

## Cerebrospinal Fluid Biomarkers Consensus guidelines for lumbar puncture in patients with neurological diseases

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## Abstract

**Introduction:** Cerebrospinal fluid collection by lumbar puncture (LP) is performed in the diagnostic workup of several neurological brain diseases. Reluctance to perform the procedure is among others due to a lack of standards and guidelines to minimize the risk of complications, such as post-LP headache or back pain.

**Methods:** We provide consensus guidelines for the LP procedure to minimize the risk of complications. The recommendations are based on (1) data from a large multicenter LP feasibility study (evidence level II-2), (2) systematic literature review on LP needle characteristics and post-LP complications (evidence level II-2), (3) discussion of best practice within the Joint Programme Neurodegenerative Disease Research Biomarkers for Alzheimer's disease and Parkinson's Disease and Biomarkers for Multiple Sclerosis consortia (evidence level III).

**Results:** Our consensus guidelines address contraindications, as well as patient-related and procedure-related risk factors that can influence the development of post-LP complications.

**Discussion:** When an LP is performed correctly, the procedure is well tolerated and accepted with a low complication rate.

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## Keywords:

Lumbar puncture; Cerebrospinal fluid; Post-LP complications; Headache; Back pain; Consensus guidelines; Evidence-based guidelines

## 1. Introduction

Lumbar puncture (LP) is a technique to sample cerebrospinal fluid (CSF) as a window into brain pathology ([Supplemental Data](#)). The procedure involves introducing a needle into the subarachnoid space of the lumbar sac, at a level safely below the spinal cord [1]. Despite modern neuroimaging techniques, LP remains an important diagnostic tool as CSF analysis provides important diagnostic information for many neurological conditions. For example, no procedure can replace the CSF analysis in differential diagnosis of infectious disorders of the central nervous system (e.g., bacterial or viral meningitis, neuroborreliosis). Moreover, CSF analysis is now at the core of the diagnostic criteria for the diagnosis of Alzheimer's disease [2–4]. In addition, an LP is the easiest procedure to perform a CSF pressure measurement. Given the use of CSF analysis for diagnosis, LPs are currently often performed to perform research to discover novel diagnostic biomarkers and understand brain pathology.

A recent large international, multicenter study on LP feasibility that included 3868 patients in a memory clinic setting showed that LPs can be safely performed [5]. The

acceptance rate of an LP was high, especially taking into consideration that there was no acute medical indication.

The most common complications of LP consist of post-LP back pain and post-LP headache (PLPH) [6]. PLPH typically begins within three days after the procedure in most patients [7]. If a patient develops typical PLPH, bed rest, adequate hydration, and simple analgesics should be started [8]. Further review of possible treatments will be given in later sections of this study.

Very rare (prevalence of <0.01%) but potential serious complications consist of post-LP infections, spinal and subdural cerebral hematoma, and cerebral venous thrombosis [1]. In the multicenter LP feasibility study, a substantial proportion (31%) of patients reported post-LP complaints; however, these were mostly mild in nature, and severe complications were very rare [5]. Back pain, headache, and typical PLPH were reported by 17%, 19%, and 9%, respectively [5]. Only 0.3% of the patients needed a blood patch, and in 0.7%, a hospitalization was required [5]. The most important risk factors for post-LP complaints were related to patient characteristics: history of headache and fear of complications.

A cutting bevel needle type appeared to be the only procedure-related risk factor for typical PLPH. The number of LP attempts was the only procedure-related risk factor for occurrence of local back pain. A large needle diameter ( $\leq 22$ G, gauge [G]) was a risk factor for severe headache [5].

To date, consensus guidelines and recommendations for the LP procedure to optimize diagnostic yield and to minimize the risk of complications are lacking. We developed consensus guidelines and recommendations for the LP procedure based on the international multicenter LP feasibility study outcomes combined with a literature-based analysis of risk factors. These guidelines will be applicable to neurological brain diseases that require a diagnostic LP. Moreover, these guidelines will serve to reduce complication rates in daily neurological practice, will be a reference for educational purposes, thus be of help for trainees in neurology, and will be a guide to comfort or give adequate information to the patients.

## 2. Materials and methods

These consensus guidelines originate from two international consortia. The EU Joint Programme Neurodegenerative Disease Research (JPND) consortium "Biomarkers for Alzheimer's disease (AD) and Parkinson's Disease (PD)" (BIOMARKAPD) aims at standardizing and harmonizing existing biomarkers for AD and PD. The Biomarkers for Multiple Sclerosis (BioMS) consortium aims at optimizing all aspects of CSF biomarkers research for multiple sclerosis and related disorders, via collaboration and developing guidelines for relevant procedures. One of the objectives of these consortia is to standardize and harmonize preanalytical procedures for CSF biomarkers that are used for or contribute to diagnosis for neurological diseases. These preanalytical procedures include the LP procedure.

To provide consensus recommendations for the LP procedure to optimize diagnostic yield and minimize the risk of complications, three consecutive steps were used:

- (1) data from the large multicenter LP feasibility study [5],
- (2) systematic literature review on LP needle characteristics and post-LP complications,
- (3) discussion within the JPND BIOMARKAPD (53 member centers) and BioMS (30 member centers) consortia.

Our consensus guidelines address contraindications, as well as patient-related and procedure-related risk factors for the development of post-LP complications. Based on U.S. preventive services task force [9], the level of evidence of these recommendations is indicated. The level of evidence was mostly level II-2 (well-designed cohort preferably with more than one research group or center [e.g., data of large multicenter LP feasibility study]) and level III (consensus evidence based on clinical experience of the two consortia involved [JPND BIOMARKAPD and BioMS]).

### 2.1. Systematic literature review search strategy

As several studies have been published with regard to the relation of LP needle characteristics and post-LP complications, we performed a systematic literature review, covering relevant articles that have been published between January 1970 and April 2016. Searches were conducted through PubMed and Google Scholar. Only English articles that contained *needle\** and *lumbar punctur\** in title and/or abstract were taken into account [1]. In total, 307 articles were found in the databases and screened/selected based on PRISMA (Supplementary Material, Supplementary Fig. 1) [10]. Case reports ( $n = 22$ ), reviews ( $n = 29$ ), articles about animal models ( $n = 6$ ), and articles that not presented a recommendation of a choice of needle were deselected ( $n = 187$ ). Of the 63 remaining articles, statements ( $n = 3$ ) and comments ( $n = 7$ ) about other publications were deselected as well. Three "statement" articles pointed out that atraumatic needles with a small-bore diameter ( $\geq 24$ G) are not often used in practice although literature often recommend using this type of needle [11–13]. Three of the seven comments had no recommendation [14–16], two agreed with the original article which recommended atraumatic needles [17,18], one article agreed on small-bore needles [19], and one article recommended small-bore atraumatic needles [20]. In total, 53 fulfilled our criteria and were subdivided into three groups. Articles that made recommendations on needle design ( $n = 24$ ), the second group consisted of articles with recommendations on needle diameter ( $n = 12$ ), and the last group that did both (needle design and diameter,  $n = 17$ ).

