MRI (B arrow) through a bony defect (C arrow) in the lateral recess of sphenoid (Sternberg's canal) (C arrow) and how it appears (*) with 45° angled endoscopic examination of the sphenoid sinus.

Diagnosis is difficult and depends mostly on disease etiology. Clinical diagnosis of a post-traumatic leak is immediate. Instead, spontaneous leaks are more complex to identify, because they are characterized by intermittent symptoms; therefore, absence of external abnormalities and infrequent symptoms cause often diagnostic delay. Spontaneous leaks comprise all leaks without recognized causal mechanisms and are more often associated with meningeal herniations (Fig. 2), multiple localizations and higher recurrence rates. The treatment of CSF leaks, posttraumatic as well as spontaneous, was until the recent past nearly exclusively referred to the neurosurgeon. Nowadays, the successful management of CSF leaks has changed almost exclusively into endonasal endoscopic approach, even if a multidisciplinary team and different treatment options, not only limited to surgery, are still necessary. Aim of this review is to provide an update on CSF leak management by discussing when and how a multidisciplinary approach could improve outcomes.

Diagnosis

The diagnostic algorithm is still a challenge and is of paramount importance for final therapeutical success. The diagnostic work up includes clinical ENT, neurosurgical and ophthalmological evaluation, in order to assess the potential etiological factors, the site and features of the CSF leak (i.e. flow, predisposing factors, etc.), laboratory findings of the

collected nasal liquid and radiological evaluation. All these specialists contribute to the diagnosis and to the decision making process in the CSF leaks, but more extensively take part to the constitution of the Skull Base Team, that take care also of the problem of reconstruction of defect following surgical treatment of pathologies rising in this region ⁷. The clinical evaluation of suspected CSF rhinorrhea can be pointed out inviting patient to perform maneuvers that can increase intracranial pressure, to reveal any leak, nasal endoscopy can confirm the presence of bone defect or meningoceles or meningoencephaloceles. The collection of nasal secretions or liquid is used to test beta-2-transferrin and beta trace protein assays, the most sensitive and specific laboratory tests for CSF leak diagnosis, the former more commonly used because of availability ⁸. The ophthalmologists can diagnose the presence of increased intracranial pressure evaluating the fundus oculi and eventual papilledema or using ultrasound to check optic nerve status ⁹. When there is a clinical suspect or clear diagnosis of CSF leak the neuroradiological evaluation is essential, detecting leaks using computed tomography, magnetic resonance imaging, or nuclear imaging ^{10,11}. The use of High Resolution Computed Tomography (HRTC) scan to assess any bony defect in the skull base, including also the petrous bone, followed by MRI that can show the presence of meningocele, meningoencephaloceles, inflammatory reaction of the nasal or middle ear mucosa, and obviously any meningeal or intracranial involvement (i.e. meningitis or meningoencephalitis, etc.). The MRI is also important in cases of spontaneous CSF leak to suggest long-standing Idiopathic Intracranial Hypertension (IIH), including empty sella, flattening of the posterior globes, optic nerve head protrusion, distention of the optic nerve sheaths, tortuosity of the optic nerve, cerebellar tonsillar herniation, meningoceles, CSF leaks, and transverse venous sinus stenosis ¹². Other radiological examination such as CT cisternography, MR cisternography are still used in IIH diagnosis ¹³, both are nowadays disused due the introduction of intrathecal use of fluorescein that allows integration of diagnosis and treatment in one procedure reducing the morbidity of such invasive radiological examination. The use of intrathecal fluorescein (ITF) is still not FDA approved and require a specific informed consent even if low-dose ITF is a safe and useful tool during endoscopic endonasal repair of CSF leaks with minimal complications and successful localization of the leak ¹⁴.

Treatment

Treatment may include:

- *conservative medical therapy*, which is first choice in patients without immediate need for intervention or pa-

tients with spontaneous healing possibilities; however, surgery might be necessary in case conservative medical therapy is ineffective;

- *surgical therapy*, which is indicated in patients without spontaneous healing chances, as for example patients with cerebral herniations, iatrogenic dural leaks, spontaneous leaks – which are highly unlikely resolvable without surgery – or patients with underlying disease, such as tumours, requiring by default surgery including dural resection.

Both approaches have the goal of preventing complications, which are recurrent meningitis, intracranial abscesses, pneumoencephaloces, and refractory epilepsy. The incidence of meningitis related to a posttraumatic CSF leak, either pre-operatively or during conservative management, ranges from 10% to 37% and is proportional to the duration of this condition ⁶.

The final decision of both therapeutical options is generally discussed in a multidisciplinary setting (Skull Base Team). Conservative medical therapy includes bed rest with the head raised by 30° for 1-2 weeks. During this period, the patient must avoid activities, which may result in increased intracranial pressure. Some surgeons prescribe patients medications such as antiemetics, stool softeners and anti-tussives ¹⁵. Corticosteroids or diuretics can be additionally administered to reduce intracranial pressure, although their effectiveness is still debated in literature ¹⁶.

