Cerebrospinal fluid rhinorrhea (ECPG)

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Abbreviations

ESBS	Endoscopic skull base surgery
CSF	Cerebrospinal fluid
CPG	Clinical Practice Guideline
GRADE	Grading of Recommendations Assessment, Development and Evaluation
CT	Computerized tomography
HRCT	High resolution CT
MRI	Magnetic Resonance Imaging
NR	Not Reported
ICP	Intracranial pressure
IIH	Idiopathic intracranial hypertension
RCT	Randomized controlled trial
LD	Lumber drain
VP	Ventriculo-peritoneal

Executive Summary

Traumatic and iatrogenic CSF leaks

Consideration for nonsurgical management within the first 7 days is feasible in traumatic skull base injuries (strong recommendation)

Lumbar drains may shorten the interval to traumatic CSF leak cessation during conservative management (conditional recommendation)

The evidence for acetazolamide in traumatic or iatrogenic CSF leaks is lacking (strong recommendation).

There is a lack of evidence to support prophylactic antibiotics administration in patients with a traumatic CSF leak (conditional recommendation).

For defects in the ethmoid roof and sphenoid, Non-iatrogenic (after conservative measures fail) and iatrogenic traumatic CSF (generally not treated conservatively) leaks can be repaired endoscopically with high success rates (strong recommendation)

For frontal sinus defects, the transnasal endoscopic approach to frontal sinus CSF leaks is safe and effective in select patients, but may have higher rates of failure than other locations (strong recommendation).

Spontaneous CSF rhinorrhea

There is a direct relationship between spontaneous CSF leaks and IIH; most spontaneous leaks represent a variant of IIH (strong recommendation).

After clinical examination, B2- transferrin and beta trace protein are the initial preferred methods of detection of CSF leaks (conditional recommendation).

For site of leak detection, High resolution CT (HRCT) and Magnetic resonance imaging (MRI) are the initial imaging modalities (non invasive). CT cysternography with intrathecal dye injection (Invasive) may be required if the previous measures failed to determine the site of leak (conditional recommendation).

Perioperative lumbar drains are not necessary for the successful repair of most spontaneous CSF leaks. Lumbar drains remain an option for adjunctive measures such as administration of intrathecal fluorescein or high-risk cases (strong recommendation) (Recommendation against except in high risk cases).

Postoperative ICP management should be considered in patients with spontaneous CSF leaks and elevated ICPs. Acetazolamide can be used as an effective ICP-lowering medication with an option of CSF shunting procedures in patients unable to tolerate medical management or with recalcitrantly elevated ICPs or recurrent CSF leaks (conditional recommendation).

Reconstructive technique should be left to the discretion of the surgeon with consideration of defect location, size and etiology (strong recommendation).

Intrathecal application is an off-label use of fluorescein for which informed consent must be obtained from the patient (conditional recommendation).

Introduction, scope and audience

Introduction

CSF rhinorrhea, results from an osseous defect in the skull base with an associated dural fistula. a. Traumatic leaks are the most common type of CSF leak and include non-iatrogenic (blunt or penetrating injuries) or iatrogenic injuries (usually unintentional violation of the skull base during rhinologic or neurosurgical procedures). Other CSF leak etiologies include spontaneous, congenital, and neoplastic origins. If untreated, it can lead to serious complications. Many controversies exist in the management of CSF rhinorrhea

Scope: The scope of the guideline is the diagnosis and management of CSF rhinorrhea of various causes and locations of the skull base. The guidelines are intended to specify the recommended diagnostic tools and the recommended management options in different situation with the aim of raising the standard of care and unifying methods of management among practitioners.

Target audience: ENT, neurosurgical and neurology physicians involved in the management of skull base pathologies.

Methods

Methods of development
Stakeholder Involvement: Individuals who were involved in the development process. Included the above-mentioned Rhinology Chief Manager, Rhinology Executive Manager, Assembly Board, Grading Board and Reviewing Board.