The 53 articles that did recommend a specific needle type were graded based on the grade system described by Leone et al. [21] (Supplementary Material, Supplementary Table 1). Articles were classified as "low evidence" if they had a total score (sum = limitations assets) of  $\leq -5$  ( $n = 5$ ), "medium evidence" articles if they had a score between  $-4$  and  $+4$  ( $n = 21$ ), and "high evidence" articles if they had a score  $\geq +5$  ( $n = 27$ ). For an extensive description of the grading approach, we refer to the Supplementary Material.

### 2.2. Selection of variables to become part of the consensus guidelines

Based on the results of the multicenter LP feasibility study [5] as well as on the systematic literature review [1], the following variables were selected to provide consensus guidelines:

- Conditions representing (potential) contraindications for LP: the risk for cerebral herniation including space-occupying lesion with mass effect, abnormal intracranial pressure due to increased CSF pressure and Arnold-Chiari malformation, increased bleeding risk (thrombocytopenia, coagulopathies, anticoagulant drugs), and local infections at the puncture site.

Table 1  
Procedures to rule out contraindications for LP

Contraindication for LP	Procedures to rule out contraindications	Required action
1. Space-occupying lesion with mass effect, increase of intracranial pressure due to increased CSF pressure 2. Posterior fossa mass 3. Arnold-Chiari malformation	Clinical neurological examination Fundoscopy	Perform brain CT/MRI scan if - Abnormal clinical neurological examination - Papilledema - (Patient has) reduced consciousness - (Patient is) immune compromised - (Patient has) previous CNS disease - (Patient had) recent seizures
4. Anticoagulant medication	Check medication before LP	Can anticoagulants temporarily be discontinued?
5. Coagulopathy 6. Uncorrected bleeding diathesis	Recent blood analysis: platelet $>40 \times 10^9/L$ ; quick $> 50\%$ ; INR $< 1.5$	Correction possible?
7. Congenital spine abnormality	Local inspection Imaging in case of suspicion of tethered cord	Guidance of LP procedure by fluoroscopy, ultrasound, or CT
8. Skin infection at puncture site	Local inspection	Treat skin infection

Abbreviations: LP, lumbar puncture; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; CNS, central nervous system; INR, international normalized ratio.

NOTE. All recommendations are based on level-III evidence.

- Patient-related factors, associated with increased risk for post-LP complications: age, gender, history of headache, and fear of LP.
- Procedure-related factors that were associated with increased risk for post-LP complications such as design and diameter of the needle, number of LP attempts, active versus passive withdrawal of CSF, reinsertion of the stylet, positioning of the patient during LP, use of local anesthetic, volume of CSF that was withdrawn during LP, as well as bed rest after LP.
- Review of the possible treatments of PLPH.

### 2.3. Strategy to reach consensus

A first set of guidelines was designed based on the results of the international multicenter LP feasibility study [5], available literature [1], and systematic literature review. These were discussed during a JPND “BIOMARKAPD” general assembly, after which the guidelines were further adapted (Mainz, Germany, spring 2014). A second version of the consensus guidelines was drafted by S.E., E.N., H.S., F.D., and C.E.T. This draft was e-mailed (July, 2014) to all participants of the JPND “BIOMARKAPD” task force on standardization of preanalytical procedures, who were invited to provide their comments and feedback. The prefinal draft was subsequently mailed (November, 2014) with an invitation for feedback to BioMS members and neurologists being key opinion leaders in neurological disorders other than neurodegenerative brain diseases. The feedback and comments obtained in this way was subsequently integrated which resulted in the present consensus guidelines. This final version of the consensus guidelines was again sent to all coauthors for final approval.

## 3. Results

### 3.1. Identification of LP contraindications

Contraindications were identified from the available literature. The most important contraindication for LP is an intracranial space-occupying lesion with mass effect as well as a posterior fossa mass because it can lead to herniation of the cerebellar tonsils, regardless of the volume of CSF that is sampled [22–26]. Other contraindications for LP include a risk for cerebral herniation caused by abnormal intracranial pressure due to increased CSF pressure or Arnold-Chiari malformation, as well as anticoagulant medication, coagulopathies and uncorrected bleeding diathesis, congenital spine abnormalities, and local skin infection at the puncture site (Table 1). Based on consensus (evidence level III); a brain computed tomography or magnetic resonance imaging scan should at least be performed before LP if an intracranial lesion with mass effect, abnormal intracranial pressure due to increased CSF pressure, or tonsillar herniation is suspected, or whenever a patient has focal neurological deficits, is immune compromised, has a previous central nervous system disease, recent seizures, impaired consciousness, or papilledema at fundoscopy. The following imaging findings should be considered as a contraindication for LP:

- Evidence for a pressure gradient across the falx cerebri. Unequal supratentorial pressure gradients can result in a lateral shift of midline structures. Asymmetry of lateral ventricles is frequently a result of congenital brain abnormality or congenital/perinatal stroke, presenting an abnormal anatomical variant. On the other hand, an asymmetry of the lateral ventricles should not be considered to be an accurate sign, as ipsilateral ventricular dilation may be caused by stroke and as

coaptation of a frontal horn may represent a normal anatomical variant. Performing an LP in patients with unequal supratentorial pressure gradients can result in compression of the ipsilateral temporal lobe, leading to uncal herniation.

- Evidence for a pressure gradient between the supratentorial and infratentorial compartments.

Such pressure gradient may be caused by elevated pressure above the tentorium cerebelli, and elevated pressure below the tentorium cerebelli. Under these circumstances, LP may lead to a bilateral uncal herniation.

- Arnold-Chiari malformation. Patients with an Arnold-Chiari malformation are prone to develop tonsillar herniation, sometimes even after removal of small volumes of CSF.