Lumbar drain might be recommended in an effort to minimize increased intracranial pressure, but drains are related to significant risks if used excessively, including drastic liquor pressure collaps and tension pneumocephalus ¹⁷.

Prophylactic antibiotics are often administered to decrease the risk of meningitis or local infection during conservative management of CSF leaks. However, this strategy carries the risk to create resistant bacteria; as a result, routine use of prophylactic antibiotics has been questioned ¹⁰⁻¹². Nevertheless, prophylactic antibiotics are indispensable for high-risk patients like those with medical history of upper airways infection or meningitis ¹⁵.

Conservative treatment should be continued for at least two weeks; if conservative treatment fails, surgical therapy becomes imperative ^{20,21}.

The risk of meningitis in cases of patients treated with conservative approach varies between 10 and 37% ^{20,21}, therefore, recent literature suggests performing surgery as early as possible (Fig. 5). The time interval between onset of the pathology and diagnosis with subsequent hospitalization is extremely variable with a duration of symptoms ranging from only few hours to two years before consulting a physician at the hospital. That delay is related to complexity of this pathology and lack of a multidisciplinary approach (i.e.

collegial integration and sharing of the clinico-radiological informations).

The surgical strategy strongly depends on leak size, but also on the type, which can be classified in three categories:

- *traumatic, non-iatrogenic skull base defect*: in this leak type, the following risk factors should be considered: location, size, bone dislocations, and meningocele (Fig. 4), meningoencephalocele or cerebral hematoma. When the fracture is linear, less than 1 cm and not associated with intracranial complications, frontal sinus posterior wall or ethmoidal roof fractures, a wait-and-watch approach can be considered, because spontaneous healing due to fibrosis might be possible. Spontaneous healing occurs in 70-80% of patients within one week and in 20-30% of patients within few months, those leaks rarely recur. In all other patients, surgical strategy should be performed;
- *traumatic, iatrogenic leaks*: early surgical repair, if possible intraoperative, should be performed, because spontaneous healing is improbable, and the risk of recurrence is quite high. Moreover, infectious risk is directly proportional to the time in which the subarachnoid space and nasal cavities are interconnected. Indeed, it is necessary to operate as soon as possible in case of CSF rhinorrhea after surgery to avoid meningitis or meningoencephalocele (Fig. 1);
- *non-traumatic leaks (recurrent or intermittent rhinoliquorrea and/or meningoencephalitis)*: non-traumatic leaks can be divided depending on the intracranial pressure, into **high-pressure leaks**, which are linked to neoplasms, hydrocephalus, idiopathic intracranial hypertension (IIH), empty sella syndrome (Fig. 5), and **low-pressure leaks**, related to congenital anomalies. Surgery should be considered in all patients. If the patient experiences a single, spontaneously resolvable episode of rhinoliquorrea, leak identification can be difficult. The risk of complications is rare and an absolute indication for surgery does not exist.

Surgical approaches for CSF leaks

Surgical therapy involves two different approaches, which are intracranial and extracranial (endoscopic) surgery. The choice between these two surgical approaches is conditioned by:

- size and location of the leak;
- recurrences;
- meningocele or meningoencephalocele;
- patient's general condition;
- surgeon's preference.

Open intracranial approach

The repair of CSF leaks has rapidly evolved over the past

30 years. Open intracranial surgery, a typical neurosurgical approach, has historically been used for CSF leak repair, but in the recent two decades, the technique was largely replaced by endonasal endoscopic approaches, given to their high success, lower morbidity and complication rates, less invasiveness and shorter hospitalization time^{20,22}.

The type of intervention depends on the location and extension of the leak. Frontal craniotomy is performed in case of anterior leaks. Temporal or posterior craniotomy is indicated in case of middle or posterior cranial fossa leaks.

The visualization of dural lesions and the adjacent cerebral cortex are advantages of this approach, especially in case of increased intracranial pressure. Open intracranial surgery has a success rate ranging from 50 to 75%. Limited visualization of the leak at the sphenoidal level can cause hematoma, edema, convulsive seizures or permanent anosmia by damaging the nervous tissue, leading to increased morbidity and prolonged hospitalization. Complications are significantly higher in patients treated with an open intracranial approach compared with an endonasal endoscopic approach: meningitis, 3.9% versus 1.1%, respectively; abscesses, 6.8% versus 0.7%, respectively; and sepsis, 3.8% versus 0%, respectively²².

Contraindications for an open intracranial approach are presence of intracranial hematomas, ethmoidal fractures extended to the orbit or frontal sinus posterior wall fractures. Instead, leak size and shape do not represent an absolute contraindication for open intracranial approach.

