Corticosteroids:
Ménière's disease, Sudden deafness, autoimmune inner ear disease, tinnitus.

**Pharmacology**

- **Naturally** corticosteroids (cortisol): adrenocortical deficiency states
- **Synthetic** corticosteroids: anti-inflammatory effects

- **Dexamethasone**
  - (9-fluoro-11b,17,21-trihydroxy-16a-methylpregna-1,4-diene-3,20-dione)
  - 1. long-acting glucocorticoid, 36- to 54-hour half-life
  - 2. metabolized in the liver, excreted by the kidneys
  - 3. endocrine, rheumatic, collagen, dermatologic diseases, allergic states, ophthalmic, respiratory, hematologic, neoplastic disease, and edema

- **Adverse reactions**
  1. Fluid and electrolyte disturbance, sodium and fluid retention, congestive heart failure, hypokalemia, hypertension, muscle weakness, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, and tendon rupture
  2. GI adverse effects
  3. Dermatologic (↓wound healing, thin fragile skin, petechiae, ecchymoses)
  4. Neurologic (convulsions, headache, psychic disturbances)
  5. Endocrine problems (menstrual irregularities, cushingoid state, ↓growth in children, latent diabetes mellitus, ↑requirements for insulin or OHA in DM patients, hirsutism)
  6. Ophthalmic (posterior cataracts, glaucoma, and exophthalmos)
  7. Other: thromboembolism, weight gain, ↑appetite, nausea, and malaise

- **Systemic steroids in ear**: ↓inflammation from labyrinthitis, ↑cochlear blood flow, against cochlear ischemia, against noise-induced HL, regulate inner ear de novo protein synthesis

- **Rarey and Curtis** (human cadaveric temporal bones)
  - glucocorticoid receptors: in cochlear and vestibular tissues
  - (highest concentration: spiral ligament)

- **Intratympanic (IT) steroids**:
  - ↑cochlear blood flow, prevent aminoglycoside toxicity, prevent drill-induced noise loss, ↑ion homeostasis
  - round window inflammation
2006 Hargunani et al  Dexamethasone (mice)
1. seen 15 minutes, highest staining intensity: 1 hour. Not seen after 24 hours
2. The strongest staining: spiral ligament, organ of Corti, spiral ganglion, and vestibular sensory epithelia.
3. Distribution of the drug paralleled locations of the glucocorticoid receptor
4. Except stria vascularis marginal cells (stained for the receptor but not drug)

Effect of steroid in ear disease~ Animal studies

Shirwany et al.
1. IV glucocorticoids: not improve cochlear blood flow.
2. IT dexamethasone in the guinea pig model:
   ↑ cochlear blood flow, no effects on auditory sensitivity or cochlear histology

Parnes et al.
1. IT corticosteroids >> cross blood-labyrinthine barrier >> higher concentration in the perilymph and endolymph than those administered systemically
2. methylprednisolone showed more effective absorption

Chandrasekhar et al.
1. compared perilymph dexamethasone concentrations after systemic and intratympanic administration in 40 guinea pigs: perilymph steroid levels IT>IV
2. histamine: ↑ dexamethasone perilymphatic concentration

Yang et al.
round window application of dexamethasone and other immunosuppressants: not prevent immune-induced hearing loss in a guinea pig model

- Yildirim et al. (60 rats)
  IT-DEX or DEX/HA (hyaluronate acid) for noise-induced temporary threshold shift: no effect

- Daldal et al
  1. IT dexamethasone: minimize inner ear damage induced by cisplatin.
  2. had protective effect on outer hair cells
  3. inhibited NOS II, (preventing iNOS-mRNA synthesis and preventing late-phase NO synthesis) without affecting cochlear blood flow or cochlear vascular tonus.