Brain and spinal hemorrhage and spinal epidural or subdural hematoma are rare but potentially serious complications of an LP. For example, in the multicenter LP feasibility study, only 1 of 3558 patients who underwent LP experienced this side effect (leading to death after restarting their oral anticoagulant) [5]. Therefore, it is advised (level-III evidence) to have a recent analysis of the platelet count (that should be  $>40 \times 10^9/L$ ) and coagulation status (quick  $>50\%$ ; international normalized ratio  $<1.5$ ). Coagulopathies and uncorrected bleeding diathesis should be absent. It is advised (level-III evidence) to discontinue anti-coagulant treatments to minimize hemorrhagic risks. The short-acting direct oral anticoagulants (DOACs) have as advantage that they can be discontinued shortly before the LP and that anticoagulation can be restarted within a few hours (6–8 hours) after the procedure [27]. The decision process should take into account the risk of discontinuation and consequent risk of thrombosis, the possibility of bridging with a low molecular weight or intravenous heparin (which is not advised in case of DOACs), as well as the potential benefit of the LP, and possible alternative examinations (e.g., amyloid positron emission tomography instead of LP to analyze AD biomarkers in CSF) [28]. Antiplatelet drugs are only a relative contraindication, and most centers do not interrupt treatment with antiplatelet drugs before LP. Studies on LP complication risks in cases taking combinations of antiplatelet drugs (e.g., clopidogrel and acetylsalicylic acid) are lacking, but it is considered safer to temporarily withhold one of both before LP (level-III evidence). In case of dual antiplatelet therapy, it is advised to continue acetylsalicylic acid, whereas the intake of thienopyridine derivatives (e.g., clopidogrel, ticlopidine) should be temporarily withheld (1 or 2 weeks) before LP unless patients are at high thrombotic risk or unless there is an urgent indication to perform an LP (level-III evidence) [29]. Congenital spine abnormalities and spinal cord abnormalities (e.g., tethered cord), or local skin infections at the LP site can be contraindications to perform an LP. In case of congenital spine abnormalities, the LP procedure can be

guided by fluoroscopy, ultrasound, or computed tomography [1,30–33]. Performing an LP through infected tissue increases the risk of central nervous system infections and reduces the diagnostic value of the LP in case of a suspected central nervous system infection.

### 3.2. Patient-related risk factors

Data from the international multicenter LP feasibility study indicate that patient characteristics are equally important as LP procedure-related factors with regard to the risk for post-LP complications (PLPH, post-LP back pain) [5].

Younger age is the most important and well-known risk factor for PLPH and post-LP back pain [5,34,35]. Both Monserrate et al. and the multicenter LP feasibility study, including patients age  $66 \pm 11$  years, did not demonstrate a gender difference [5,36], although it was repeatedly reported that PLPH is more common in women than in men, and especially women aged less than 40 years seem to have a substantially higher risk of PLPH [7,34,35,37–39]. Patients with history of headache had a higher risk to develop PLPH and post-LP back pain (Figs. 1 and 2) [5]. Although age was accounted for, a diagnosis of mild cognitive impairment or dementia was still associated with a risk reduction of these post-LP complications in a memory clinic setting. Although these patient-related risk factors for post-LP complaints cannot be modified, these variables can be of help to identify those patients that are at high risk to develop post-LP complications. This information can be used by physicians for counseling purposes (level II-2 evidence).

In the multicenter LP feasibility study, it was shown that fear of LP was an important independent risk factor for experiencing post-LP complaints (Figs. 1 and 2) [5]. Hence, there seems to be a psychological effect of anxiety relating to more complaints, which might be explained by lack of information beforehand, personality characteristics, or even a placebo effect of the LP [40]. As fear of the LP and post-LP complications can be influenced by the attitude of the physician and nursing staff and can be decreased by giving reassuring but adequate information, it is of most importance to carefully inform the patient. Moreover, although use of local anesthesia is not related to reduced post-LP complaints, it may help to control the fear of the LP procedure. The physician should explain the procedure and should outline the potential complications as well as the diagnostic benefits from having an LP. Some of the patient-related risk factors for post-LP complications can also be used to reassure patients (e.g., when there is no history of headache, patients are older or optimal needle type is used). During the LP procedure, it is important to explain the different steps of the LP procedure, thereby reducing eventual anxiety and discomfort, meanwhile considering the eventual cognitive deficits that affect memory and language comprehension, which requires a stepwise approach (level II-2 evidence).

