

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

### Interventional procedure overview of lumbar infusion test for the investigation of normal pressure hydrocephalus

Normal pressure hydrocephalus (NPH) is a condition in which a clear, colourless fluid called cerebrospinal fluid (or CSF) accumulates around the brain and spinal cord. Symptoms include abnormal gait, urinary incontinence and impaired cognitive function. NPH can be managed by surgical intervention, for example with shunt surgery. The lumbar infusion test may be useful for selecting those patients who are most likely to benefit from this type of surgery. This test involves the insertion of a lumbar needle through the skin of the lower back into the spinal sac, recording the pressure of the CSF as fluid is infused into the spinal sac.

#### Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

#### Date prepared

This overview was prepared in November 2007.

#### Procedure name

- Lumbar infusion test for the investigation of normal pressure hydrocephalus

#### Specialty societies

The following societies were approached to nominate Specialist Advisers.

- Association of British Neurologists
- Society of British Neurological Surgeons

## Description

### *Indications*

Normal pressure hydrocephalus is an accumulation of cerebrospinal fluid (CSF) around the brain and spinal cord, which can cause symptoms such as abnormal gait, urinary incontinence and impaired cognitive function. It usually occurs in the elderly, and is characterised by enlarged cerebral ventricles, but with normal CSF pressure on lumbar puncture.

### *Current treatment and alternatives*

Normal pressure hydrocephalus is usually treated by surgical insertion of a shunt. A shunt is a system that diverts CSF from the brain (or lumbar spinal sac) to the abdominal cavity where it is then absorbed into the circulation. It may relieve gait disturbance and halt the progression of other symptoms, including permanent loss of cognitive function.

It is important to distinguish NPH from other causes of gait disturbance, urinary incontinence and cognitive decline, such as normal cerebral atrophy, where shunting may be harmful. Therefore, diagnosis of NPH based on clinical and radiological signs alone can be problematic and additional testing may be required to determine which patients could benefit from shunting.

This may include a large volume lumbar puncture test (also known as a spinal or CSF tap test). A baseline evaluation of the patient is performed, which may include a mini-mental state examination and walking tests. Under local anaesthetic, a spinal needle is inserted between the lumbar vertebrae into the spinal sac and CSF is collected. Several hours later the evaluation is repeated to assess the effect of removing CSF. Clinical improvement after the lumbar puncture (which may be sustained for several days or weeks) indicates that the patient is likely to benefit from shunting; however, the test is not completely reliable.

### *What the procedure involves*

The lumbar infusion test (also known as the intrathecal infusion test) aims to assess the adequacy of the patient's CSF absorptive ability. The principle underlying the test is that although patients with NPH may have a normal CSF pressure (when this is measured at a simple lumbar puncture), abnormalities in CSF absorption may be revealed with the administration of a 'fluid challenge'. An abnormal and sustained rise in CSF pressure in the face of the challenge is indicative of reduced absorptive capacity (and of NPH).

Under local anaesthetic a needle is inserted through the skin of the lower back and into the lumbar spinal sac. The needle is connected to a pressure monitor and baseline CSF pressure is recorded. Fluid is then infused while CSF pressure is monitored.

Different aspects of the CSF pressure profile during the test may be used to determine which patients are most likely to benefit from shunt surgery. Most IP overview: Lumbar infusion test for the investigation of normal pressure hydrocephalus

commonly, the resistance to CSF outflow (measured in mmHg/ml/min) is calculated based on the pressure gradient (mmHg) in the face of a constant infusion (ml/min). Alternatively, the plateau pressure (measured in mmHg) may be used, which is the pressure at which a balance between CSF absorption and infusion is reached.

### **Efficacy**

A case series of 101 patients assessed the ability of CSF outflow resistance (measured by the lumbar infusion test) to predict shunt response. Of patients with CSF outflow resistance greater than 18 mmHg/ml/min ( $n = 36$ ), 92% (33/36) had improved NPH scale scores after shunting. Two thirds of patients with CSF outflow resistance below 18 mmHg/ml/min ( $n = 59$ ) also showed some clinical improvement <sup>1</sup>.

Sixty-six patients from a case series of 83 individuals (80%) met the criteria for shunt surgery (CSF outflow resistance  $\geq 12$  mmHg/ml/min or highly suggestive symptoms). Clinical improvement (based on a consensus between the neurologist and the patient) at least 1 year after shunt surgery was reported in 59% (39/66) of these patients <sup>2</sup>.

In a case series of 83 patients, only 30 underwent lumbar infusion testing with 19 of these patients meeting the criteria for shunt surgery (CSF outflow resistance  $\geq 16$  mmHg/ml/min). Seventeen of these patients (90%) improved clinically after surgery. Of the 11 patients who did not undergo surgical shunting, eight had an unchanged clinical condition at follow-up (median follow-up of 8 months), with the final three patients lost to follow-up <sup>3</sup>.

In a case series of 68 patients who underwent both a lumbar infusion test and a CSF tap test, 47 met the criteria for, and underwent, shunt surgery. Of the 38 patients who improved after surgery, 32 (84%) had a positive lumbar infusion test and 16 (42%) had a positive CSF tap test. (A positive lumbar infusion test result was indicated by a plateau pressure  $\geq 22$  mmHg.) Of the nine patients who did not improve clinically, one had a negative lumbar infusion test and eight had a negative CSF tap test <sup>4</sup>.

