Learning Objectives:
1. understand the therapies available to treat idiopathic intracranial hypertension
2. know the evidence available for interventions and possible efficacy for IIH treatments
3. understand complications of the various IIH therapies

CME Questions:
1. A 32 year old woman presents with daily headaches, transient visual obscurations, and pulse synchronous tinnitus. She has no visual loss on perimetry. All of the following are reasonable therapeutic plans except:
   a. Begin a weight loss program
   b. Refer for venous sinus stenting
   c. Start Diamox at one gram a day in divided doses
   d. Begin sodium restriction
   e. Start furosemide at 20 mg bid.

2. Treatment decisions should based primarily on all of the following except:
   a. Rapidity and degree of visual loss
   b. Change in papilledema grade
   c. Frequency of pulse synchronous tinnitus
   d. Headache severity
   e. Size of the blind spot

Key Words: idiopathic intracranial hypertension, pseudotumor cerebri, acetazolamide, furosemide, weight loss, corticosteroids, optic nerve sheath fenestration, shunt.

Medical Therapy
Treatment of raised intracranial pressure is both medical and surgical. It is aimed mainly at lowering of intracranial pressure and secondarily at treating symptoms directly (e.g. headache). Unfortunately, all reports to date are anecdotal as there have not been any controlled clinical treatment trials for idiopathic intracranial hypertension.

Weight Loss Weight loss has been used to treat IIH for many years. Newborg in 1974 reported remission of papilledema in all nine patients placed on a strict diet. She used a low calorie adaptation of Kempner’s rice diet. Each patient’s intake was 400-1000 calories per day by fruits, rice, vegetables and occasionally 1-2 oz of meat. Fluids were limited to 750-1250 ml/day and sodium to less than 100 mg/day. All patients had reversal of their papilledema. Unfortunately, there was no mention of the patients’ visual testing. The beneficial effects of weight loss have also been reported more recently. Kupersmith and colleagues retrospectively reviewed the charts of 250 IIH medically treated IIH patients from two centers and tabulated results on 56 patients that had at least 6 months of follow-up and otherwise met entry criteria. The mean time to improve one papilledema grade was about 4 months in patients with weight loss compared with about 1 year in patients without weight loss. Papilledema resolved in 28/38 patients with weight loss compared with 8/20 without weight loss.

Johnson and coworkers retrospectively studied 15 IIH patients treated with acetazolamide and weight loss for 24 weeks. They reported 3.3% weight loss in patients having one grade of improvement in their papilledema grade. Nine of 10 patients that improved took acetazolamide as did the four patients that did not lose weight and had no improvement in papilledema grade. Our experience from a pilot study with 29 patients has also been that improvement often occurs with only modest degrees of weight loss. Greer however, reported a group of six obese patients that became asymptomatic without weight loss. Resolution of IIH in a patient following surgically induced weight loss (gastric exclusion procedure) was first reported by Amaral. Sugarman and coworkers performed gastric weight reduction surgery in 24 morbidly obese women with IIH. Five patients were lost to follow-up. Symptoms resolved in all but one patient within 4 months of the procedure. Two patients regained weight associated with return of their symptoms. There were many significant but treatable surgically-related complications.

Since marked recent weight gain is a predictor of visual deterioration and we have observed papilledema resolve with weight loss as the only treatment, we strongly encourage our patients to pursue a supervised weight loss program. As Friedman and Streeten have
shown, there is a subset of IIH patients with orthostatic edema. Low salt diets and fluid restriction may also be beneficial for many IIH patients. This may be especially true in patients that lose only a few percent of their total body mass yet have resolution of their optic disc edema. It is not yet clear whether improvement occurs because of weight loss per se or other changes in diet such as fluid or sodium restriction.

**Lumbar Puncture** Lumbar puncture without CSF leak has only a short-lived effect on CSF pressure; Johnston and Paterson found a return of pressure to pre-tap level after only 82 minutes. Interestingly, Weisberg reported 6 of 28 patients treated with serial lumbar punctures symptomatically improved. This beneficial effect may relate to dilation of transverse sinus venous stenosis associated with pressure lowering and temporary improvement in venous flow. Repeated lumbar punctures also raise the risk of developing intraspinal epidermoid tumors presumably caused by implantation of epidermal cells. Manno et al., reported 41% of intraspinal epidermoid tumors in their series could be traced to prior lumbar punctures. Lastly, repeated lumbar punctures to measure CSF pressure at only one point in time. Since CSF pressure fluctuates widely, this information has only limited clinical use for modifying treatment plans.