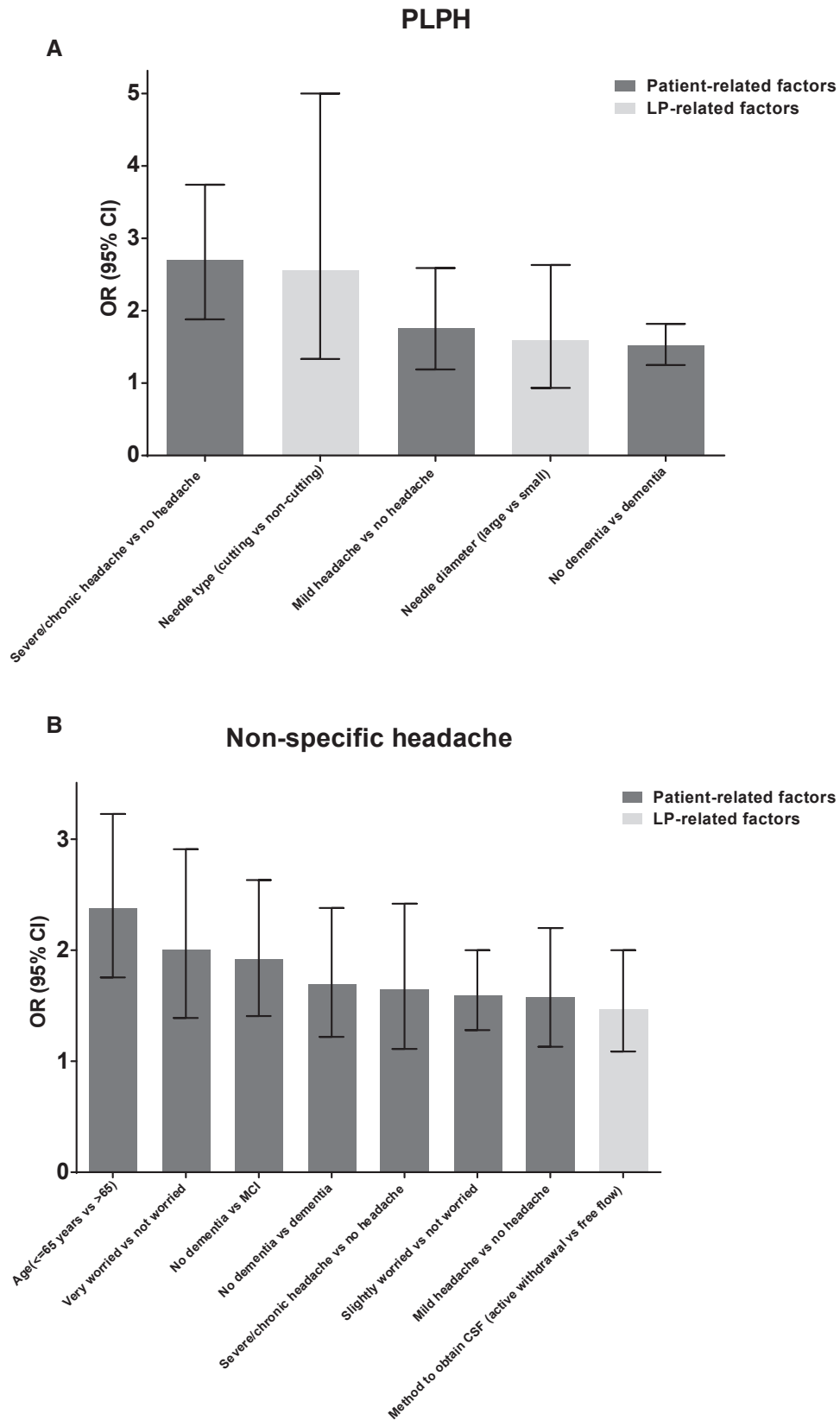


Fig. 1. Risk factors for PLPH (A) and nonspecific headache (B) ranked by magnitude (defined by odds ratio) as reported by the multicenter LP feasibility study [5]. Abbreviations: CI, confidence interval; LP, lumbar puncture; OR, odds ratio; PLPH, post-LP headache.

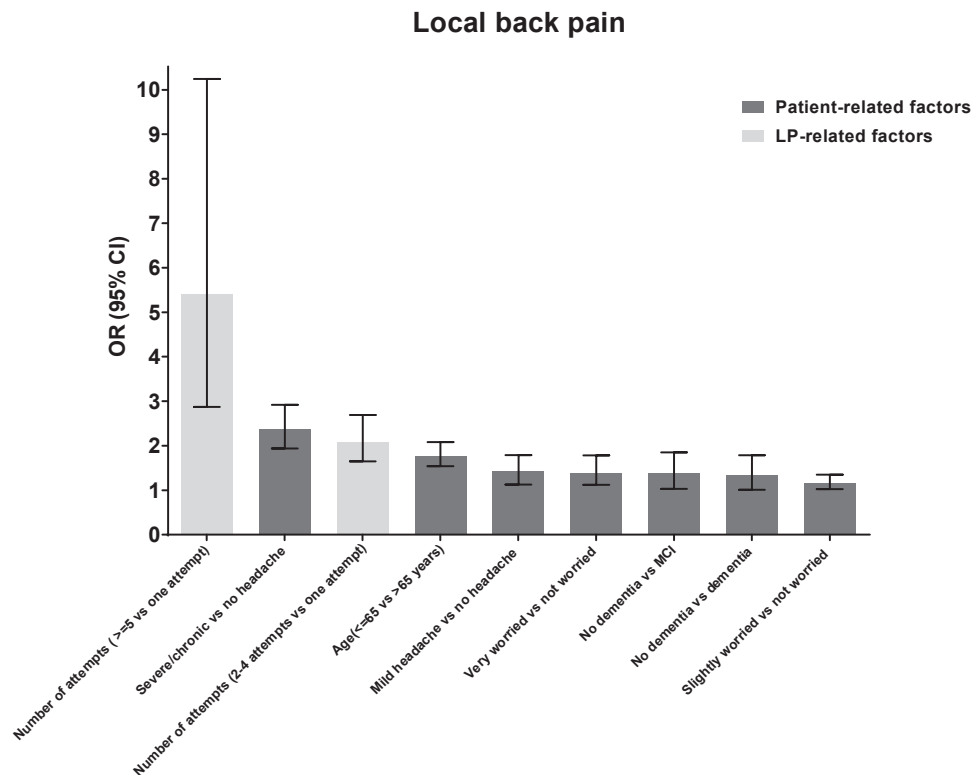


Fig. 2. Risk factors for back pain ranked by magnitude (defined by odds ratio) as reported by the multicenter LP feasibility study [5]. Abbreviations: CI, confidence interval; LP, lumbar puncture; OR, odds ratio.

### 3.3. LP procedure-related factors

#### 3.3.1. LP procedure

Infection is a rare but potentially serious complication of an LP. Therefore, also in an outpatient setting, an aseptic technique should be applied using sterile gloves, and a thorough disinfection of the lumbar region of the patient. Furthermore, the physician can use a mask to minimize the risk for infection. Excess of the antiseptic solution should be removed from the skin before needle insertion (level-III evidence). We refer to Fig. 3 for the LP procedure [1,41], which holds true for both atraumatic and cutting bevel needles [39,42,43].

During a minority of the LP procedures, nerve root irritation may occur [44]. The patient should be informed on beforehand that this may occur, albeit not dangerous, nor linked to any complications (level-III evidence).

#### 3.3.2. LP needle

The optimal needle length, diameter, and design should be chosen when an LP is performed. This choice also depends on the medical indication (e.g., LP as urgent procedure in case of acute bacterial meningitis vs. an LP to sample CSF to analyze AD biomarkers). Important variables are as follows: adequate flow rate, fast and accurate transduction of CSF pressure, minimizing traumatic taps, leakages, failures, and post-LP complications. LP needles differ with regard to length, diameter, and design. The choice

of the needle depends on a patient's age and weight, the purpose of the LP procedure, and should be focused on minimizing discomfort and risk for complications (Table 2).

Interestingly, the multicenter LP feasibility study showed that effects of needle design and diameter were not as important for post-LP complications as suggested by results of previous studies (Figs. 1 and 2) [5]. Nevertheless, a cutting bevel needle is a risk factor for typical PLPH (odds ratio [OR] [95% CI], 2.6 [1.3–5.0]) and a large-bore needle diameter ( $\leq 22$ G) may be a risk factor for severe PLPH (OR [95% CI], 1.6 [0.9–2.7]) [5].