Information about target population experiences were **not applicable** for this topic.

Search Method
Electronic database searched:
Pubmed, Medline, Egyptian Knowledge Bank, Medscape, WebMD, Google Scholar

Keywords
CSF rhinorrhea, Endoscopic skull base surgery, skull base repair

The adaptation cycle passed over: set-up phase, adaptation phase (Search and screen, assessment: currency, content, quality & /decision/selection) and finalization phase that included revision and external reviewing.

Time period searched: from 2009 to 2019.

Results
The guidelines were chosen and formulated by the assembly team which consisted of four national otorhinolaryngologists. **The International Consensus Statement on Allergy and Rhinology: Endoscopic Skull Base Surgery (ICAR: ESBS), 2019** gained the highest scores as regards currency, contents and quality.

It was graded (GRADE) by 17 experts and reviewed by three expert reviewers to improve quality, gather feedback on draft recommendations.

The external review was done through a rating scale as well as open-ended questions.

Setting: primary, secondary and tertiary care centers & hospitals and related specialties.

Interpretation of strong and conditional recommendation for an intervention

Audience	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action; only a small proportion would not. Formal decision aides are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to the recommendation could be used as a quality criterion or performance indicator.	Different choices will be appropriate for individual patients, who will require assistance in arriving at a management decision consistent with his or her values and preferences. Decision aides may be useful in helping individuals make decisions consistent with their values and preferences.
Policymakers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

WHO handbook for guideline development – 2nd ed.
Chapter 10, page 129

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to Decision frameworks (GRADE Working Group 2013)

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Recommendations,

The following statements were adapted from **The International Consensus Statement on Allergy and Rhinology: Endoscopic Skull Base Surgery (ICAR: ESBS), 2019** which received the highest scores as regards the currency, contents, and quality.

Recommendations statements

Accepted statements	
Modified statements	
Added statements	

The flowchart was developed from the assembly board to simplify the statements and putting it in a practical way. The flowchart has the same information contained in the statements.

	Clinical issue	Action recommendation	Evidence quality	Strength of recommendation	Study type	reference s
		Traumatic and iatrogenic CSF leaks				
1	Non surgical management	Consideration for nonsurgical management within the first 7 days is feasible in traumatic skull base injuries.	Moderate	Strong recommendation	RCT (12) And retrospective case series (13, 16)	1, 12, 13, 16
2		Lumbar drains may shorten the interval to traumatic CSF leak cessation during conservative management.	Moderate	Conditional recommendation	RCT (12) And retrospective case series 13, 16)	1, 12, 13, 16
3		The evidence for acetazolamide in traumatic or iatrogenic CSF leaks is lacking.	Moderate	Strong recommendation (against)	RCT (12) And retrospective case series (13, 16)	1, 12, 13, 16
4	Prophylactic antibiotics	There is a lack of evidence to support prophylactic antibiotics administration in patients with a traumatic CSF leak.	Moderate	Conditional recommendation	RCT (12) and retrospective case series (13,14,15,16)	1, 12, 13, 14, 15,
5	Defects of the ethmoid roof and sphenoid	Non-iatrogenic (after conservative measures fail) and iatrogenic traumatic CSF (generally not treated conservatively) leaks can be repaired endoscopically with high success rates.	Moderate	Strong recommendation	Systematic review (2,4)	1, 2, 4
6	Frontal sinus defects	The trans-nasal endoscopic approach to frontal sinus CSF leaks is safe and effective in select patients, but may have higher rates of failure than other locations.	Low	Strong recommendation	Retrospective case series (9, 10, 11)	1, 9, 10, 11