Extracranial approach

Extra-cranial non-endoscopic-endonasal surgery consisting in a bicoronal or eyebrow incision to create anterior osteoplastic flaps is nowadays rarely performed. Although the approach has a high success rates (86-100%), other concomitant abnormalities are not resectable and the approach causes visible scars compared with endoscopic approaches. Several techniques – external ethmoidectomy, trans-orbital ethmoidectomy (Lynch technique), trans-ethmoidal sphenoidotomy, trans-tectal sphenoidotomy and trans-antral – can be performed during extra-cranial non-endoscopic-endonasal surgery to implant autologous and/or heterologous materials.

Endonasal endoscopic treatment

In the last three decades, a complete revolution of surgical approach towards the endoscopic surgery occurred²³, which in the primary cases has almost completely replaced the open intracranial intervention^{24,25}, nowadays almost entirely reserved to complex cases. In 1981, Wigand et al.²³ described first an endoscopic approach to repair CSF leaks. Since then, several case series and reports described vari-

ous endoscopic methods and materials for leak repair, with success rates varying between 60% and 100%, averaging around 90%²⁵ and nowadays the endonasal endoscopic approach is considered a gold standard^{26,27}. The endoscopic approach allows a wider view of the operating field, resulting in more precise and advanced interventions, which lead to a higher initial CSF leak repair success rate, and reduced complications and hospitalization time²².

Furthermore, new endoscopic technologies led to further diagnostic characterization as well as treatment improvements^{28,29}. For example, ENTs, supported by neurosurgeons, perform nowadays endonasal endoscopy and have a predominant role to manage extensive intradural neoplasms where reconstruction of wide and complex CSF leaks is necessary. In particular, those leaks of the posterior cranial fossa require specific competences and simultaneous use of more tools during a four-handed endonasal endoscopic approach at the dural and intradural section of the skull.

The endonasal endoscopic approach can be described as follows:

- first, both imaging and endoscopic exploration should be employed to localize the exact site of the leak. Intrathecal fluorescein can be used to aid an exact diagnosis and localization of CSF leaks^{30,31}. It is necessary to observe carefully the spread of fluorescein at the terminal middle turbinate. If fluorescein spreads medial, at the level of the sphenoid-ethmoidal recess, the leak is probably at the sphenoidal level, posterior ethmoidal or close to the lamina cribrosa; instead, fluorescein in the middle meatus indicates that the leak is located at the level of the anterior ethmoid or frontal sinus;
- secondly, CSF leaks mucoperiosteal edges should be accurately detached for at least 1 cm to regularize residual bone margins. It is crucial not to remove any residual lamellae to facilitate healing and closing of the CSF leak. The endoscopic procedure is based on a “four-hand” technique to act with multiple surgical instruments in both nostrils under endoscopic vision. Depending on leak location, size and type, surgeons choose one out of five possible access ways/techniques:
 - *direct parasagittal to the olfactory fissure* - This technique is used in case the leak is localized at the level of the anterior third of the olfactory fissure and if the possible herniated mass has lateralized the lateral lamella of the middle turbinate. The approach avoids major damage to the ethmoidal structures. Initially, electrocoagulation of herniated sac pedicles is performed, which might require the additionally removal of the entire lesion in case of larger hernias. The second step involves intracranial skeletonization of the dural edge with subsequent mucosa removal of the

surrounding defect area at the level of the olfactory fissure, corresponding portions of the nasal septum and lateral wall, to prepare the transplant area;

- *direct parasagittal with sphenoidotomy* - This access way allows reaching the sphenoidal sinus’ posterior wall, when the leak is located at the sellar floor or sinus roof; however, the sphenoid sinus is usually obliterated during intervention. The procedure involves the endoscopic identification and enlargement of the sphenoid sinus ostium to remove the intersphenoid septum and to create a single cavity. In the event that the natural ostium is unrecognizable, the sphenoid rostrum is opened in medial position to prevent internal carotid or iatrogenic optic nerve damage to gain access. The rostrum and posterior nasal septum end is additionally removed allowing the use of both nasal passages for a four-hand approach. Advantages is that the clivus region can be reached and a nasoseptal mucosa flap can be used;
- *trans-ethmoidal with conservation of the basal lamina of the ethmoidal cornets* - This approach is preferable when the defect is located at the ethmoidal level, particularly if laterally to the lamina of the cornets. The ethmoidal roof must be fully exposed to identify the precise lesion site. The technique involves the removal of the ethmoid labyrinth with exposure of the skull base and paranasal sinuses. The use of intrathecal fluorescein and endoscopic blue and yellow light filters allows identifying further leak locations, which might have remained unobserved during the diagnostic phase;
- *trans-ethmoidal with removal of the basal lamina of the ethmoidal cornets* - This approach is used in case the defect is located at the level of the middle and/or posterior third of the olfactory fissure, or at the level of the ethmoidal roof with medial involvement of the olfactory fissure. In case of smaller lesions, not entirely involving the olfactory fissure leaving the olfactory mucosa and olfactory filaments substantially intact, the middle turbinate and the entire basal lamina of the ethmoid cornets are obliterated to obtain a regular plane. On this regular plane a septal or turbinal mucoperiosteal graft is implanted, which can only be achieved with overlay positioning. If the defect is localized at the ethmoidal roof level, the bone defect should be regularized by dissecting the epidural space even if this means enlarging the defect. After this step, the leak is closed with multilayer technique;
- *transethmoidal-pterigoido-sphenoidal* - This technique is performed to treat lateral wall sphenoid sinus leaks and other leaks requiring ethmoido-sphe-