##### 3.3.2.1. Length of the needle

In case of a dry tap (punctio sicca), the needle should be advanced further to obtain CSF. Long spinal needles ( $>90$  mm) are used in patients with obesity. Nevertheless, length of the needle is not the only factor that contributes to a possible LP failure, experience of the operator is important as well [45]. The procedure will be more difficult when longer needles are used as these needles will be more flexible and often divert off track during the procedure [46].

##### 3.3.2.2. Diameter of the needle

Many considerations can be taken into account to decide on needle gauge. Twenty-eight studies, published between 1970 and 2016 (references in this paragraph resulted from the systematic literature review, Table 3), compared the performance and complications of different diameters of needles. No differences were detected in six studies

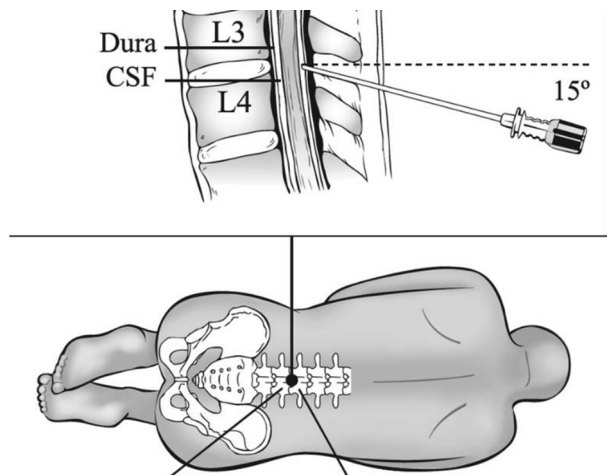


Fig. 3. Lumbar puncture procedure and position of the needle during a lumbar puncture. The procedure involves introducing a needle or its respective introducer at the superior aspect of the inferior spinal process into the subarachnoid space of the lumbar sac, at the L4/L5 level or other level safely (L3/L4) below the spinal cord. The technique is for both atraumatic and cutting bevel needles the same, but when using an atraumatic needle, an introducer is inserted into the interspinous ligament first, after which the smaller atraumatic needle is inserted through the introducer. The introducer should be inserted no more than 2/3 – 1/4 of the total length, depending on the adipose tissue availability. During the procedure, the needle stylet is removed every 2-mm interval to check for flow of CSF. In case a nonrecommended cutting bevel needle is used, it is preferred to hold the bevel in the sagittal plane as this diminishes injury to the dura mater by separating its longitudinal fibers rather than cutting through them and reduces the risk of leakage of CSF after the LP. Abbreviations: CSF, cerebrospinal fluid; LP, lumbar puncture.

comparing different needle diameters [47–52], whereas one study concluded that needles with a larger diameter ( $\leq 22\text{G}$ ) had a positive effect on collection time and resulted in less failures [53]. The LP feasibility study performed in memory

clinic settings did not show that large-bore diameter needles confer independent risk compared with small bore needle types. However, smaller bore needles (defined as  $\geq 24\text{G}$ ) are recommended by most studies [5,36,38,54–71], based on lower incidence of PLPH, back pain, and discomfort. A lower incidence of complications resulted in less medical assistance and less medication after the procedure.

Small-bore needles result in less blood contamination ( $>5/\mu\text{L}$  red blood cells in the first tube of CSF collected) [34]. Advantages of large-bore spinal needles are a faster CSF flow (e.g., when large volumes of CSF should be collected like in case of an evacuating LP), and a shorter time needed to equilibrate CSF pressure, when a manometer is used. For CSF, pressure measurement needles that are smaller than 22G (thus  $>22\text{G}$ ) are not suitable. Moreover, the smallest needle types (27G–29G) are not recommended because more technical difficulties occur, which might result in more failures, and due to the prolonged duration of the LP procedure [72]. On the other hand, large-bore needles ( $\leq 22\text{G}$ ) are not recommended as they result in large dural perforations and increased risk of post-LP complications and blood contaminations [56,62].

On the basis of the systematic literature analysis (level II-2 evidence), a balance between risk of PLPH, procedure duration, and technical failure has to be considered for each individual patient when choosing for a specific needle type. In daily clinical practice, a 22G or larger diameter ( $<22\text{G}$ ) needles are most often used [73,74]. Moreover, because there was no risk with large needles in the LP feasibility study, this needle can be chosen in memory clinics. Once the practitioner is more confident, by a more frequent usage, small-bore needles should be considered in other populations, which can then be used with a small number of failures [39,75].

Table 2

Needle characteristics are compared based on needle length, size, and design (systematic literature review 2016 [1])

Needle	Comparison	Advantages	Disadvantages
Length	Regular (70–90 mm) Long ( $>90$ mm)	Adults Obesity	— Challenging approach
Diameter in gauge	Small ( $\geq 24\text{G}$ )  Large ( $\leq 22\text{G}$ )	Reduced complication rates Reduced pain and discomfort Decreased risk factor: blood contaminations Requires less medical assistance and medications	Decreased flow rates, increased sampling times More failures Requires training and practice
Design	Cutting bevel  Atraumatic	Increased flow rates Decreased sampling times Fewer failures Penetration is felt through skin	Increased complication rates Perforations are larger Increased risk factor: contaminations Increased complication rates. Requires more use of medications and medical assistance, which results in increased costs. Decreased flow rates, increased sampling times Increased amount of attempts and failures Penetration through skin is difficult to feel
		Reduced complication rates Reduced medical health care costs due to less post-LP complications, medical assistance, and medications Decreased traumatic taps	

Abbreviation: G, gauge.



Table 3  
Needle diameters compared through a systematic literature review [1]

Conclusions	Diameters of needles compared	Motivations	References
No difference: in needle diameters	20G versus 22G	No difference: PLPH, complaints, traumatic tap incidence, CSF pressure measurement	[47–49]
	22G versus 25G	No difference: PLPH, complaints, attempts	[50,51]
	23G versus 25G	No difference: PLPH, low back pain, attempts	[52]
Favors: large-bore diameters	20G versus 22G versus 24G versus 25G	Reduced: collection times Faster: CSF pressure measurement	[53]
Favors: small-diameter bores	18G versus 20G versus 22G versus 24G versus 25G	Lower frequency: PLPH	[54]
	18G versus 20G versus 22G versus 24G versus 25G versus 26G versus 27G	Reduced: collection times Faster: CSF pressure measurement	[55]
	19G versus 20G versus 22G	Lower frequency: PLPH	[56]
	22 G versus 25G versus 27G	Lower frequency: PLPH, complaints, blood patch rates	[57–61]
	20G versus 22G versus 23G	Increased: collection times	[62]
	20G versus 22G versus 25G	Lower frequency: PLPH Lower frequency: PLPH	[63]
	20G versus 24G	Increased: collection times	[36]
	20 G versus 23G versus 25G versus 26G	More: practice, failures	[36]
	22G versus 24G	Lower frequency: PLPH	[64]
	22G versus 25G	Lower frequency: PLPH, low back pain, complaints Reduced: costs (health care) Lower frequency: leakage	[65–67]
22G versus 26G	Lower frequency: PLPH, pain	[38,68,69]	
22G versus 29G	More: practice Lower frequency: PLPH,	[70]	
25G versus 26G versus 27G	Reduced: failures Lower frequency: PLPH Reduced: blood patch rates	[71]	

Abbreviations: G, gauge; PLPH, postlumbar puncture headache; CSF, cerebrospinal fluid.