	Spontaneous CSF rhinorrhea					
7	The relationship between idiopathic intracranial hypertension (IIH) and spontaneous CSF rhinorrhea.	There is a direct relationship between spontaneous CSF leaks and IIH; most spontaneous leaks represent a variant of IIH.	Moderate	Strong recommendation	Evidence based review (19) Retrospective case series (17, 18) Case control studies (20, 21)	1, 17, 18, 19, 20, 21
8	Confirmation of leak by Lab testing.	After clinical examination, B2- transferrin and beta trace protein are the initial preferred methods of detection of CSF leaks.	Very low	Conditional recommendation	Retrospective case series (7,22,23,24)	1, 7, 22, 23, 24
9 **9**	Site of leak localization.	The chronological order of the investigations is: -High resolution CT (HRCT), (non invasive). -Magnetic resonance imaging (MRI) (Non invasive). -CT cysternography with intrathecal dye injection (Invasive) if the above measures failed.	Very low	Strong recommendation	Retrospective case series (7,22)	1, 7, 22
10	Role of perioperative ICP management with lumbar drains.	Perioperative lumbar drains are not necessary for the successful repair of most spontaneous CSF leaks. Lumbar drains remain an option for adjunctive measures such as administration of intrathecal fluorescein or high-risk cases.	Moderate	Strong recommendation (against)	Systematic review (25) Randomized prospective (26) Retrospective case series	1, 25, 26, 27
11	Role of postoperative ICP management with acetazolamide or shunting.	Postoperative ICP management should be considered in patients with spontaneous CSF leaks and elevated ICPs. Acetazolamide can be used as an effective ICP-lowering medication with an option of CSF shunting procedures in patients unable to tolerate medical management or with recalcitrantly elevated ICPs or recurrent CSF leaks.	Low	Conditional recommendation	Randomized prospective (26) Retrospective case series (28,29,30)	1, 26, 28, 29, 3

12	Technique of reconstruction and reconstruction materials.	Reconstructive technique should be left to the discretion of the surgeon with consideration of defect location, size and etiology.	Very low	Strong recommendation	Retrospective case series (18, 30) Systematic review (2, 31)	1, 2, 18, 30, 31
13	Intrathecal fluorescin.	Intrathecal application is an off-label use of fluorescein for which informed consent must be obtained from the patient. Recommendations are to inject 0.05 to maximally 0.1 ml per 10 kg body weight; in no case however, more than 1.0 ml, not even in a massively overweight patient must be applied.	Very low	Conditional recommendation	Retrospective case series (7,32,33,34,35)	1, 7, 32, 33, 34 35

Implementation considerations

Research needs

- There is a need to conduct randomized controlled trials (RCTs) to determine the safety of using intrathecal fluorescein in localizing skull base defect.
- There is a need to conduct RCTs to compare between grafts and vascularized flaps in repair of skull base defects.
- There is a need to conduct RCTs to detect the safety and efficacy of repair of frontal sinus leaks using the endoscopic technique.
- More studies are needed to determine the ideal duration of conservative Nonsurgical management options in traumatic and iatrogenic CSF leaks.
- More studies are needed to evaluate the effect and optimal duration of medical management of idiopathic increase intracranial tension

Monitoring and evaluating the impact of the guideline

Monitoring/ Auditing Criteria:

Clinicians should be able to

- Take full history and perform clinical examination including endoscopic assessment
- Follow the order of investigation from starting by the non-invasive (CT and MRI) and resorting to the invasive (intrathecal contrast) only in case of need
- Be able to detect clinical and radiological criteria of increased intracranial pressure
- Make good consultation and referral if the setting and expertise are insufficient at his place of practice.
- Follow up and detect symptoms and signs of complications specifically meningitis and pneumocephalus

Updating of the guideline

Updating Procedure:

Any recommendation of this guideline will be updated when new evidence that could potentially impact the current evidence base for this recommendation is identified. If no new reports or information are identified for a particular recommendation, the recommendation will be revalidated. The focus will be on recommendations supported by very-low- or low certainty evidence and where new recommendations or a change in the published recommendations may be needed.