noidotomy and a large middle meatal anastomosis³². The posterior fontanelle area is during the technique obliterated to expose the posterior wall of the maxillary sinus and the pterygoid base. The septal and nasal branches of the sphenopalatine artery are subsequently cauterized. After, the anterior wall of the sphenoid sinus and the pterygoid base are milled to dominate the lateral wall of the sphenoid sinus and to access the lesion in order to perform the dural repair at the level of the middle cranial fossa.

Repair materials for CSF leaks

Studies comparing different graft types are still lacking in literature; in consequence, standardized criteria to choose adequate repair material are absent. The choice of CSF repair material depends much on location, size, bone dehiscence, surgeon's preference as well as availability and quality of the materials^{16,33}.

The primary goal of a reconstruction is to separate intracranial and extracranial spaces to prevent complications such as pneumocephalus, leak and infection. Secondary aim is to promote rapid scarring, to protect neural and vascular tissues and to minimize morbidity.

Grafts should be at least 30% larger than the bone defect, because of post-operative retraction, and should perfectly fit in the implant site, to avoid tension³⁵.

Generally, graft types can be distinguished in autologous and heterologous.

Heterologous grafts (e.g. synthetics) have a greater rejection risk, which can cause infections. The effectiveness of the CSF leak repair, with different kind of heterologous materials, is related revascularization, which varies widely. Poor or insufficient revascularization of flaps depends on adjacent tissue transfer, and atrophic or previously irradiated nasal mucous membranes, which increases the risk of CSF leak recurrence.

Different heterologous grafts can be considered:

- *absorbable collagen sponges (e.g. DuraGen®Secure, Dural Regeneration Matrix)* - This type of graft is used to close smaller CSF leaks, after tumour removal such as pituitary adenoma, chordoma and Rathke cysts, using a trans-sphenoid endonasal access. Absorbable collagen sponge grafts have three major advantages: First, onlay positioning of the sponge on the dura mater allows a fast fibrinic adhesion of the collagen to the dura to promote, from the first day on, fibroblast penetration into the collagen matrix and proliferation. Second, the collagen sponge, created using a bovine flexor tendon, is inert and well tolerated, which means that it does not cause

chronic inflammation nor rejection. Third, this technique does not require autologous grafts or fibrin glue;

- *hydroxyapatite cement (HAC)* - Less utilized.

Autologous grafts can be divided into nasal and extra-nasal. To repair CSF leaks abdominal fat, muscles, deep temporal, fascia lata (Fig. 1), and pericranial flap, or middle turbinate mucoperiosteal and septal mucopericondral flaps (Fig. 5) can be used. Septum mucopericondral flaps are most commonly used for leaks smaller than 20 mm, because of their availability on the surgical site; they are easy to prepare and adapt to bony surfaces; their capillarity and the reduced postoperative traction minimize potential CSF leak recurrence. Additionally, muscle, temporal and abdominal fat grafts can be considered CSF leak larger than 20 mm, which can be subsequently covered by septal mucosa flaps. A composed tissue graft might be considered, if associated with cartilage or bones. In 2003, Schick et al.³⁴ demonstrated that compound tissue grafts are most suitable for dura mater graft surgery, as they facilitate cell migration (fibroblasts and epithelial cells) to the center of the dural perforation. This is contrary to synthetic materials or cartilage, which limit or even inhibit this process. But the real revolution is in the use of pedicled vascularized different mucoperiosteal and mucopericondral flaps that strongly improved the success rate of reconstruction of skull base defect.

Autologous grafts can be placed with different techniques:

- *underlay technique* - During underlay technique, the dura mater is separated from the skull base dehiscence edges to obtain an adequate support plan. This support plan has the aim to stabilize the autologous graft, which must be prepared or shaped accordingly to fit between the bone and dura mater on all dehiscence sides;
- *overlay technique* - The overlay technique foresees to remove the mucosa and in a second step, the autologous graft is placed above the dural lesion and the exposed bone margins. Mucopericondral and mucoperiosteal flaps are most frequently used, which are placed with the connective side towards the defect;
- *obliterative technique* - This technique is mainly used in case of a poorly pneumatized sphenoid (Fig. 3) and frontal sinus. In a first step, complete removal of sinus mucosa should be achieved to avoid mucocoeles; secondly, sinus cavities should be filled with autologous abdominal fat used preferably in a monobloc; after, the anterior sinus wall should be coated with a free autologous graft of mucopericondrium or muco-periosteum³⁵.