### 3.3.2.3. Design of the needle

Different needle designs are available. Cutting bevel needles (standard Quincke [76] and Yale) are the standard needles with a medium cutting bevel and an orifice at the needle tip. Atraucan, Pecan, Sprotte, and Whitacre needles are noncutting, pencil-point, and atraumatic needles (Fig. 4). Medium (23G–24G) cutting bevel needles are most frequently

used in clinical practice. As most atraumatic needles have smaller bores, these needles are associated with the same disadvantages of small-bore needles described previously [34,35,39,73–75,77,78].

Thirty-seven studies, published from 1970 till 2016, compared needle designs (all references in the following paragraphs are based on the systematic literature review,

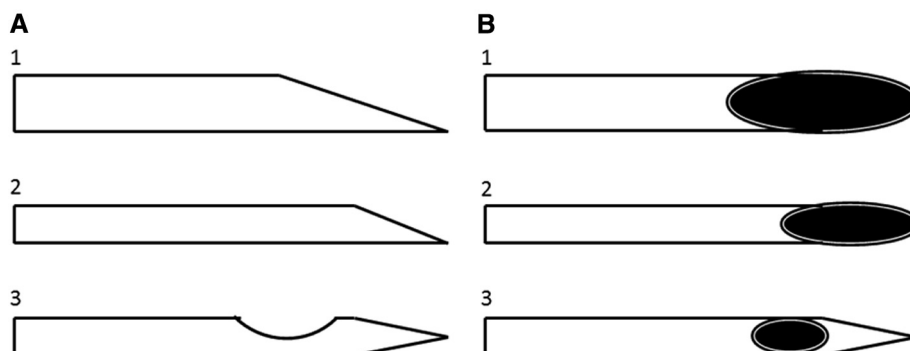


Fig. 4. Schematic representative of lateral (A) and superior (B) aspects of the tips of spinal needles: 1, standard large-bore beveled needle; 2, standard small-bore beveled needle; and 3, atraumatic small-bore needle.

Table 4  
Needle designs compared through a systematic literature review [1]

Conclusion	Needle designs compared	Motivations	Comments	References
Favors: atraumatic needle	Quincke versus Pencan	Lower frequency: PLPH, low back pain	Reduced: PLPH interval	[66]
	Quincke versus Pencan	Lower frequency: PLPH, post-LP complaints		[67]
	Quincke versus Sprotte	Lower frequency: PLPH, post-LP complaints, nausea/vomiting	Availability of atraumatic is less	[49,57,75,79–85]
		Reduced: costs (health care) due to less medications and medical assistance	Same concentrations of IgM in CSF and serum	
		Reduced: traumatic taps	Training increases the confidence of handling atraumatic needles	
		More: training		
	Quincke versus Sprotte	Lower frequency: PLPH		[86]
Quincke versus Sprotte versus Whitacre	Increased: failure rates			
Questionnaire to medical institutions. Favors: atraumatic needle	Quincke versus Sprotte versus Whitacre	Lower frequency: PLPH	Fewer cells attached to needle (size of cells are smaller), minor epithelial cells	[63,87,88]
	Quincke versus Sprotte versus Whitacre	Lower frequency: PLPH		[53]
	Quincke versus Whitacre	Lower frequency: PLPH, post-LP complaints		[48,60,65,71,89–91]
		Reduced: blood patch rates		
		Lower frequency: leakage		
	Quincke versus Sprotte	Lower frequency: PLPH		[73,75]
		More: practice, training		
No difference: in needle designs	Quincke versus Sprotte versus Whitacre	Increased: costs (needles)		[92]
	Quincke versus Sprotte versus Whitacre	Lower frequency: PLPH		
		Reduced: costs (health care)		
		More: practice, training		
	Quincke versus Sprotte versus Whitacre	No difference: flow properties	No influence of the performance of needle designs (on flow properties)	[55]
Quincke versus Whitacre	No difference: PLPH, low back pain	Same incidence (of PLPH and low back pain) for both needle designs	[93,94]	
Quincke versus Whitacre	No difference: counts in RBC, leakage		[95]	
Yale versus Pencan	No difference: success rates	No influence of the performance of needle designs (on success rates in children)	[96]	
Yale versus Sprotte	No difference: PLPH, traumatic taps	Same incidence (of PLPH and traumatic tap) for both needle designs	[97]	

Abbreviations: PLPH, postlumbar puncture headache; LP, lumbar puncture; CSF, cerebrospinal fluid; RBC, red blood cell.

Table 4). Four studies did not reveal a difference with regard to incidence of traumatic tap of vascular structures, procedure time and success rate in children, through comparison of transdural fluid leakage and vascular trauma associated with blood contamination in CSF (Pencan vs. Yale, Quincke vs. Yale, Whitacre vs. Quincke) [93,95–97]. One study investigated the incidence of PLPH and low back pain and did not reveal any difference (Whitacre vs. Quincke) [94]. Two studies compared the flow rates and reported no significant differences for both needle designs (atraumatic vs. cutting bevel needles, Whitacre vs. Sprotte vs. Quincke) [55,98].

However, atraumatic needles are recommended by most of the 37 articles as the best needle to perform LPs. Indeed, when comparing different needle designs, atraumatic needles resulted in a lower prevalence of post-LP complaints, including PLPH, low back pain or nausea/vomiting (Table 4) [5,36,48,49,53,54,57,58,60,61,63–67,71,75,79–91]. A lower frequency of complications results in reduced health care costs due to less medication or medical assistance, such as blood patches [48,49,53,54,57,61,64,66,75,79–84,86–91,93,96]. A lower incidence of traumatic taps has been reported when using atraumatic needles. However, atraumatic needles result in more attempts and failures [86]. No data are

available concerning post-LP complaints other than PLPH, number of traumatic taps, attempts, or failures. The technical drawbacks of atraumatic needles can be overcome with more training. Therefore, we conclude that the disadvantages are less decisive compared with the reduced risk of PLPH, which results in the time and cost savings for the health care system and less discomfort for the patient [11,81,82,92,99,100].