A case series of 155 (out of 200) patients, who underwent shunt surgery and had a follow-up assessment at 7 months, reported that patients with a CSF outflow resistance greater than 15 mmHg/ml/min (measured by the intrathecal infusion test) had significantly more favourable clinical outcomes than patients with a lower CSF resistance ( $p = 0.01$ ) <sup>5</sup>.

### **Safety**

Five of the six published articles reported no adverse events related to the lumbar infusion test. In one study of 200 patients, 19% reported headache (absolute number not reported) after the lumbar infusion test and two patients developed meningismus without signs of inflammation in the CSF <sup>6</sup>.

## Literature review

### *Rapid review of literature*

The medical literature was searched to identify studies and reviews relevant to the lumbar infusion test for the investigation of normal pressure hydrocephalus. Searches were conducted of the following databases, covering the period from their commencement to 30/10/07: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy).

The following selection criteria were applied to the abstracts identified during the literature search (Table 1). Where selection criteria could not be determined from the abstracts the full paper was retrieved.

**Table 1 Inclusion criteria for identification of relevant studies**

| Characteristic    | Criteria   |
|-------------------|--|
| Publication type  | Clinical studies were included. Emphasis was placed on identifying good quality studies.<br>Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.<br>Conference abstracts were also excluded because of the difficulty of appraising methodology. |
| Patient           | Patients with suspected hydrocephalus requiring shunting   |
| Intervention/test | Lumbar infusion test   |
| Outcome           | Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.  |
| Language          | Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.   |

### *List of studies included in the overview*

This overview is based on six case series.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (Table 2) are listed in appendix A.

### *Existing reviews on this procedure*

One published evidence-based guideline titled 'The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal-pressure hydrocephalus' was identified at the time of the literature search <sup>7</sup>.

This guideline made the following recommendations.

- A positive response to a spinal tap test is better for predicting a positive shunt response than clinical examination. However, a tap test cannot be used as an exclusionary test because of its low sensitivity.
- Determination of CSF outflow resistance via an infusion test has a higher sensitivity compared with the spinal tap test.
- Prolonged external lumbar drainage has a high sensitivity and positive predictive value.

The guideline concluded that a single standard for the prognostic evaluation of patients with idiopathic NPH is lacking. However, supplemental tests can increase the predictive accuracy of prognosis to greater than 90%. Additional multicentre prospective randomised controlled trials of these supplemental tests are required.

**Table 2 Summary of key efficacy and safety findings on lumbar infusion test for the investigation of normal pressure hydrocephalus**