**The optimal drug, dosage, schedule, and duration of treatment**

- **Drug**: Dexamethasone (2-4mg/mL to 25 mg/mL), methylprednisolone (32 mg/mL to 62.5 mg/mL)...
- **Amount**: 0.3~0.4mL
- **Method**:
  1. 25- or 27-gauge needle through a small site (previously anesthetized)
  2. Large myringotomy (for endoscopy and removal of round window adhesions)
  3. Laser assisted myringotomy
  4. 2 myringotomies
  5. Ventilation tubes (for serial treatments)
  6. The use of wicks for self-treatment with dexamethasone ophthalmic drops
  7. Implantable pump (constant infusion)
- **Duration and schedule**: varied according to disease and symptoms

**Intratympanic steroid treatment of Meniere's disease**

The success rate of intratympanic injections of corticosteroids for vertigo, hearing loss, and tinnitus has been varied

- In 1991, Itoh and Sakata (61 p'ts)
  80% improvement in vertigo, 74% reduction in tinnitus
- **Shea and Ge** (28 p'ts)
  IV+ IT corticosteroids: 67.9% improvement in hearing, 96.4% control of vertigo
- **Shea** (48 patients) (2 years study)
  35% improvement in hearing, 63% control of vertigo
- In 2001, Hamid (60 p'ts): concentrated dose of dexamethasone 24 mg/mL
  90% control of vertigo in followed 2 years
- **Hillman et al.** (50 p'ts) 1~3 dexamethasone (IT):
  40% hearing improved, average ↑ 14.2 dB
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of ears</th>
<th>Drug</th>
<th>Delivery method</th>
<th>Total dosage (mg/ml)</th>
<th>Pre-PTA (dB)</th>
<th>Post-PTA (dB)</th>
<th>Pre-WDS (%)</th>
<th>Post-WDS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arriaga and Goldman, 1998 (13)</td>
<td>15</td>
<td>Dex</td>
<td>RW Gelfoam</td>
<td>8</td>
<td>57</td>
<td>51</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Barrs, 2001 (12)</td>
<td>21</td>
<td>Dex</td>
<td>Tube/intratympanic</td>
<td>4.8–8</td>
<td>–2.7</td>
<td>–2.7</td>
<td>–2.7</td>
<td>–2.7</td>
</tr>
<tr>
<td>Hirvonen et al., 2000 (10)</td>
<td>17</td>
<td>Dex</td>
<td>Intratym inj</td>
<td>9.6–19.2</td>
<td>49</td>
<td>53</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Silverstein et al., 1998 (14)</td>
<td>20</td>
<td>Dex</td>
<td>Intratym inj</td>
<td>4.8–6.4</td>
<td>48</td>
<td>48</td>
<td>68</td>
<td>74</td>
</tr>
</tbody>
</table>

PTA, pure-tone average; WDS, word discrimination score; Dex, dexamethasone; RW, round window; Intratym inj, intratympanic injection.

- **Arriaga and Goldman** (15 p’ts)
  - single injection of dexamethasone+ hyaluronan: **not** detect any hearing gain
- **Barrs et al.** (21 p’ts) weekly IT dexamethasone 4 mg/ml, 1 month.
  - Complete relief of vertigo: 11/21 (52%) at 3 months, in 43% at 6 months
- **Hirvonen et al.** (17 p’ts)
  - IT dexamethasone hyaluronate (16 mg/ml, 0.2–0.4 ml) 3 times/week.
  - 1. 76% control vertigo
  - 2. no improvements in hearing loss or tinnitus
- **Silverstein et al.** (20 p’ts)
  - no hearing improvement (PTA, speech threshold, tinnitus scales)
- **Sennaroglu et al.**
  - 1.72% satisfactory control of vertigo,
  - 2.16% improved hearing, 8% worsened hearing (>20 dB)
  - no effect on hearing levels or tinnitus

### Intratympanic steroid in sudden deafness and other ear disease
- 1996 **Silverstein et al.** (32 p’ts)
  - 15 (47%) improvement of the tinnitus, 16 (50%) unchanged, 1 worse
- **Sakata et al.** IT dexamethasone (for tinnitus)
- 2-year period, 1,266 ears (for vertigo and tinnitus) (4 times/1-2 weeks).
  - Some received a second course 3 months after completion of the first one
  - 77% short-term efficacy, 68% after 6-month period
  - highest efficacy (tinnitus): COM, Ménière’s disease, labyrinthine syphilis