The choice between these techniques depends on different variables. Regarding the leak diameter, usually the bigger the diameter, the easier and safer an underlay graft can

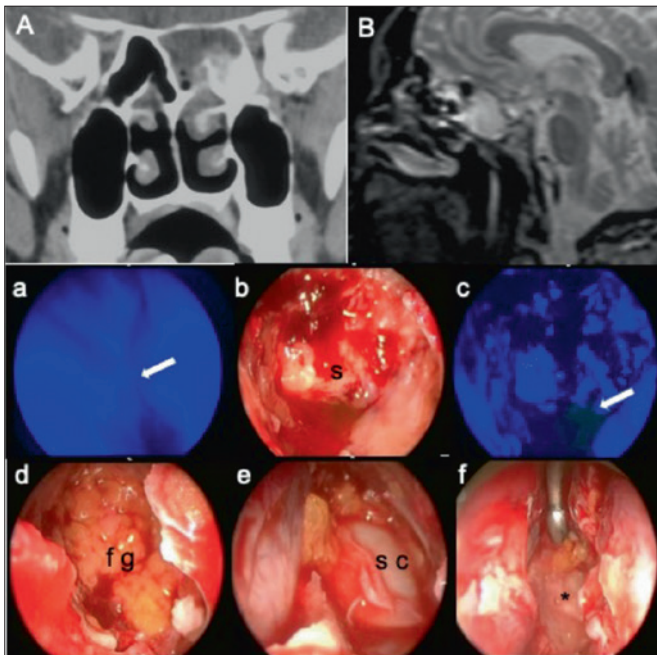


Figure 3. Coronal CT scan (A) and sagittal (B) T2 weighted MRI showed the presence of sphenoiditis and erosion of the clivus in a 54-year-old male patient with rinoliquorrea 2 years after chemoradiotherapy for a nasopharyngeal cancer. The precise site of leakage was uncertain at the imaging so we used intrathecal fluorescein for a precise localization. The endoscopic pictures shows fluorescein coming out from the sphenoid ostium (a) and after sphenodotomy the trasudation of the liquor (b, c) throught the clivus and below the sella (S). An obliterative technique (d) was preferred using an autologous fat graft (fg), a cartilage graft of the nasal septum (e) in a gasket seal way on the sphenoidotomy, and fibrin glue (*).

be implanted. Concerning leak location, in case the leak is placed at level of lamina cribrosa, dura is very difficult to detach from the intracranial bone at the level of olfactory fissure, because of tenacious adhesion between dura and olfactory holes. Therefore, overlay technique should be performed. Furthermore, the space to move surgical instruments should be considered; overlay technique is more preferable in smaller spaces.

Regarding large ventral skull leaks (over 2 cm), comprising bone and dura, but even smaller leaks associated with high intracranial pressure, multilayer technique is recommended. This multilayer technique should consist of an intradural collagen graft between dura and brain, a second onlay graft in contact with the dura and bone and as a third layer a vascularized or mucosa flap^{36,37}. In a further step, some defects might be supplemented with adipose tissue. Numerous variations of these techniques are successfully used today^{38,39}.

Generally, rigid reconstruction with bone or allograft material is less recommended because this type of graft is related to a higher migration and infection risk.

Reconstructions based on the location of the leak

Snyderman et al.¹⁷ tried to standardize various reconstructions types based on the leak location. Particularly, authors described intervention types more suitable for anterior, middle and posterior cranial fossa reconstruction.

Anterior cranial fossa: lesions in the anterior cranial fossa, necessitating surgery, are typically caused by sinonasal tumours and less commonly by cranio-facial traumas. If they originated from large sized anterior cranial base defect, they usually extend frontal from one orbit to the other and sagittal from the planum sphenoidale to the posterior wall of the frontal sinus. Generally, a three-layer reconstruction is performed. Circumferential dissection of the epidural plane facilitates to implant the graft in the epidural space. The three layers are represented by a first internally placed layer that prevents liquor flow, without totally sealing off the leak. This layer can be autologous or heterologous, and has to be shaped that it exceeds for 1 cm the dural edges. It is positioned between the cerebral and dural surface with incisions on the grafts edges to allow anterior adaptation to both sides of the cerebral falx.

As a second or middle graft layer, non-porous materials need to be used. The autologous fascia lata graft is generally preferred among the various options of several autologous materials, such as cadaveric tissues, as it is easy to implant and obtain, and well tolerated, because it heals fast. An adequate size needs always to be considered, as the graft must generously overlap the edges of the leak. Importantly, complete demucosization should be achieved to avoid mucocoeles and to allow adherence.