| Study details   | Key efficacy findings   | Key safety findings                              | Comments  |                               |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
|---|---|--|---|-------------------------------|----------------|--|-------------|---|---|------------------|---|---|------------------|---|----|------------------|----|----|------------------|---|----|------------------|---|---|---------------|---|----|--|-----------------|-----------------|------------------|-------------------------------|----|----|----|-----|----|----|----|----|-----|----|----|----|----|-----|----|----|----|----|-----|----|----|----|----|-----|----|----|----|-----|---|-----|--|--|
| <p>Boon A et al. (1997) <sup>1</sup></p> <p><i>Dutch normal-pressure hydrocephalus study: prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid.</i></p> <p>Multicentre randomised study</p> <p>Four centres in the Netherlands</p> <p>Study period: Sept 1990 – July 1995</p> <p>n = 101</p> <p>Population and indications: patients under 85 years diagnosed with NPH (based on clinical symptoms and CT scan). Most patients had idiopathic NPH (percentage not reported). Mean age: 73.7 years. Male: 60%</p> <p>Technique: lumbar constant flow infusion test</p> <p>Selection for shunt surgery: all patients were randomly allocated to receive either a low- or medium high-pressure shunt regardless of the results of lumbar constant flow infusion test.</p> <p>Mean follow-up assessment: 10.9 months (± 3 months)</p> | <p><b>Clinical improvement after shunt surgery</b><br/>(n = 95; five patients died of unrelated causes before the first follow-up examination at 1 month, while the lumbar test could not be carried out in one patient due to incorrect needle insertion)</p> <table border="1" data-bbox="674 501 1648 874"> <thead> <tr> <th rowspan="2">CSF outflow resistance (mmHg/ml/min)</th> <th colspan="2">Difference between baseline and postoperative NPH scale score</th> </tr> <tr> <th>No improvement</th> <th>Some improvement (moderate, marked or excellent)</th> </tr> </thead> <tbody> <tr> <td>&lt;10 (n = 6)</td> <td>3</td> <td>3</td> </tr> <tr> <td>10-11.9 (n = 10)</td> <td>5</td> <td>5</td> </tr> <tr> <td>12-14.9 (n = 14)</td> <td>2</td> <td>12</td> </tr> <tr> <td>15-17.9 (n = 29)</td> <td>10</td> <td>19</td> </tr> <tr> <td>18-20.9 (n = 15)</td> <td>0</td> <td>15</td> </tr> <tr> <td>21-23.9 (n = 11)</td> <td>3</td> <td>8</td> </tr> <tr> <td>≥ 24 (n = 10)</td> <td>0</td> <td>10</td> </tr> </tbody> </table> <ul style="list-style-type: none"> <li>CSF outflow resistance greater than 18 mmHg/ml/min was the best predictor of improvement in NPH scale score (100% of patients improved).</li> <li>Two thirds of patients with CSF outflow resistance below 18 mmHg/ml/min also showed some improvement in NPH scale score.</li> </ul> <p><b>CSF outflow resistance as a predictor of shunt response</b> (based on efficacy analysis of 95 patients using improvement in NPH scale score as outcome measure)</p> <table border="1" data-bbox="674 1129 1648 1410"> <thead> <tr> <th>CSF outflow resistance cut off (mmHg/ml/min)</th> <th>Sensitivity (%)</th> <th>Specificity (%)</th> <th>Likelihood ratio</th> <th>Positive predictive value (%)</th> </tr> </thead> <tbody> <tr> <td>10</td> <td>96</td> <td>13</td> <td>1.1</td> <td>78</td> </tr> <tr> <td>12</td> <td>89</td> <td>35</td> <td>1.4</td> <td>81</td> </tr> <tr> <td>15</td> <td>72</td> <td>44</td> <td>1.3</td> <td>80</td> </tr> <tr> <td>18</td> <td>46</td> <td>87</td> <td>3.5</td> <td>92</td> </tr> <tr> <td>21</td> <td>25</td> <td>87</td> <td>1.9</td> <td>86</td> </tr> <tr> <td>24</td> <td>14</td> <td>100</td> <td>~</td> <td>100</td> </tr> </tbody> </table> | CSF outflow resistance (mmHg/ml/min)             | Difference between baseline and postoperative NPH scale score |                               | No improvement | Some improvement (moderate, marked or excellent) | <10 (n = 6) | 3 | 3 | 10-11.9 (n = 10) | 5 | 5 | 12-14.9 (n = 14) | 2 | 12 | 15-17.9 (n = 29) | 10 | 19 | 18-20.9 (n = 15) | 0 | 15 | 21-23.9 (n = 11) | 3 | 8 | ≥ 24 (n = 10) | 0 | 10 | CSF outflow resistance cut off (mmHg/ml/min) | Sensitivity (%) | Specificity (%) | Likelihood ratio | Positive predictive value (%) | 10 | 96 | 13 | 1.1 | 78 | 12 | 89 | 35 | 1.4 | 81 | 15 | 72 | 44 | 1.3 | 80 | 18 | 46 | 87 | 3.5 | 92 | 21 | 25 | 87 | 1.9 | 86 | 24 | 14 | 100 | ~ | 100 | <p>No complications related to the lumbar infusion test were reported.</p> | <p>Study objective: to determine the positive and negative predictive values of CSF outflow resistance obtained using a lumbar infusion test for the outcome of surgical shunting in patients with NPH.</p> <p><b>All patients in this study were treated with shunt surgery.</b></p> <p>NPH scale: combined scores of a gait scale and a dementia scale (ranging from 6 to 80)</p> <p>The authors state that most patients had idiopathic NPH (as opposed to secondary NPH), but the actual numbers in each group are not reported. Furthermore, the results are not reported separately for each group.</p> <p>The results are not reported according to which type of shunt was used.</p> |
| CSF outflow resistance (mmHg/ml/min)  | Difference between baseline and postoperative NPH scale score   |  |   |                               |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
|   | No improvement  | Some improvement (moderate, marked or excellent) |   |                               |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
| <10 (n = 6)   | 3   | 3  |   |                               |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
| 10-11.9 (n = 10)  | 5   | 5  |   |                               |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
| 12-14.9 (n = 14)  | 2   | 12   |   |                               |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
| 15-17.9 (n = 29)  | 10  | 19   |   |                               |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
| 18-20.9 (n = 15)  | 0   | 15   |   |                               |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
| 21-23.9 (n = 11)  | 3   | 8  |   |                               |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
| ≥ 24 (n = 10)   | 0   | 10   |   |                               |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
| CSF outflow resistance cut off (mmHg/ml/min)  | Sensitivity (%)   | Specificity (%)                                  | Likelihood ratio  | Positive predictive value (%) |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
| 10  | 96  | 13   | 1.1   | 78                            |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
| 12  | 89  | 35   | 1.4   | 81                            |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
| 15  | 72  | 44   | 1.3   | 80                            |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
| 18  | 46  | 87   | 3.5   | 92                            |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
| 21  | 25  | 87   | 1.9   | 86                            |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |
| 24  | 14  | 100  | ~   | 100                           |                |  |             |   |   |                  |   |   |                  |   |    |                  |    |    |                  |   |    |                  |   |   |               |   |    |  |                 |                 |                  |                               |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |    |     |    |    |    |     |   |     |  |  |

|                                   |  |  |  |
|-----------------------------------|--|--|--|
| Conflict of interest: none stated |  |  |  |
|-----------------------------------|--|--|--|

| Abbreviations used: CT, computed tomography; GDS, global deterioration scale; MMSE, mini mental state examination; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NPH, normal pressure hydrocephalus   |  |  |  |
|--|--|--|--|
| Study details  | Key efficacy findings  | Key safety findings  | Comments   |
| <p>Delwel EJ et al. (2005)<sup>2</sup><br/> <i>The prognostic value of clinical characteristics and parameters of cerebrospinal fluid hydrodynamics in shunting for idiopathic normal pressure hydrocephalus.</i></p> <p>Prospective case series</p> <p>The Netherlands</p> <p>Study period: not stated</p> <p>n = 83</p> <p>Population and indications: consecutive patients with symptoms and radiological signs of NPH. Of those who underwent shunt surgery (n = 66): mean age: 69.5 years; male: 65%.</p> <p>Technique: constant flow lumbar infusion test</p> <p>Selection for shunt surgery: CSF outflow resistance of 12 mmHg/ml/min or higher (NB five patients with symptoms highly suggestive of NPH were shunted despite CSF outflow resistance &lt;12 mmHg/ml/min)</p> <p>Follow-up assessment: after at least 1year</p> <p>Conflict of interest: none stated</p> | <p>80% (66/83) of patients met the criteria for shunt surgery and were operated on.</p> <p><b>Clinical improvement after shunt surgery: 59% (39/66)</b></p> <p><i>Improvement was based on a consensus between the neurologist and the patient (or their relatives) at least 1 year after shunt surgery on obvious and lasting amelioration of at least one clinical symptom</i></p> | <p>No complications related to the lumbar infusion test were reported.</p> | <p>Study objective: to investigate which clinical characteristics, CT parameters and parameters of CSF dynamics could predict improvement after surgical shunting.</p> <p>This study is from the same centre as study described above (Boon et al. 1997) and thus may have enrolled some of the same patients.</p> |