- Main protocols for **sudden deafness**
  1. **Initial or primary** treatment for sudden SNHL without systemic steroids;
  2. **Adjunctive** treatment given concomitantly with systemic steroids
  3. **Salvage therapy** after failure of systemic steroids for sudden SNHL.
<table>
<thead>
<tr>
<th>Author</th>
<th>P't No</th>
<th>Steroid (mg/mL)</th>
<th>from HL</th>
<th>No. for injection</th>
<th>improved criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverstein et al</td>
<td>8</td>
<td>Dex</td>
<td>HL</td>
<td>3/week, for 3-4 weeks</td>
<td>sal</td>
</tr>
<tr>
<td>1999</td>
<td>13</td>
<td>MP(40) or Dex</td>
<td></td>
<td>2d-6w</td>
<td>sal</td>
</tr>
<tr>
<td>Kapke et al</td>
<td>3, 6</td>
<td>MP (62.5)</td>
<td>&gt;6w</td>
<td>microcatheter, 14 days</td>
<td>sal</td>
</tr>
<tr>
<td>Gianoli and Li</td>
<td>23</td>
<td>Dex(25) or MP(125)</td>
<td>72w</td>
<td>4/10-14 days (rate 10µL/h)</td>
<td>sal</td>
</tr>
<tr>
<td>Chandrasekhar</td>
<td>11</td>
<td>Dex(2-4)</td>
<td>33d</td>
<td>1-15</td>
<td>sal</td>
</tr>
<tr>
<td>Lefebre and Staeker</td>
<td>6</td>
<td>MP(62.5)</td>
<td>10d</td>
<td>microcatheter, 8-10 days</td>
<td>sal</td>
</tr>
<tr>
<td>Jackson</td>
<td>19</td>
<td>Dex(2-24)</td>
<td>Microwick, 3gtt(tid)(2-4w)</td>
<td>sal</td>
<td></td>
</tr>
<tr>
<td>Gouveris</td>
<td>21</td>
<td>Dex(8)</td>
<td>5.45d</td>
<td>(1-7) (average 2.7)</td>
<td>sal</td>
</tr>
<tr>
<td>Ho et al</td>
<td>15</td>
<td>Dex(4)</td>
<td>19.7d</td>
<td>3/3 weeks</td>
<td>sal</td>
</tr>
<tr>
<td>Lauteraman et al</td>
<td>13</td>
<td>MP(32)</td>
<td>2-3d</td>
<td>5/5 days</td>
<td>ad</td>
</tr>
<tr>
<td>Battista</td>
<td>25</td>
<td>Dex (24)</td>
<td>28d</td>
<td>4/14d (profound HL)</td>
<td>CR8%, par12%</td>
</tr>
<tr>
<td>Her and Marzo</td>
<td>17</td>
<td>Dex(10)MP(62.5)</td>
<td>6.3w</td>
<td>Microwick or pump, 8-14d</td>
<td>sal</td>
</tr>
<tr>
<td>Slattery et al</td>
<td>20</td>
<td>MP(62.5)</td>
<td>3m</td>
<td>4/2 weeks</td>
<td>sal</td>
</tr>
<tr>
<td>Choung</td>
<td>33</td>
<td>Dex(5)</td>
<td>28d</td>
<td>2/w,(for 2w)</td>
<td>sal</td>
</tr>
<tr>
<td>Dallan et al</td>
<td>8</td>
<td>MP(40)</td>
<td>21.5d</td>
<td>Single</td>
<td>sal</td>
</tr>
<tr>
<td>Xenellis et al</td>
<td>19</td>
<td>MP(40)</td>
<td>21d</td>
<td>4/15d</td>
<td>sal</td>
</tr>
<tr>
<td>Haynes et al</td>
<td>40</td>
<td>Dex(24)</td>
<td>40d</td>
<td>single</td>
<td>sal</td>
</tr>
</tbody>
</table>

- **Choung et al**
  1. IT steroid: secondary treatment (∵ not more effective and inconvenient)
  2. Hypothesis: IT → round window → basal turn > apex → ↑ high frequencies
  Actual: more effective in the patients with HL in **low frequencies**

- **Ho et al**
If the hearing did not improve within the first two injections, the patient is less likely to benefit from further treatment

- Kakehata et al (in DM patients)
  1. IT-DEX treatment is at least as effective as IV-DEX treatment
  2. Advantages: daily blood sugar measurements and insulin injections are not necessary.