**Corticosteroids** Paterson first reported the efficacy of corticosteroids for treating IIH in five of six consecutive patients. Fifteen of Weisberg’s patients that did not respond to repeated lumbar punctures were treated with corticosteroids. Thirteen had prompt resolution within three days and had no recurrence following cessation of therapy seven to 14 days later. A fourth subgroup of 35 patients was treated initially with corticosteroids and 32 of these responded promptly. Of those responding favorably to corticosteroid therapy, all showed improvement of symptoms or signs within four days. In a study of 38 children treated with various regimens for IIH, four who failed repeated lumbar punctures were treated with corticosteroids. All responded with resolution of symptoms and signs. Twelve other patients had clinical improvement with a combination of repeated lumbar punctures and corticosteroids. The study concluded there was an inverse relation of steroid dosage to intracranial pressure. Although most patients in their series that were treated with steroids also responded, there was recurrence with rapid tapering of the dose. A prolonged tapering may prevent return of symptoms. Corticosteroids are still used to treat IIH but their mechanism of action remains unclear. The side effects of weight gain, striae, and acne are particularly unfortunate for these obese patients. Although patients treated with steroids may respond well, there may be recurrence of papilledema with rapid tapering of the dose. This may be accompanied by marked worsening of visual function. A prolonged tapering may prevent return of symptoms and signs in some patients. Use of corticosteroids to treat IIH patients has been abandoned by most neuro-ophthalmologists.

**Thiazide Diuretics** Jefferson and Clark treated 30 patients with various types of oral dehydrating agents (chlorthalidone, hydroflumethiazide, glycerol and urea). All patients were also placed on a weight reduction diet. They used blind spot size as their main outcome measure. This measure can be problematic for many reasons including changes in refractive error and changes in stimulus speed and reaction times between exams. Fourteen of these patients had reduced visual acuity, and in all, vision improved with therapy. Friedman treated 30 women with IIH and orthostatic edema with chlorthalidone and spironolactone. In 15, dextroamphetamine or phenteramine was added and 18 patients also were treated with acetazolamide. This treatment did not consistently reduce headaches and only four of the 30 patients had improvement in their papilledema.

**Acetazolamide** In 1974, McCarthy and Reed showed inhibition of CSF flow but not until over 99.5% of choroid plexus carbonic anhydrase was inhibited. Lubow and Kuhr, in 1976, reported a series of IIH patients, many of whom were treated successfully with acetazolamide (Diamox®) and weight reduction. An important study was published in 1978 by Gücer and Viernstein. They used intracranial pressure monitoring before and after treatment in four IIH patients. They monitored acetazolamide treatment in two of the patients and showed gradual CSF pressure reduction in both. They only reported the dose in one of the patients (four grams of acetazolamide per day). Ten years later, Tomsak et al., documented resolution of papilledema with photographs of the optic disc in four patients treated with one gram of acetazolamide a day. Acetazolamide appeared to be an effective medication in their patients with results occurring over several months. The mechanism of action of acetazolamide is likely multifactorial. It has been found to reduce CSF production in humans by 6-50%. It has been thought to
work by inhibition of carbonic anhydrase that causes a reduction in transport of sodium ions across choroid plexus epithelium. In addition, it changes the taste of foods and causes carbonated beverages to taste metallic. This may aid the patient in weight loss. Additionally, some patients experience nausea, further helping them to lose weight.

The most effective dose is not yet determined. In addition to the gustatory side effects, patients commonly experience tingling in the fingers, toes, and perioral region, and less commonly, malaise, nausea and anorexia are reported. Rarely patients will develop renal stones. Metabolic acidosis, evidenced by lowered serum bicarbonate, is a good measure of compliance. Younger patients tolerate acetazolamide better than older ones and the Diamox 500mg sequels appeared to be better tolerated. Aplastic anemia is so rare, some advocate not monitoring complete blood counts. Zimran and Beutler estimate the cost of finding one case would be $1.5 million.