| Abbreviations used: CT, computed tomography; GDS, global deterioration scale; MMSE, mini mental state examination; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NPH, normal pressure hydrocephalus   |  |                             |                             |          |    |    |      |     |     |   |  |  |  |                      |                       |             |             |                                    |             |             |  |   |     |   |             |            |  |  |
|--|--|-----------------------------|-----------------------------|----------|----|----|------|-----|-----|---|--|--|--|----------------------|-----------------------|-------------|-------------|------------------------------------|-------------|-------------|--|---|-----|---|-------------|------------|--|--|
| Study details  | Key efficacy findings                    |                             | Key safety findings         | Comments |    |    |      |     |     |   |  |  |  |                      |                       |             |             |                                    |             |             |  |   |     |   |             |            |  |  |
| <p>Bech-Azeddine R et al. (2005)<sup>3</sup><br/><i>Intraventricular or lumbar infusion test in adult communicating hydrocephalus? Practical consequences and clinical outcome of shunt operation.</i></p> <p>Prospective case series</p> <p>Denmark</p> <p>Study period: 1998–2000</p> <p>n = 83</p> <p>Population and indications: patients with symptoms and radiological signs of idiopathic NPH (n = 33) or secondary communicating hydrocephalus (n = 50).</p> <table border="1"> <thead> <tr> <th></th> <th>NPH</th> <th>Communicating hydrocephalus</th> </tr> </thead> <tbody> <tr> <td>Mean age</td> <td>66</td> <td>56</td> </tr> <tr> <td>Male</td> <td>42%</td> <td>52%</td> </tr> </tbody> </table> <p>Technique: lumbar infusion test</p> <p>Selection for shunt surgery: CSF outflow resistance of 16 mmHg/ml/min or higher. Patients with CSF outflow resistance of 12–16 mmHg/ml/min went on to have an intraventricular infusion test</p> <p>Follow-up assessment: 1–3 months and then after at least 1 year postoperatively in all patients</p> <p>Conflict of interest: none stated</p> |  | NPH                         | Communicating hydrocephalus | Mean age | 66 | 56 | Male | 42% | 52% | <p>47/83 (57%) patients met criteria for shunting and were operated on (30 of these patients had communicating hydrocephalus and 17 had suspected NPH)</p> <p><b>Clinical improvement after shunt surgery</b></p> <ul style="list-style-type: none"> <li>All patients: 83% (39/47)</li> <li>Patients with NPH: 76% (13/17)</li> <li>Patients with communicating hydrocephalus (1 patient died after shunt surgery): 90% (26/29)</li> </ul> <p><i>Improvement was based on a total score of at least 2 points where +1 was given for each degree of improvement and –1 for each degree of reduction in ordinal scales of gait, incontinence, MMSE and GDS.</i></p> <table border="1"> <thead> <tr> <th></th> <th>Met criteria for, and had, shunt surgery</th> <th>Clinical improvement</th> </tr> </thead> <tbody> <tr> <td>All patients (n = 83)</td> <td>57% (47/83)</td> <td>83% (39/47)</td> </tr> <tr> <td>Lumbar infusion test only (n = 30)</td> <td>63% (19/30)</td> <td>90% (17/19)</td> </tr> <tr> <td>Lumbar + intraventricular test (n = 4)</td> <td>0</td> <td>N/A</td> </tr> <tr> <td>Intraventricular infusion test only (n = 16; all patients with communicating hydrocephalus)</td> <td>69% (11/16)</td> <td>90% (9/10)</td> </tr> </tbody> </table> <p><b>Patients who had lumbar infusion test only (n = 30)</b></p> <ul style="list-style-type: none"> <li>19 (63%) patients met the criteria for shunting and were operated on, of whom 17 (90%) improved clinically</li> <li>11 patients did not meet the criteria for shunting, of whom eight had an unchanged clinical condition at follow-up (median: 8 months) with the final three patients lost to follow-up</li> </ul> |  |  | Met criteria for, and had, shunt surgery | Clinical improvement | All patients (n = 83) | 57% (47/83) | 83% (39/47) | Lumbar infusion test only (n = 30) | 63% (19/30) | 90% (17/19) | Lumbar + intraventricular test (n = 4) | 0 | N/A | Intraventricular infusion test only (n = 16; all patients with communicating hydrocephalus) | 69% (11/16) | 90% (9/10) | <p>No complications related to the lumbar infusion test were reported.</p> | <p>Study objective: to investigate the therapeutic consequences of restricting the CSF dynamic evaluation to a lumbar infusion test, as opposed to the formerly applied intraventricular infusion assessment in patients with communicating hydrocephalus.</p> |
|  | NPH                                      | Communicating hydrocephalus |                             |          |    |    |      |     |     |   |  |  |  |                      |                       |             |             |                                    |             |             |  |   |     |   |             |            |  |  |
| Mean age   | 66                                       | 56                          |                             |          |    |    |      |     |     |   |  |  |  |                      |                       |             |             |                                    |             |             |  |   |     |   |             |            |  |  |
| Male   | 42%                                      | 52%                         |                             |          |    |    |      |     |     |   |  |  |  |                      |                       |             |             |                                    |             |             |  |   |     |   |             |            |  |  |
|  | Met criteria for, and had, shunt surgery | Clinical improvement        |                             |          |    |    |      |     |     |   |  |  |  |                      |                       |             |             |                                    |             |             |  |   |     |   |             |            |  |  |
| All patients (n = 83)  | 57% (47/83)                              | 83% (39/47)                 |                             |          |    |    |      |     |     |   |  |  |  |                      |                       |             |             |                                    |             |             |  |   |     |   |             |            |  |  |
| Lumbar infusion test only (n = 30)   | 63% (19/30)                              | 90% (17/19)                 |                             |          |    |    |      |     |     |   |  |  |  |                      |                       |             |             |                                    |             |             |  |   |     |   |             |            |  |  |
| Lumbar + intraventricular test (n = 4)   | 0  | N/A                         |                             |          |    |    |      |     |     |   |  |  |  |                      |                       |             |             |                                    |             |             |  |   |     |   |             |            |  |  |
| Intraventricular infusion test only (n = 16; all patients with communicating hydrocephalus)  | 69% (11/16)                              | 90% (9/10)                  |                             |          |    |    |      |     |     |   |  |  |  |                      |                       |             |             |                                    |             |             |  |   |     |   |             |            |  |  |