Finally, for the third layer a nasoseptal flap is usually used, which can be raised from the antero-superior portion of the nasal septum, and might be additionally enlarged to the lateral wall rather than to the floor of the sphenoid sinus. If additional material is required to reach the required length, the clival recess can be obliterated with fat grafting. However, it is not necessary to cover entirely the fascia lata with the nasoseptal flap, because vascularization of the central part of the fascia lata graft initiates early. If for surgical or oncological reasons a nasoseptal flap cannot be used, an extracranial flap of pericranium can be alternatively raised by a bicoronal incision and implanted through a bone window measuring 1.5 x 2.5 cm at the root of the nose from one orbit to the other. The flap pedicles can be attached unilaterally or bilaterally to the supraorbital arteries. If unilaterally attached, an obstruction of the frontal sinuses is less likely, because the rotation arch is greater; instead, if bilaterally attached the blood support will be more robust, but the rotation arch is inferior and increased compression

on the vascular pedicles from the bone window can cause postoperative edema. Endoscopic graft positioning allows keeping the proximal frontal sinus in contact with the posterior bone table; laterally the flap can be pushed between orbital content and orbital roof or can be used to reconstruct the periorbita, if previously resected to verify tumour margins. Both types of flaps should be stabilized with nasal packing to keep them in place for 5-7 days¹⁷.

Posterior cranial fossa: the typical defect requiring reconstruction – often associated with the treatment of tumours such as nasopharyngeal cancer, chordomas and chondrosarcomas – extends from the dorsum sellae floor above the inferior foramen magnum in the sagittal plane and is limited by the carotids. Clival defects are located in an area with intense liquor flow and therefore most difficult to reconstruct. Reconstruction with vascularized flaps is essential, especially in case of irradiated tissue and exposed carotid arteries⁴⁰. Clival bone coverage helps to prevent from osteoradionecrosis and consequent osteomyelitis.

Instead, at the posterior cranial fossa level, a multilayer reconstruction is mandatory with inlay and onlay grafts similar to previous used materials, which cover the entire defect with a vascularized flap. Unlike the anterior skull base, the clival defect should be filled with body fat above the lata fascia onlay graft to allow easier positioning of the vascularized flap and contact with the underlying surface, which reduces the risk of pontine herniation of the paraclival carotids. Nasoseptal flaps extending at the floor and lower meatus of the nasal fossa, are widely used to reconstruct the posterior cranial fossa and to obtain a greater mucous surface; they can be horizontally oriented when transferred. If unavailable, temporoparietal, pericranial fascia or lateral nasal wall flaps can be used. However, the lateral nasal wall is more difficult to prepare and has a limited rotation arc¹⁷.

Middle cranial fossa: defects are located in the Meckel's cave and limited by the inferior and medial internal carotid arteries, the upper orbital fissure and the orbit above. They are less common, smaller and necessitate generally a two-layer reconstruction; an inlay and a vascularized layer might be sufficient even though a classic three-layer approach can be performed using nasoseptal flaps, which require generally a transpterygoid approach from the affected side¹⁷.

Stabilization of the graft with “fixers”

Once reconstruction is completed, grafts should be stabilized. A fixer called fibrin glue is mainly used for autologous free grafts such as mucosa, fat, muscle and mucoperiosteal flaps. Another type of “fixer” are nasal swabs. Merocel and surgical are most widely used and in alternatives avitene, gelfoam and lyfoam can be utilized.

Drainage types after reconstruction

Lumbar or spino-peritoneal drainage can be placed during the intervention, which can remain in place for about three days. The advantage of spino-peritoneal drainage is that during this period, liquor pressure can be directly measured to monitor and regulate the eventual recurrence of liquorrea. Additionally, fluorescein can be intrathecally injected³¹. Once the intervention is completed, presence of fluorescein in liquor allows a quick and immediate intraoperative control if the CSF leak repair was successful. The place of the pre-existing leak is displayed with a blue light filter: a negative finding confirms leak closure. Operation's success can also be verified through Valsalva maneuver, realized with anesthesiologists help.

Instead, placement of a permanent drainage (ventricle-peritoneal or spino-peritoneal) is reserved to selected cases and should be discussed in a multidisciplinary team.