In summary, head-to-head studies are in favor of atraumatic type needles with regard to the lower incidence of PLPH (level II-2 evidence).

### 3.3.3. Number of LP attempts

In case of an unsuccessful attempt, the needle (in case of cutting bevel needle) or the guide (in case of atraumatic needle) has to be withdrawn partially to the subcutaneous tissue and has to be reangled [101]. If the attempt is still unsuccessful, repalpation should reassure that the needle is in the midline. Multiple attempts may lead to local swelling and/or bruising as well as muscle spasms and is therefore associated with a higher risk for back pain [5]. Furthermore, it will obscure surface anatomical landmarks, making future attempts technically more difficult [46].

The number of LP attempts was significantly associated with post-LP back pain (Fig. 2) [5]. In case of 2–4 attempts, the OR [95% CI] was 2.1 [1.7–2.7], whereas in case of  $\geq 5$  attempts, the OR [95% CI] increased to 5.4 [2.9–10.2] [5]. A total of four attempts is regarded as an acceptable maximum (level II-2 evidence).

### 3.3.4. Active versus passive withdrawal of CSF

Active withdrawal obviously reduces the procedural time, especially with small-bore needles, but this may be less important than the higher risk of PLPH. Passive withdrawal of CSF resulted in a lower risk for nonspecific headache (OR [95% CI] 0.68 [0.50–0.92]), and a strongly lower risk for severe headache (OR [95% CI] 0.52 [0.33–0.84]) [5]. In addition, using a syringe results in negative pressure and might cause subdural hemorrhage or herniation or might result in paresthesia, pain, or injury in case a spinal nerve root was pulled, although these complications occur rarely. Active CSF withdrawal using a syringe, in combination with an adequate needle diameter, is often performed in the course of collection of large volumes for research purposes, but should only be performed when a long procedure is not appropriate for the patient or clinical setting (level II-2 evidence).

### 3.3.5. Other LP-related factors

An LP can be performed with the patient in the lateral recumbent position, also known as supine position, or in sitting position. In the lateral recumbent position, the patient should be positioned with knees-to-chest and with the back flexed as far as possible toward the physician performing the LP, and the coronal plane of the trunk should be perpendicular to the floor with one hip exactly above the other. In this position, lumbar lordosis is overcome and the neck is in a neutral position. The needle should stay in the midline of

the spine, and therefore, it is placed parallel to the floor. In the sitting position, the patient completely flexes neck and back as this facilitates the course of the needle by widening the gap between adjacent lumbar spinal processes. The preferred position depends on the physician and on the patient's clinical conditions (level-III evidence). In case of immobilized patients and/or patients being unable to sit up, the lateral recumbent position should be applied. This position may be included in the clinical training/practice of residents, to be familiar with the procedure. For CSF pressure measurement, patients need to be in the lateral recumbent position [101,102]. The sitting position has the advantage of a higher CSF pressure and flow, which reduces the sampling time. In the multicenter LP feasibility study, positioning of the patient was not associated with PLPH or post-LP back pain [5]. However, additional analysis showed that sitting position during LP procedure appeared to be a risk factor for severe headache, not for typical PLPH. Monserrate et al. mentioned also a trend for developing headache after LP in the sitting position [36].

When using an atraumatic needle, it is recommended to reinsert the stylet to the tip of the needle before removing the needle as this was associated with a lower prevalence of PLPH [103].

In the multicenter LP feasibility study, local anesthesia was used in 41% of the patients, mostly when the LP was performed with a large-bore diameter needle [5]. The application of local anesthesia or not was not associated with post-LP complaints. In addition, bed rest after LP and the volume of CSF withdrawn (up to 12 mL and more) were not associated with change in prevalence of PLPH or post-LP back pain [5]. Therefore, there is no recommendation to apply local anesthesia and bed rest after the LP to reduce postpuncture complaints. Collection of up to 30 mL of CSF is well tolerated and safe [36] and is advised as an acceptable maximum. Nevertheless, other LP procedure-related factors should depend on patient's-related, physician-related, and/or clinical setting-related factors (level II-2 evidence). For example, very small needle bores will extend the collection time for this volume.

## 3.4. Treatment of PLPH

More than 85% of PLPH will resolve without any other specific treatment [104]. The only evidence-based treatment for typical severe PLPH (severe usually frontal headache possibly accompanied by nausea and vomiting which is relieved by recumbent posture) is an epidural blood patch [105]. The most efficient volume of blood appears to be 20–30 mL [104]. This procedure has a success rate of 70%–98% if carried out more than 24 hours after the LP [104]. If a first epidural blood patch fails to resolve the headache, repeating the procedure has a similar success rate [104]. There is a lack of evidence to recommend pharmacological treatments of typical PLPH [106]. The few randomized clinical trials that have been performed included a

limited number of patients and half of the participants were postpartum women in their 30s, limiting the generalizability [106]. Taking into account these limitations, caffeine decreased the proportion of subjects with persisting PLPH and the subjects requiring supplementary interventions compared with placebo [106]. Gabapentin, hydrocortisone, and theophylline decreased pain severity scores [106].

#### 4. Conclusions: Recommendations

Based on the results of the international, multicenter LP feasibility study, literature-based analysis of risk factors, and best clinical practices discussed in the previous sections, we formulate the following consensus guidelines and recommendations for the LP procedure in adults. These recommendations should minimize post-LP complications, the most frequent being PLPH and post-LP back pain. The recommendations are summarized in **Box 1** and **Table 5**. As these are guidelines, every professional can adapt the guidelines based on their own experience and based on the patient's comfort and benefits. We refer to the last article in a series of four articles on issues in the development and use of clinical guidelines, which focuses on how clinical guidelines should be used, in health care settings but also by an individual clinician [107].

First, contraindications for LP should be ruled out (**Table 1**). The following recommendations are consensus based (level-III evidence).

- It is advised to perform brain imaging before LP, whenever an intracranial lesion with mass effect, abnormal intracranial pressure due to increased CSF pressure, or tonsillar herniation is suspected based on medical history or neurological examination, and in case of recent seizures, impaired consciousness, or papilledema.
- Coagulation status and platelet count (should be higher than  $40 \times 10^9/L$ ) should be checked by (recent) blood analysis before LP.