| Abbreviations used: CT, computed tomography; GDS, global deterioration scale; MMSE, mini mental state examination; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NPH, normal pressure hydrocephalus  |   |                           |                     |   |                           |                                   |            |            |  |             |             |                                |             |             |  |   |                           |   |             |             |  |           |           |   |              |              |   |  |
|---|---|---------------------------|---------------------|---|---------------------------|-----------------------------------|------------|------------|--|-------------|-------------|--------------------------------|-------------|-------------|--|---|---------------------------|---|-------------|-------------|--|-----------|-----------|---|--------------|--------------|---|--|
| Study details   | Key efficacy findings   |                           | Key safety findings | Comments  |                           |                                   |            |            |  |             |             |                                |             |             |  |   |                           |   |             |             |  |           |           |   |              |              |   |  |
| <p>Kahlon B et al. (2002) <sup>4</sup><br/> <i>Comparison between the lumbar infusion and CSF tap test to predict outcome after shunt surgery in suspected normal pressure hydrocephalus.</i></p> <p>Prospective case series</p> <p>Sweden</p> <p>Study period: 1996–2000</p> <p>n = 68</p> <p>Population and indications: consecutive patients with suspected NPH. Mean age: 72 years. Male: 43%</p> <p>Technique: constant-rate lumbar infusion test followed immediately by CSF tap test</p> <p>Selection for shunt surgery: either a positive lumbar infusion test (plateau pressure ≥ 22 mmHg) (n = 36) or a positive CSF tap test (clinical improvement after test) (n = 19).</p> <p>Mean follow-up assessment: 6 months</p> <p>Conflict of interest: none stated</p> | <p>69% (47/68) patients met the criteria for shunt surgery and were operated on.</p> <p><b>Clinical improvement at 6-month follow-up (n = 68)</b></p> <table border="1"> <thead> <tr> <th></th> <th>Objective improvement (from baseline in at least two out of four tests)</th> <th>Self-reported improvement</th> </tr> </thead> <tbody> <tr> <td>Patients not operated on (n = 21)</td> <td>24% (5/21)</td> <td>19% (4/21)</td> </tr> <tr> <td>Positive lumbar infusion test (n = 40)</td> <td>80% (32/40)</td> <td>98% (39/40)</td> </tr> <tr> <td>Positive CSF tap test (n = 17)</td> <td>94% (16/17)</td> <td>94% (16/17)</td> </tr> </tbody> </table> <p><b>Test result combinations</b></p> <table border="1"> <thead> <tr> <th></th> <th>Objective improvement (from baseline in at least two out of four tests)</th> <th>Self-reported improvement</th> </tr> </thead> <tbody> <tr> <td>Lumbar test positive / CSF test negative (n = 30)</td> <td>73% (22/30)</td> <td>97% (29/30)</td> </tr> <tr> <td>Lumbar test negative / CSF test positive (n = 7)</td> <td>86% (6/7)</td> <td>86% (6/7)</td> </tr> <tr> <td>Lumbar test positive / CSF test positive (n = 10)</td> <td>100% (10/10)</td> <td>100% (10/10)</td> </tr> </tbody> </table> <p>Tests agreed (either both positive or both negative) in 31 patients (45%)</p> <p>Of the 38 patients with objective improvement in symptoms after shunt surgery:</p> <ul style="list-style-type: none"> <li>• 84% had a positive lumbar test</li> <li>• 42% had a positive tap test</li> </ul> <p>Of the nine patients with no objective improvement in symptoms after shunt surgery:</p> <ul style="list-style-type: none"> <li>• one had a negative lumbar test</li> <li>• eight had a negative tap test</li> </ul> |                           |                     | Objective improvement (from baseline in at least two out of four tests) | Self-reported improvement | Patients not operated on (n = 21) | 24% (5/21) | 19% (4/21) | Positive lumbar infusion test (n = 40) | 80% (32/40) | 98% (39/40) | Positive CSF tap test (n = 17) | 94% (16/17) | 94% (16/17) |  | Objective improvement (from baseline in at least two out of four tests) | Self-reported improvement | Lumbar test positive / CSF test negative (n = 30) | 73% (22/30) | 97% (29/30) | Lumbar test negative / CSF test positive (n = 7) | 86% (6/7) | 86% (6/7) | Lumbar test positive / CSF test positive (n = 10) | 100% (10/10) | 100% (10/10) | <p>There were no complications or side effects related to the lumbar infusion test or the CSF tap test.</p> | <p>Study objective: to compare the lumbar infusion test and the CSF tap test for predicting the outcome of shunt surgery in patients with suspected NPH.</p> |
|   | Objective improvement (from baseline in at least two out of four tests)   | Self-reported improvement |                     |   |                           |                                   |            |            |  |             |             |                                |             |             |  |   |                           |   |             |             |  |           |           |   |              |              |   |  |
| Patients not operated on (n = 21)   | 24% (5/21)  | 19% (4/21)                |                     |   |                           |                                   |            |            |  |             |             |                                |             |             |  |   |                           |   |             |             |  |           |           |   |              |              |   |  |
| Positive lumbar infusion test (n = 40)  | 80% (32/40)   | 98% (39/40)               |                     |   |                           |                                   |            |            |  |             |             |                                |             |             |  |   |                           |   |             |             |  |           |           |   |              |              |   |  |
| Positive CSF tap test (n = 17)  | 94% (16/17)   | 94% (16/17)               |                     |   |                           |                                   |            |            |  |             |             |                                |             |             |  |   |                           |   |             |             |  |           |           |   |              |              |   |  |
|   | Objective improvement (from baseline in at least two out of four tests)   | Self-reported improvement |                     |   |                           |                                   |            |            |  |             |             |                                |             |             |  |   |                           |   |             |             |  |           |           |   |              |              |   |  |
| Lumbar test positive / CSF test negative (n = 30)   | 73% (22/30)   | 97% (29/30)               |                     |   |                           |                                   |            |            |  |             |             |                                |             |             |  |   |                           |   |             |             |  |           |           |   |              |              |   |  |
| Lumbar test negative / CSF test positive (n = 7)  | 86% (6/7)   | 86% (6/7)                 |                     |   |                           |                                   |            |            |  |             |             |                                |             |             |  |   |                           |   |             |             |  |           |           |   |              |              |   |  |
| Lumbar test positive / CSF test positive (n = 10)   | 100% (10/10)  | 100% (10/10)              |                     |   |                           |                                   |            |            |  |             |             |                                |             |             |  |   |                           |   |             |             |  |           |           |   |              |              |   |  |