Intraoperative navigation systems for skull base reconstructions and CSF leak

Real-time intraoperative navigation systems are a new technology, which process pre-operatively acquired CT and MR images (Fig. 4), to establish the position of surgeon's instruments on a monitor during the surgery²⁸. This system allows visualization of deeper portions of the skull to avoid lesions of vascular and nervous structures. Additionally, surgical navigation systems can be useful to diagnose neoplastic forms, allowing targeted biopsies. Through imaging fusion tools, it is possible to map any areas removed to verify radicality of surgical treatment. On the monitor, various

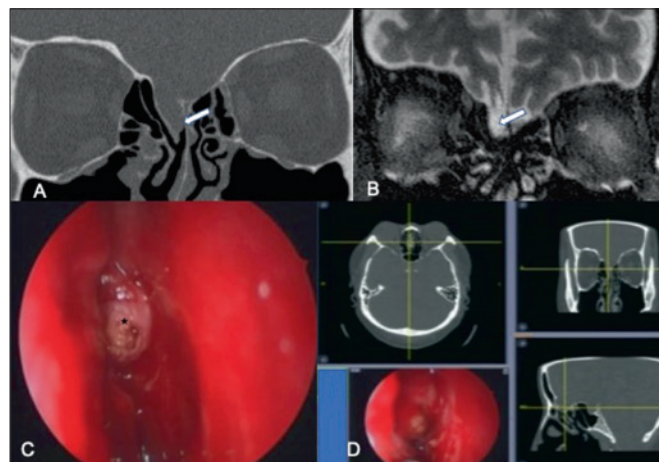


Figure 4 Coronal CT scan (A) and T2 weighted MRI of a case of spontaneous CSF leak due to meningocele of the right olfactory groove. The endoscopic view (C) after precise localization using Navigation System (D) yellow cross-air in the 3 planes and endoscopic view of the tip of the instrument.

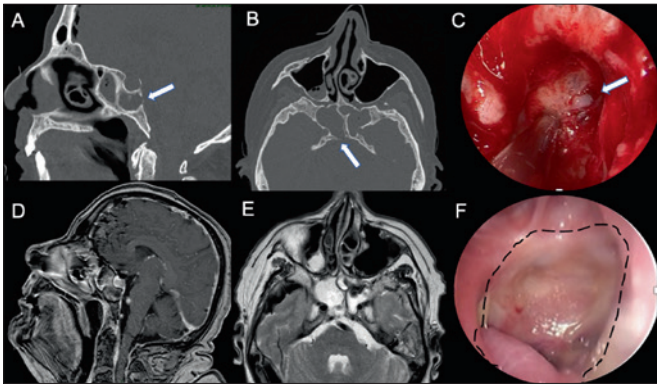


Figure 5. CT scan in sagittal (A) and axial view (B) in a case of meningococcal meningitis (shown in the Sagittal post Contrast Enhancement MRI (D) and T2 weighted MRI (E) The bony erosion on the clivus as it appear endoscopically (arrow) The lesion was treated with multilayer technique and finally nasoseptal flap was used (dotted line in F) as it appear 2 months after surgery.

CT and MR images are simultaneously reported and the location of surgical instruments and video endoscopes are indicated in real-time.

This imaging technique is especially helpful if the surgeon faces the following several difficulties during surgery: anatomical variants, excessive bleeding reducing visibility; absence of reference points due to previous surgeries or invasive diseases, and loss of depth perception related to endoscopy. Mainly two categories of navigation systems exist: those using electromagnetic signals and those using optical signals. Recently, hybrid systems have been developed, which allow using both technologies, depending on the intervention type. New technologies are in constant evolution and can be used for an increasing number of nasosinusal diseases like neoplastic pathologies, severe polyposis, invasive mycotic sinusitis, traumas, orbital decompression, drainage of orbital abscesses, closure of rhinoliquoral fistulas, trans-sphenoidal access to pituitary, coanal atresia, and skull base mucocele (cordomas, chondrosarcoma). Further technological progress concerns the add-on of new generation surgical instruments like 3D, 4K endoscopic systems in addition to the neuronavigation^{4,42,43}.

Post-operative management

Time of hospitalization and post-operative therapeutic measures vary according to patients' general condition and leak features. Life parameters and diuresis should be constantly monitored. The most important element is bed rest. As previously described, patients must remain in supine position for 48 hours, with the head 30° inclined. The nasal package is usually removed during the fifth post-operative day. It is necessary to perform daily nasal hygiene

with physiological solution. Antibiotics should be taken for at least ten days after surgery to prevent from infections. Patients are usually discharged between the fifth and seventh post-operative day, with the indication to avoid physical stress, sneezing or other activities causing increasing of intracranial pressure for about 30 days. Air travel is not recommended. At discharge, a first follow-up visit after 10-15 days from surgery is scheduled in which nasal debridements and residues of the reabsorbable material are removed. Fibrin and the intranasal clots should be aspirated to examine clearly patency of the sinotomies, graft tightness and vitality. A normal or uneventful post-operative course foresees follow-up visits every three months for one year with MRI scheduled at least every 6 months. After that semi-annual checks including MRI visits are planned for two years. Finally, annual checks including MRI for two more years should be performed.

Discussion

CSF leaks are historically difficult to diagnose and treat because of their wide variability¹⁴. Recent years' technical innovations, increasingly combined by multidisciplinary collaborations, have changed the diagnostic and therapeutic paradigm, which is mostly related to a better comprehension of CSF leaks anatomical and physiological aspects^{19,41}.