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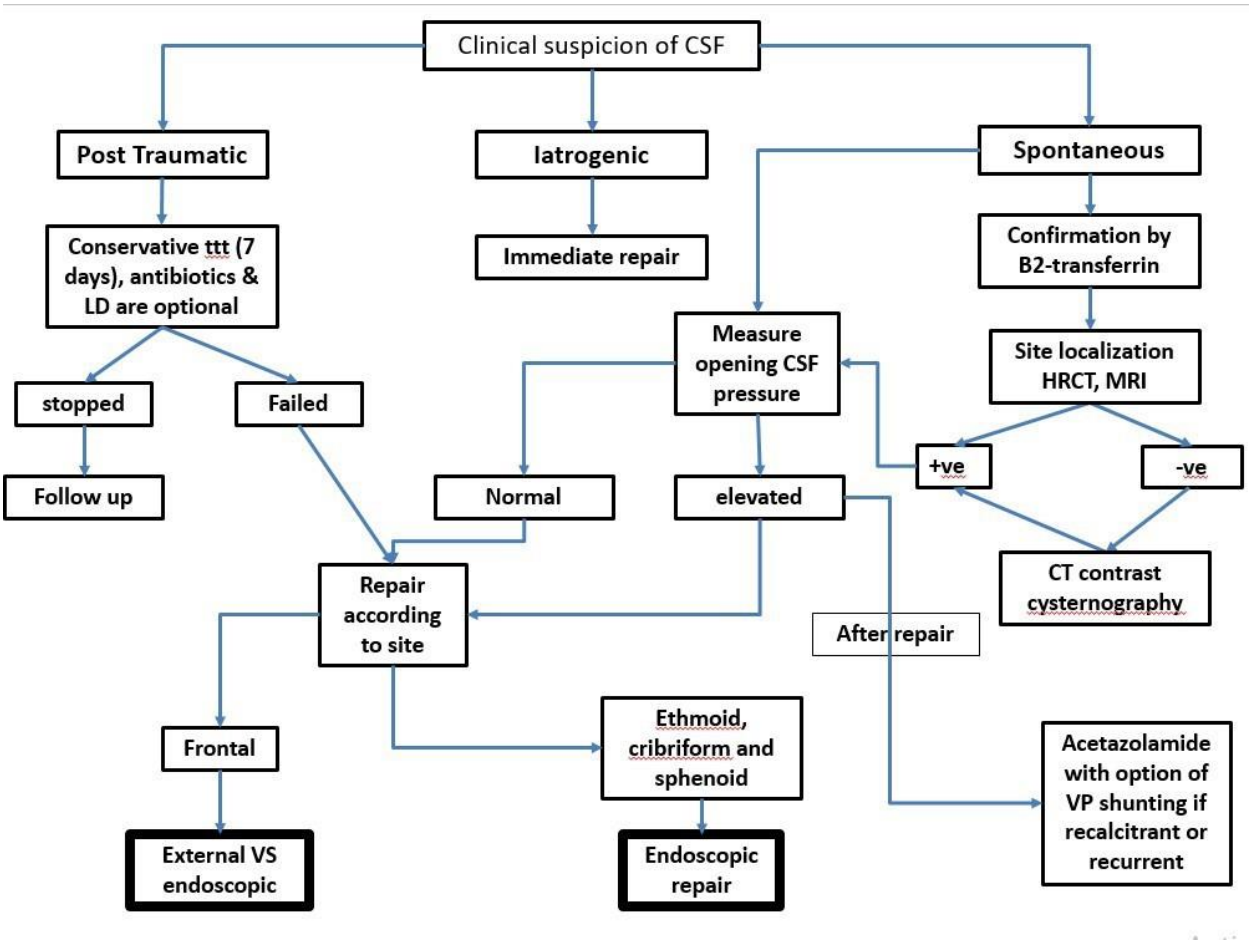
Annexes

Editorial Independence:

- This guideline was developed without any external funding.
- All the guideline development group members have declared that they do not have any competing interests.