| Abbreviations used: CT, computed tomography; GDS, global deterioration scale; MMSE, mini mental state examination; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NPH, normal pressure hydrocephalus  |   |  |   |
|---|---|--|---|
| Study details   | Key efficacy findings   | Key safety findings  | Comments  |
| <p>Meier U et al. (2004)<sup>5</sup><br/><i>Predictors of outcome in patients with normal-pressure hydrocephalus.</i></p> <p>Prospective case series</p> <p>Germany</p> <p>Study period: May 1982–Jan 1997</p> <p>n = 200</p> <p>Population and indications: patients with proven NPH undergoing shunt surgery. Mean age: 52 years. Male: 61%</p> <p>Technique: computer-assisted constant flow intrathecal infusion test (measuring CSF resistance outflow) and CSF tap test.</p> <p>Patients were proven to have NPH according to pathologically high CSF resistance during an infusion test. All patients in this series underwent shunt surgery.</p> <p>Mean follow-up assessment: 7-months in 78% (155/200) of patients</p> <p>Conflict of interest: none stated</p> | <p><b>Clinical improvement after shunt surgery</b><br/>(from 155 patients who had a 7-month follow-up assessment)</p> <p><i>Clinical improvement was assessed by the Black grading scale (ranging from excellent, same level activity as prior to illness, to poor, no change or worsened condition)</i></p> <ul style="list-style-type: none"> <li>• Poor recovery rate: 19.4%</li> <li>• Fair recovery rate: 41.3%</li> <li>• Excellent/good recovery rate: 39.4% (absolute numbers not available)</li> <li>• Patients with a CSF outflow resistance of greater than 15 mmHg/ml/min (measured by intrathecal infusion test) had significantly more favourable clinical outcomes than patients with a lower CSF resistance (p = 0.01)</li> <li>• CSF tap test results were not significant predictors of clinical outcome after shunt surgery</li> </ul> | <p>No complications related to the lumbar infusion test were reported.</p> | <p>Study objective: not stated.</p> <p><b>All patients in this study were treated with shunt surgery.</b></p> |