The main objective of the diagnostics has been to improve the anatomical localization of the leak. It is essential to assess precisely leak dimensions and localization to create adequate therapeutic planning. Nowadays, the combination of multiple CT and RMN fusion imaging strategies allow obtaining a 91% accurate identification pre-operatively. The interaction and role of expert neuroradiologist is of paramount importance. Moreover the development of new and detailed RMN sequences has helped to outline complex CSF leaks. In addition, the possibility to obtain a more sophisticated image navigation systems allows comparing various types of defects and helps to understand differences between CSF leaks and their presentation.

Several critical issues require close collaboration of neurosurgeons and all other professional figures involved in the Skull Base Team, who contribute to manage this complex pathology from an anatomic-functional point of view.

Collaboration with neurosurgeon starts during non-invasive preoperative functional diagnostic and allows clarifying the diagnostic field and gives the possibility to acquire preoperative information on liquor dynamics, intracranial pressure development and differentiation between high and low flow leaks to create a targeted surgical setting. Whenever possible a dedicated radiologist assesses, in collaboration

with ENT and neurosurgeon, MRI and CT scans to identify likely idiopathic intracranial hypertension. Posterior Sclera flattening, widening of optic nerve subarachnoid space widening, optic nerve head protrusion, arachnoid pits (bony scalloping) skull base foramina enlargement, bilateral transverse sinus stenosis, total/partial empty sella are amongst the most common signs of this hypertension type⁴.

Body mass index (BMI), especially in female gender, has a linear relationship with intracranial hypertension, which is closely related to leak's complexity⁴². This population need a strict diagnostic follow-up and a preventive treatment of intracranial hypertension in order to prevent leak's onset. In this population, even after repair intervention, permanence of underlying risk factors involves a chronic increase of intracranial pressure itself with a remodeling and a thinning of basicranium at the level of the thinnest bone limiting. That process favors meninges' bulging through orifices³⁶⁻³⁸. Careful monitoring methods allow early recognition of complications and make it possible to make a second surgical exploration. This kind of multidisciplinary collaboration, could finally allow to deeper and better understand etiology of pathologies still poorly clarified (as in the case of spontaneous CSF leaks).

In recent years, technological advances overcome many of the obstacles associated with endonasal cranial base surgery. The most recent visualization technologies (e.g. 3D and 4K cameras), angled instruments⁴⁹ and their different applications aided also by navigation systems contributed to the fact that the endoscopic endonasal approach become the best surgical approach to treat CSF leaks by offering the best surgical outcomes.

This approach allows achieving success rates of almost 95%, and reduces significantly patient morbidity if performed by highly skilled surgeons²². Although ENT surgeons are directly involved in the surgical procedure, neurosurgeons are necessarily involved to manage and choose complex dural and intracranial reconstruction and to treat eventual complications. Therefore, surgeons need intensive training to acquire surgical skills and experience^{50,51}. To date, no adequate risk stratification to outline reconstructive algorithms still exist. The development of a treatment algorithm based on leaks localization (regardless from causes), dimension and presentation methods is therefore most desirable.

Moreover the predictive criteria to support decision-making on lumbar drain in patients with spontaneous leaks and intracranial hypertension are still absent. It remains unclear how different factors like time of placement (before during or after surgery), intensity of adjustment (more or less than 10 cc/h), and time of removal (correlated to infection

risk) influence outcomes^{17,44}. Neurosurgeons' experience is essential to answer these unsolved questions and to decide on lumbar drain placement during the multidisciplinary assessment in preoperative setting. Increased risks for infections and pneumocephalus causing higher morbidity, mortality, longer hospitalization and cost are well known and need to be considered. Until now the placement of lumbar drain can be generally considered in cases of spontaneous CSF leak due to intracranial hypertension, in case of large dural defects, and high flow fistulas in the anterior and posterior cranial fossa and it is generally not indicated in the reconstruction of sellar or suprasellar defects. Lumbar drain can reduce fistula recurrence from 41% to 5% after transsphenoidal surgery^{52,53}.

Conclusions

CSF leaks remain a challenging issue requiring new and innovative techniques for early diagnosis and treatment. Dynamic multidisciplinary teams, who apply various imaging techniques represented by newer diagnostic and endoscopic technologies to diagnose, treat and rigorously follow up patients, are the future for CSF leak management. Additionally, neurosurgeon's experience will contribute significantly to develop new biomaterials with increased durability, which may replace autologous grafts in the future. New biomaterials might facilitate multilayer repairs and standardize heterogeneity of repair methods, which is related to variability of materials used today and still conditioned largely only by surgeon's preferences.

Conclusively, the correct diagnosis and best treatment can only be determined in a dedicated Skull Base Team composed by neurosurgeons, otolaryngologists, neuroradiologists, ophthalmologists, endocrinologists, in order to completely evaluate a patient with CSF leak from the first visit, during treatment and follow-up.

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