Topiramate has been proposed as a treatment for IIH. It has been well documented that furosemide (Lasix®) can lower intracranial pressure. Furosemide has also been used to treat IIH. It is usually combined with mannitol in neurosurgical emergencies like herniation syndromes and its effects appear to be additive to the mannitol. It appears to work by both diuresis and reducing sodium transport into the brain. Based on an assumption by McCarthy and Reed that the effects of acetazolamide and furosemide might be additive, Schoeman treated pediatric IIH patients with this combination therapy. In a controlled trial of children with tuberculous meningitis, 57 with communicating hydrocephalus were randomly assigned to three treatment groups: antituberculous drugs only; or additional intrathecal hyaluronidase or oral acetazolamide and furosemide in addition to antituberculous treatment. Acetazolamide and furosemide in combination was significantly more effective in achieving normal ICP than antituberculous drugs alone.

Schoeman then treated eight pediatric IIH patients with oral acetazolamide (37-100 mg/kg) and furosemide (1 mg/kg) until the papilledema cleared. He used continuous 1-hour lumbar cerebrospinal fluid pressure monitoring these children with IIH on admission and at weekly intervals until the baseline pressure became normal. Six children had an increased baseline cerebrospinal fluid pressure, whereas raised intracranial pressure was diagnosed in three children based on an abnormal pulse wave and/or pressure waves. The mean baseline pressure normalized in all patients within 6 weeks of start of therapy. As with all treatments of IIH, all reports to date are anecdotal and recommended treatments vary widely.

**Glycerol** Oral glycerol is a form of cerebral dehydration first recommended in 1963 to reduce intracranial pressure. A single dose of one gram/kg of glycerol will raise serum osmolality from 295 to 320 mOsm / L in 90 minutes, and reduce CSF pressure for 3 to 5 hours. Doses every four hours can cause a reversed osmotic gradient and a rebound increase in intracranial pressure while a six hour interval is too long and allows the high pressure to recur. Together, the added calories the large volume of glycerol needed, the awkwardness for a working person to use this medication, the nauseating side effects, and other side effects make this a cumbersome medication for IIH. Digoxin has been used to treat IIH since it may reduce CSF production. The evidence it is efficacious in IIH is weak.

**Treatment of Headache** Sometimes, in spite of full medical therapy to reduce CSF pressure, headaches persist. We have success in some patients with standard prophylactic vascular headache remedies. However, caution should be used in patients with visual loss as the hypotension that accompanies many of these medications can accelerate the visual loss.

Patients with idiopathic intracranial hypertension also have other headache syndromes. Especially in patients with a migraine history, analgesic rebound or caffeine rebound headaches may coexist. It may require IV dihydroergotamine or metoclopramide to break this troublesome headache syndrome.

**Surgical Therapy in IIH** The surgical forms of therapy now used are various shunting and optic nerve decompression procedures.

**Optic nerve sheath fenestration:** De Wecker pioneered treatment for papilledema in 1856 when he performed the first optic nerve sheath fenestration. The procedure fell into disfavor until the 1960s when Hayreh, using a primate model, demonstrated bilateral relief of papilledema with a unilateral optic nerve sheath fenestration; he also demonstrated communication between the lumbar subarachnoid space and the orbital sub-
arachnoid space. Later, Smith and coworkers reported successful relief of papilledema in a human. Optic nerve sheath fenestration consists of either creating a window or making a series of slits in the optic nerve sheath just behind the globe. This treatment is used for the patient with progressive visual loss with mild or easily controlled headaches, although over 50% of patients after surgery gain adequate headache relief. Since improvement in papilledema may occur in the unoperated eye and fistula formation has been demonstrated, the mechanism of action may be local decompression of the subarachnoid space. Occasional failure of the fellow eye to improve and the asymmetry of papilledema may be explained by the resistance to CSF flow produced by the trabeculations of the subarachnoid space. Others have proposed the long-term mechanism of action of optic nerve sheath fenestration may be closure of the subarachnoid space in the retro-laminar optic nerve by scarring.

Large case series suggest efficacy of this technique (Table 1). In these series, postoperative visual acuity or fields were as good as or better than preoperative studies in 90%. However, about 10% of patients lost vision in the perioperative period.