| Abbreviations used: CT, computed tomography; GDS, global deterioration scale; MMSE, mini mental state examination; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NPH, normal pressure hydrocephalus  |  |   |  |
|---|--|---|--|
| Study details   | Key efficacy findings  | Key safety findings   | Comments   |
| <p>Meier U et al. (2001)<sup>6</sup><br/> <i>The importance of the intrathecal infusion test in the diagnostic of normal-pressure hydrocephalus.</i></p> <p>Prospective case series</p> <p>Germany</p> <p>Study period: May 1982 – Jan 1997</p> <p>n = 200</p> <p>Population and indications: patients with suspected NPH.<br/>                     Mean age: 52 years. Male: 61%</p> <p>Technique: computer-aided intrathecal infusion test</p> <p>Selection for shunt surgery: pathologically increased CSF resistance (n = 107)</p> <p>Follow-up assessment: none</p> <p>Conflict of interest: none stated</p> | <p><b>Results of intrathecal infusion test</b></p> <ul style="list-style-type: none"> <li>• 54% (107/200) of patients had high CSF resistance and 102 (51%) went on to have shunt surgery</li> <li>• One patient died before the operation and four refused the procedure and were lost to follow-up</li> <li>• 47% (93/200) patients had normal CSF resistance during the infusion test. Therefore, they were diagnosed with cerebral atrophy and did not undergo shunt surgery.</li> </ul> <p><b>No outcomes after shunt surgery were reported</b></p> | <p>19% of 107 patients (absolute numbers not available) reported headache after the procedure and two patients developed meningismus without signs of an inflammation in the CSF.</p> | <p>Study objective: to develop a diagnostic system to identify patients who derive the most benefit from shunt surgery and those who have already developed brain atrophy.</p> <p>This study is likely to include some of the same patients as those reported in the study described previously (Meier et al (2004)).</p> <p>This study did not follow-up patients after shunt surgery. It was included in this table because of its evidence on safety.</p> |

### ***Validity and generalisability of the studies***

- Studies were selected for inclusion in this overview if:
  - they were clinically relevant and if they included patients with NPH who underwent shunt surgery and whose clinical outcome was assessed after shunting, or if they included evidence on safety,
  - the results of the lumbar infusion test (with or without subsequent tests) were used to either select patients for shunt surgery or to assess the relationship between the test results and shunt response and the test was conducted before shunt surgery (studies were not included if the test was used to assess CSF resistance after shunting, and
  - they were published from 1980 onwards
- Most of the studies used measurements of CSF outflow resistance to select patients appropriate for shunt surgery (for example, Boon et al. 1997, Meier et al. 2001 and 2004, Delwel et al. 2005, Bech-Azeddine et al. 2005). However, one study used measurements of CSF plateau pressure to select patients for shunt surgery (Kahlon et al 2002).
- Several studies used different cut-offs points of CSF outflow resistance for selection of patients for shunt surgery

### **Specialist advisers' opinions**

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society

Mr Richard Ashpole (Association of British Neurologists), Carl Hardwidge, Alistair Jenkins (Society of British Neurosurgeons).

- All Specialist Advisers stated that this procedure was established practice and no longer new.
- Theoretical adverse events included: infection, post-procedure headache, bleeding, localised pain and nerve root damage.
- One Specialist Adviser stated that there were no uncertainties about the safety of this procedure as the risks are the same as those for normal lumbar puncture

- The key efficacy outcomes of the procedure are diagnosis of NPH and to test the functioning of CSF diversionary procedures.
- There is uncertainty about the diagnostic significance of different measures of CSF absorption (such as CSF outflow resistance).
- The interpretation and significance of test results (in conjunction with other clinical indicators) is of more uncertainty than the way the test is conducted.

## **Issues for consideration by IPAC**

- Consider changing title to 'lumbar infusion test for investigating/diagnosing normal pressure hydrocephalus'.

## References

1. Boon AJ, Tans JT, Delwel EJ et al. (1997) Dutch normal-pressure hydrocephalus study: prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. *Journal of Neurosurgery* 87: 687-93.
2. Delwel EJ, de Jong DA, and Avezaat CJ. (2005) The prognostic value of clinical characteristics and parameters of cerebrospinal fluid hydrodynamics in shunting for idiopathic normal pressure hydrocephalus.[erratum appears in *Acta Neurochir (Wien)*. 2006 Jan;148(1):99-100]. *Acta Neurochirurgica* 147: 1037-42.
3. Bech-Azeddine R, Gjerris F, Waldemar G et al. (2005) Intraventricular or lumbar infusion test in adult communicating hydrocephalus? Practical consequences and clinical outcome of shunt operation. *Acta Neurochirurgica* 147: 1027-35.
4. Kahlon B, Sundbarg G, and Rehncrona S. (2002) Comparison between the lumbar infusion and CSF tap tests to predict outcome after shunt surgery in suspected normal pressure hydrocephalus.[see comment]. *Journal of Neurology, Neurosurgery & Psychiatry* 73: 721-26.
5. Meier U, Konig A, and Miethke C. (2004) Predictors of outcome in patients with normal-pressure hydrocephalus. *European Neurology* 51: 59-67.
6. Meier U and Bartels P. (2001) The importance of the intrathecal infusion test in the diagnostic of normal-pressure hydrocephalus. *European Neurology* 46: 178-86.
7. Marmarou A, Bergsneider M, Klinge P et al. (2005) The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal-pressure hydrocephalus. [Review] [25 refs]. *Neurosurgery* 57: S17-28.

## Appendix A: Additional papers on lumbar infusion test for the investigation of normal pressure hydrocephalus not included in summary table 2