- Battaglia et al (combine therapy)
  1. Hearing recovery: combination therapy (HDPT + IT-Dex) > HDPT alone
  2. HDPT + IT-Dex: initial treatment for ISSNHL.
  3. initiated as quickly as possible (<10 days of onset of hearing loss)

- Ahn et al (combine therapy)
  1. ITD + systemic steroids: no additional benefits compared with systemic steroids alone
  2. +ITD: improvement at a lower frequency (250 Hz).

**Advantage if intratympanic steroids**

1. **Ease of administration**
   Local anesthesia: phenol, tetracaine, EMLA cream or lidocaine
   Dry ear precautions (until the myringotomies heal)

2. **Avoidance of surgery**
   nondestructive, fast, and inexpensive compared with traditional surgery

3. **Contraindications to systemic therapy**
   1. DM, HTN
   2. TB: Isoniazid 300 mg daily
   3. Partial aseptic necrosis of the femoral head, severe osteoporosis, or psychosis
   Systemic steroids should not be given

4. **Intolerance of systemic therapy**
   common side effects of systemic steroid: insomnia and gastric disturbance

5. **Salvage therapy when systemic treatment fails**
   IT steroids can partially or completely recover some cases of idiopathic sudden sensorineural hearing loss up to 6 weeks after onset, when high-dose systemic therapy has failed.

6. **Selection of the active ear for treatment**
   Unlike systemic therapy, IT steroids allow one ear to be selected for treatment

**Complication of intratympanic steroids**

1. **Pain**
   - Barrs et al. (21 patients)
All patients: mild pain (with phenol) under administration

- **Parnes et al.** (37 patients)
  1. SoluMedrol: more pain than dexamethasone IT steroids
  2. 2 p'ts unable to tolerate serial injections (with the addition of lidocaine)
  3. One p’t: burning of ear and throat for 6 hours after administration

2. **Otitis media and tympanic membrane perforation**

- **Silverstein et al.** (46 patients)
  Perforation: heal slowly.

- **Sennaroglu et al.** (24 patients)
  1. 1/24 otitis media
  2. one perforation persisted for 1 month (closed with a paper patch)

3. **Vertigo**
   Temporary vertigo is common, (∵ temperature and use of lidocaine

4. **Hearing loss**
   The risk of worsening hearing: low
   - In treatment of Ménière’s disease cannot be evaluated because of spontaneous fluctuations
   - **Shea** (0.5 ml hyaluronan + 16 mg/ml of dexamethasone)
     worse hearing : 3/48 ears
   - **Barrs et al.**: 1/29 significant deterioration in hearing (↓35 dB)
   - **Arriaga and Goldman** (Gelfoam sponge in round window niche, filled middle ear with dexametha-sone/hyaluronan mixture, 8 mg/ml): 3/21 hearing deterioration
   - In the treatment of sudden deafness and autoimmune inner ear disease difficult to evaluate, further losses may occur because of the natural progression of the disease.
   - **Parnes et al.**: (29 p'ts) no patients with worsened hearing
   - **Chandrasekhar** (dexamethasone 2 mg/ml and 4 mg/ml)
     2/11: lost hearing (average: ↓12.5 dB and 12% discrimination)

5. **Others**
   1. ↑ insulin requirements in DM p'ts after injection of 0.5 ml of a 24-mg/ml solution of dexamethasone.
   2. Osteonecrosis of the hip occurring after single doses of steroids
Reference


3. Guan-Min, Ho MD, PhD; Hung-Ching, Lin MD; Min-Tsan, Shu MD; Cheng-Chien, Yang MD; Hsun-Tien, Tsai MD, PhD. Effectiveness of Intratympanic Dexamethasone Injection in Sudden-Deafness Patients as Salvage Treatment. Laryngoscope. 114(7):1184-1189, July 2004.


13. Yildirim, Altan MD; Coban, Levent MD; Satar, Bulent MD; Yetiser, Sertac MD; Kunt, Tanfer MD. Effect Of Intratympanic Dexamethasone on Noise-Induced Temporary Threshold Shift. Laryngoscope. 115(7):1219-1222, July 2005.