Table 1. Results of optic nerve sheath fenestration.

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Year Published</th>
<th>Vision Worse</th>
<th>Vision not Worse</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hupp</td>
<td>1987</td>
<td>6</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Sergott</td>
<td>1988</td>
<td>0</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Brouerman</td>
<td>1988</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Corbett</td>
<td>1988</td>
<td>9</td>
<td>31</td>
<td>40</td>
</tr>
<tr>
<td>Kelman</td>
<td>1992</td>
<td>1</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Plotnik</td>
<td>1993</td>
<td>4</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>Acheson</td>
<td>1994</td>
<td>3</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Goh</td>
<td>1997</td>
<td>3</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Banta</td>
<td>2000</td>
<td>10</td>
<td>148</td>
<td>158</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>36</strong></td>
<td><strong>314</strong></td>
<td><strong>350</strong></td>
</tr>
</tbody>
</table>

Spoor and coworkers have raised the issue that patients undergoing optic nerve sheath fenestration may have substantial long-term failure rates. They reported results of 75 eyes of 54 patients undergoing optic nerve sheath fenestration who had stable visual acuity and 4 or more visual field examinations during 6 – 60 months of follow-up. They defined stability as a mean deviation within 2 dB of the preoperative visual field and worsening, more than a 2 dB mean deviation deterioration. Using this definition, 51 of 75 eyes (68%) showed improvement or stabilization and 24 eyes (32%) worsening. However, 2 dB or greater mean deviation is well within observed retest variability with moderate to marked visual field damage and these conclusions should be viewed with skepticism.

CSF Shunting Procedures: Various shunting procedures have been employed for the treatment of IIH including lumbar subarachnoid-peritoneal shunts, ventriculoatrial, ventriculojugular, ventriculopleural and ventriculoperitoneal shunts, and cisternaoarial shunts. These case series are difficult to compare because the types of shunts are different, the shunts used have different complications, and there are different indications and procedure techniques employed. In general, the indication for a CSF diversion procedure in these series’ was failed medical therapy or intractable headache. The case series published document efficacy, but frequent failure and the need for multiple revisions in at least half the patients limit its use. Shunting procedures appear to be successful in selected patients. Unfortunately, complications are very common including shunt occlusion and intracranial hypotension. Shunt occlusion can be accompanied by the rapid onset of severe visual loss, limiting the effectiveness of this procedure. Less common complications are back pain, abdominal pain, disc space infection, meningitis, disconnection of tubing, and Chiari malformation.

Venous Sinus Stenting: There have been several anecdotal retrospective reports of venous sinus stenting to
This procedure is based on the finding of the presence of a pressure gradient between the proximal and distal portions of the lateral third of the transverse venous sinus. However, it has been shown that lowering CSF pressure abolishes the venous pressure gradient. This implies that the gradient is a result rather than a cause of IIH. Results of efficacy to date have been inconclusive.

**Summary of Therapies.** There is no clear consensus of therapeutic intervention and the mechanisms of the treatments are unclear. In general, patients in early stages are told to lose weight and given pharmacologic therapy, most often with acetazolamide. Some physicians use acetazolamide, while others use furosemide; less commonly, corticosteroids or repeated lumbar punctures are employed. Although there are large variations in practice, most physicians wait until later stages to recommend surgical interventions. Optic nerve sheath fenestration is most commonly used for progressive visual loss refractive to medical therapy while CSF shunting procedures are used when headache is a dominant feature of the patient’s presentation.

In the words of Lueck and Mcllwaine from their Cochrane review: “There is insufficient information to generate an evidence-based management strategy for idiopathic intracranial hypertension. Of the various treatments available, there is inadequate information regarding which are truly beneficial and which are potentially harmful. Properly designed and executed trials are needed.”

**Idiopathic Intracranial Hypertension Treatment Trial (IIHTT)** The IIHTT Study Group has proposed a multicenter randomized controlled clinical trial to determine treatment efficacy in IIH. The schematic of figure 1 summarizes the study design. The study is under review by the NIH.

Figure 1. Study design of the IIHTT.

![Study design of the IIHTT](image-url)
References


CME Answers:
1. b
2. e