The following table outlines studies considered potentially relevant to the overview not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

| Article title   | Number of patients/<br>follow-up   | Direction of conclusions   | Reasons for non-inclusion in Table 2   |
|---|--|--|--|
| Bech-Azeddine R, Waldemar G, Knudsen GM et al. (2001) Idiopathic normal-pressure hydrocephalus: evaluation and findings in a multidisciplinary memory clinic. <i>European Journal of Neurology</i> 8: 601–11.   | n = 71<br><br>Follow-up: not stated                                      | Results were not reported separately for patients who underwent the lumbar infusion test and patients who underwent other tests.   |  |
| Boon AJ, Tans JT, Delwel EJ et al. (1998) Does CSF outflow resistance predict the response to shunting in patients with normal pressure hydrocephalus? <i>Acta Neurochirurgica Supplement</i> 71: 331–3.  | n = 101<br><br>Follow-up: 12 months                                      | The best predictor of shunting response was a CSF outflow resistance of 18 mmHg/ml/min or higher. Two thirds of patients under 18 years also improved after shunting.  | Likely to be the same patients as those reported in Boon et al. 1997 in Table 2.   |
| Kahlon B, Sundbarg G, Rehncrona S. (2005) Lumbar infusion test in normal pressure hydrocephalus. <i>Acta Neurologica Scandinavica</i> 111: 379–84.  | n = 55   | CSF outflow resistance from the lumbar infusion test has no advantage over steady-state plateau pressure for selecting patients for surgery.   | Likely to be the same patients as those reported in Kahlon et al. 2002 in Table 2. |
| Kahlon B, Sjunnesson J, Rehncrona S. (2007) Long-term outcome in patients with suspected normal pressure hydrocephalus. <i>Neurosurgery</i> 60: 327–32.   | n = 75<br><br>Mean follow-up: 5.5 years                                  | Patients who had shunt surgery (selected according to results of the lumbar infusion test or CSF tap test) benefited from surgery for at least 5 years.  | Likely to be the same patients as those reported in Kahlon et al. 2002 in Table 2. |
| Maksymowicz W, Czosnyka M, Koszewski W et al. (1989) The role of cerebrospinal compensatory parameters in the estimation of functioning of implanted shunt system in patients with communicating hydrocephalus (preliminary report). <i>Acta Neurochirurgica</i> 101: 112–16. | n = 12<br><br>(All patients had lumbar infusion test and shunt surgery.) | 3/12 patients had no clinical improvement (CSF dynamics measured by the infusion test were normal).<br><br>9/12 patients had clinical improvement (various CSF dynamics measured by the infusion test were highlighted as factors responsible for improvement after shunting). | Larger or more recent studies included in Table 2.                                 |



| Article title  | Number of patients/<br>follow-up  | Direction of conclusions  | Reasons for non-inclusion in Table 2  |
|--|---|---|---|
| Munch TN. (2007) Evaluation of the lumbar and ventricular infusion test in the diagnostic strategy of pediatric hydrocephalus and the therapeutic implications. <i>Child's Nervous System</i> 23: 67–71.   | n = 40 children with hydrocephalus  | Results were not reported separately for patients who had a lumbar infusion test and those who had an intraventricular infusion test.   |   |
| Savolainen S, Hurskainen H, Paljarvi L et al. (2002) Five-year outcome of normal pressure hydrocephalus with or without a shunt: predictive value of the clinical signs, neuropsychological evaluation and infusion test. <i>Acta Neurochirurgica</i> 144: 515–23. | n = 51<br>(Patients had various tests including a lumbar infusion test. Results of the intracranial test were used to select patients for shunt surgery.) | The infusion test was of no value in diagnosing NPH.  | The results of the lumbar infusion test were not used to select patients for shunt surgery or reported in any detail. |
| Sorteberg A, Eide PK, Fremming AD. (2004) A prospective study on the clinical effect of surgical treatment of normal pressure hydrocephalus: the value of hydrodynamic evaluation. <i>British Journal of Neurosurgery</i> 18: 149–57.                              | n = 17<br>(All patients underwent shunt surgery.)<br><br>Follow-up: 6 months  | CSF outflow resistance (measured by the lumbar infusion test) was positively correlated with the clinical state of the patients before shunting. After surgery, the CSF outflow resistance correlated well with improvements in gait and NPH score. | Larger or more recent studies included in Table 2.  |

## **Appendix B: Related published NICE guidance for lumbar infusion test for the investigation of normal pressure hydrocephalus**

| <b>Guidance programme</b> | <b>Recommendation</b> |
|---------------------------|-----------------------|
| Interventional procedures | None applicable       |
| Technology appraisals     | None applicable       |
| Clinical guidelines       | None applicable       |
| Public health             | None applicable       |

## Appendix C: Literature search for lumbar infusion test for the investigation of normal pressure hydrocephalus

| IP 680 Lumbar infusion test for the investigation of normal pressure hydrocephalus |               |                             |
|--|---------------|-----------------------------|
| Database   | Date searched | Version searched            |
| Cochrane Library   | 31/10/2007    | Issue 4, 2007               |
| CRD databases (DARE & HTA)   | 31/10/2007    | Issue 4, 2007               |
| EMBASE   | 31/10/2007    | 1980 to 2007 Week 43        |
| MEDLINE  | 31/10/2007    | 1950 to October Week 3 2007 |
| PREMEDLINE   | 31/10/2007    | October 30, 2007            |
| CINAHL   | 31/10/2007    | 1982 to October Week 4 2007 |
| British Library Inside Conferences   | 31/10/2007    | –                           |
| NRR  | 31/10/2007    | Issue 4, 2007               |
| Controlled Trials Registry   | 31/10/2007    | –                           |

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

|    |                                    |
|----|------------------------------------|
| 1  | (infusion\$ adj3 test\$).tw.       |
| 2  | (lumbar\$ adj3 infusion\$).tw.     |
| 3  | 1 or 2                             |
| 4  | exp Hydrocephalus/                 |
| 5  | hydrocephal\$.tw.                  |
| 6  | exp Cerebrospinal Fluid/           |
| 7  | (cerebrospinal\$ adj3 fluid\$).tw. |
| 8  | exp Cerebrospinal Fluid Pressure/  |
| 9  | or/4-8                             |
| 10 | 3 and 9                            |