- Concomitant medication should be checked before LP. In case of intake of anticoagulants, an LP is contraindicated unless the risk of the procedure outweighs the potential benefit. Direct acting anticoagulants can be temporarily interrupted. An LP can be performed without substantial risk when patients take one type of antiplatelet drug.
- Infections at the LP site are relative contraindications.

As patient-related characteristics are among the most important risk factors for PLPH and post-LP back pain, the physician should determine the risk profile of the patient. Although the patient-related risk factors cannot be modified, these can be of help to identify those patients that are at high risk to develop post-LP complaints. Moreover, as fear of complications is an important risk factor for post-LP complaints, the patient should be informed thoroughly and should be reassured, before and during the LP procedure (level-III evidence). Recommended based on level II-2 and III evidence:

- Younger age, being a female aged less than 40 years, previous history of headache, and fear of post-LP complications are risk factors for PLPH and post-LP back pain.
- Post-LP complaints are less prevalent in patients with cognitive deterioration [5].

Recommendations with regard to the LP procedure itself are based on level II-2 and III evidence:

- It is recommended to use 25G atraumatic needles given the reduced incidence of PLPH.
- A total of four attempts may be regarded as an acceptable maximum, as the risk for back pain significantly increased with more than 4 attempts [5].
- Active CSF withdrawal using a syringe should only be performed when a patient cannot tolerate a long procedure. If a large volume of CSF has to be withdrawn (e.g., for research purposes or in case of an evacuating LP), a larger needle diameter is recommended instead of active withdrawal by using a syringe.

#### Box 1

**Recommendations to minimize post-LP complaints and complications (All recommendations are at least level II evidence, type 2)**

Patient-related characteristics with regard to post-LP complaints and complications:

- Risk factors: younger age, being female <40 years old, previous history of headache, and fear of post-LP complications
- Less risk: cognitive deterioration
  - Serve to identify patients that are at high risk to develop post-LP complaints
  - Serve to inform and reassure patients, before and during the LP procedure

LP procedure:

- Use 25G atraumatic needles
- Not more than four LP attempts
- Passive withdrawal of CSF
- Collection of up to 30 mL of CSF is well tolerated and safe
- Lateral recumbent position

No influence of local anesthesia and bed rest after LP.

Abbreviations: CSF, cerebrospinal fluid; G, gauge; LP, lumbar puncture.

Table 5  
Recommendations based on level II-2 and III evidence described by graded risk factors

Recommended procedure	Risk factors	Grading risk factors	Level of evidence
<b>Rule out contraindications</b>			
1. Brain imaging before LP, in case of - an intracranial lesion with mass effect, - abnormal intracranial pressure, - tonsillar herniation is suspected (based on medical history or neurological examination), - recent seizures, - impaired consciousness, - papilledema		–	III
2. Check platelet and coagulation status: platelet $>40 \times 10^9/L$ ; quick $>50\%$ ; INR $<1.5$	Coagulopathy	+/-	III
	Uncorrected bleeding diathesis	–	III
3. Check medication before LP	Anticoagulant medication	+/-	III
<b>Patients-related risk factors:</b>			
1. Determine risk profile and inform and reassure patients before and during LP procedure			
<b>Risk factors</b>			
1. Younger age	PLPH, back pain	++	II-2, III
2. Being female $<40$ years old	Post-LP complaints	+/-	III
3. History of headache	PLPH, back pain	++	II-2
4. Fear of post-LP complaints	Post-LP complaints	+	II-2
<b>Less risk</b>			
1. Cognitive deterioration	PLPH, back pain	+	II-2, III
<b>Procedure-related risk factors</b>			
1. 25G atraumatic needle: small needle atraumatic needle	Post-LP complaints	+	III
	PLPH	++	II-2, III
2. $<4$ LP attempts	Back pain	++	II-2
3. Passive withdrawal	Severe headache	+	II-2, III
4. Lateral recumbent position	Post-LP complaints	+/-	III
5. Collection up to 30 mL	Headache	+	II-2, III

Abbreviations: LP, lumbar puncture; INR, International normalized ratio; PLPH, postlumbar puncture headache; G, gauge.

NOTE. Grading the impact on risk factors: + high (mentioned in multicenter LP feasibility study as one of the most important factors that influences post-LP complications), + high (mentioned in multicenter LP feasibility study as factor that influences post-LP complications or reported in other study with high quality evidence), +/- moderate (not detected as risk factor in multicenter LP feasibility study, based on consensus and literature), – low (not detected as risk factor in multicenter LP feasibility study, based on consensus and sparse literature). Level of evidence: II-2 = well-designed cohorts preferably with more than one research group or center (e.g., data of large multicenter LP feasibility study, systematic review); III = consensus evidence based on clinical experience of the two consortia (JPND BIOMARKAPD and BioMS).

- It is recommended to perform an LP in the lateral recumbent position due to the fact that the sitting position was associated with more severe headache [5,36]. For CSF pressure measurement, patients need to be in the lateral recumbent position.
- The collection of up to 30 mL of CSF is well tolerated and safe [36].

As local anesthesia and bed rest after LP are not associated with increased prevalence of post-LP complications, there are no recommendations to apply (level II-2 and III evidence).

In conclusion, an LP is a common and generally well-tolerated diagnostic procedure with a high diagnostic yield. The application of these evidence-based guidelines will help to reduce complication rates.

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### Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.dadm.2017.04.007>.

### RESEARCH IN CONTEXT

1. Systematic review: Consensus guidelines and recommendations for the lumbar puncture (LP) procedure to obtain cerebrospinal fluid (CSF) to minimize risk of complications and to optimize diagnostic yield are lacking. CSF analysis is increasingly relevant for diagnosis and research for neurological diseases, even at the core criteria for dementia diagnosis.
2. Interpretation: It is recommended to use 25G atraumatic needles. A total of four LP attempts is an acceptable maximum, active CSF withdrawals should be avoided. It is advised to perform LP in the lateral recumbent position, and collection up to 30-mL CSF is well tolerated and safe. There is no recommendation to apply local anesthesia and bed rest after the LP to reduce postpuncture complaints.
3. Future directions: The application of these evidence-based guidelines will help to reduce complication rates. Moreover, these guidelines will be a reference for educational purposes, thus be of help for trainees in neurology, and will be a guide to comfort or give adequate information to the patients.

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