Annex 1: Guideline Flowchart



Annex 2: <u>Tables of appraisal of selected guidelines:</u> Currency (table 1), Content (table 2) and Quality (table 3) of the selected guidelines.

No	Guidelines name	year of pblication	The Organizaion	Age of Demography
1	ICAR (international consensus statement allergy and rhinology)- ESBS	2019	the American Rhinologic Society and the American Academy of Otolaryngic Allergy	Adult and children
2	Europian position paper on endoscopic management of tumors of the nose, PNS and skull base	2015	European Rhinologic Society	Adult and children
3	A systematic review of secondery CSF rhinorrhea (2017)	2017	*Department of Otolaryngology—Head and Neck Surgery, Mount Sinai Medical Center,*	Adult and children
4	The endoscopic endonasal repair for iatrogenic and non iatrigenic CSF leaks and encephaloceles of the anterior cranial fossa (2014	2014	Weill Cornell Medical College, New York Presbyterian Hospital, New York, New York, USA	Adult and children

(Table 1): assessment of currency table

Criteria	Guideline A (ICAR-ESBS)	Guideline B (EPOS)	Guideline C *A systematic review of secondery CSF rhinorrhea (2017), Mount Sinai Medical Center*	Guideline D *The endoscopic endonasal repair for iatrogenic and non iatrigenic CSF leaks and encephaloceles of the anterior cranial fossa (2014) Weill Cornell Medical* *College, New York*
Credibility	9	8	7	7
Observability	9	8	7	7
Relevance	9	9	7	6
Relative advantage	9	6	6	7
Easy to install and understand	9	8	8	7
Compatibility	8	8	8	8
Testability	8	8	8	8
Total Score	61	55	51	52

(Table 2) assessment of content table

	Guideline A (ICAR-ESBS)	Guideline B (EPOS)	Guideline C *A systematic review of secondery CSF rhinorrhea (2017),Mount Sinai Medical Center*	Guideline D *The endoscopic endonasal repair for iatrogenic and non iatrigenic CSF leaks and encephaloceles of the anterior cranial fossa (2014Weill Cornell Medical* *College, New York*
Transparency	**A**	**A**	**B**	**B**
Conflict of interest	**B**	**B**	**B**	**B**
Development group	**B**	**C**	**C**	C
Systematic revie	**A**	**A**	**A**	**B**
Grading of evidence	**A**	**A**	**B**	**B**
recommendation	**A**	**B**	**C**	**C**
External review	**B**	**NR**	**NR**	**NR**
updating	**B**	**B**	**B**	**B**

(Table 3) assessment of quality table

Annex 3: The risks and benefits of added and/or modified statements

Changed or added statement	Benefit	risk
Consideration for nonsurgical management within the first 7 days is feasible in traumatic skull base injuries. (**Recommendation**)	It will avoid unnecessary interventions for many **accidental** non iatrogenic CSF leaks as chance of spontaneous closure is high and risk of meningitis is low during the 1st week of injury	Though little chance, meningitis can still occur during the first week of CSF leaks
After clinical examination, B2- transferrin and beta trace protein are the initial preferred methods of detection of CSF leaks	Of help in cases of symptomatic patients with no radiological detection of leak site	No harm but the test is not available in most clinical settings
The chronological order of the investigations is -High resolution CT (HRCT), (non invasive) -Magnetic resonance imaging (MRI) (non invasive) -CT cysternography with intrathecal dye injection (invasive) if the above measures failed	This order of asking investigations for site of leak detection avoids unnecessary exposure to invasive procedure in the majority of patients	No harm
Intrathecal application is an off-label use of fluorescein for which informed consent must be obtained from the patient. Recommendations are to inject 0.05 to maximally 0.1 ml per 10 kg body weight; in no case however, more than 1.0 ml, not even in a massively overweight patient must be applied	Benefit is high and risk is very low according to most studies	although rare, some adverse effects can still occur