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## Amblyopia

Amblyopia is a unilateral or bilateral condition that causes the in which the **best corrected visual acuity (VA) is worse than 20/20 in the presence of a normal healthy eye (no structural abnormalities or ocular disease)** [1]. Amblyopia develops during the critical period, typically in **patients <6-8 years old** (critical period) [2]. Depending on the level of VA reduction the prevalence changes:

- Using VA of 20/40 or worse – prevalence is 1.4% of the population [3]
- Using VA of 20/30 or worse – prevalence is 3.5% of the population [3]

In addition to a reduction in BCVA, patients with amblyopia can also have: crowding effect, unsteady fixation, poor tracking, reduced contrast sensitivity and inaccurate accommodative responses [4].

Below we will classify amblyopia based on the condition that leads to the reduction in best corrected VA.

### CROWDING

Patients impacted by the crowding effect will perform better with lines of letters than blocks of letters and better with single letters than lines of letters.

## Form Deprivation Amblyopia

Form deprivation amblyopia occurs when there is an obstruction in the visual axis that precludes a clear image on the retina. Common conditions that can lead to form deprivation amblyopia include [5] [6] [7] [8]:

- Congenital cataract (most common)
- Traumatic cataract
- Corneal opacities
- Congenital ptosis
- Vitreous opacification
- Prolonged uncontrolled patching
- Prolonged unilateral blepharospasm
- Prolonged unilateral atropinization

## Refractive Amblyopia

Refractive amblyopia results from a blurred image on the retina in one or both eyes that prevents the normal development of the visual pathway resulting in **a reduction in VA at the level of the visual cortex** [1].

Refractive amblyopia can be classified as either isoametropic or anisometropic.

### Isoametropic

**Isoametropic refractive amblyopia** occurs when there is an **equal but high** uncorrected refractive error in both eyes that leads to significant retinal blur and reduced VA.

### Anisometropic

**Anisometropic refractive amblyopia** occurs when there is an **unequal** uncorrected refractive error between the two eyes that leads to significant retinal blur and reduced VA.

Typically amblyopia is larger (deeper with worse VA) for larger differences in refractive error [9].

Amblyogenic Refractive Errors [9] [10] [11] [12]			
	Myopia	Hyperopia	Astigmatism
Isoametropic	> 8.00 D	> 5.00 D	> 2.50 D
Anisometropic	> 3.00 D	> 1.00 D	> 1.50 D

TABLE 1: COMMON REFRACTIVE AMBLYOGENIC RISK FACTORS

### Hyperopic Anisometropia

Since patients with hyperopia will accommodate the least amount necessary at **distance and near to see clearly**, less anisometropia is required to cause amblyopia since the less hyperopic eye will be used for both distance and near.

### Myopic Anisometropia

Since patients with myopia will use the **less myopic eye** for **distance** and the **more myopic eye** for **near** amblyopia will tend not to occur until there is more than a 3 diopter difference between the eyes.

### Strabismic Amblyopia

Strabismic amblyopia most commonly occurs when there is **constant, unilateral strabismus** during the critical period. Since there is no bifoveation, each eye sees different images, which can lead to **confusion** (central retina) and **diplopia** (peripheral retina). If confusion and/or diplopia lasts for long enough, the patient will actively **suppress** the non-corresponding retinal images which will lead to **amblyopia** [13].

Additional sensory adaptations can occur to eliminate confusion and diplopia. These include:

- **Eccentric fixation** – occurs when a patient uses a non-foveal point (typically of the strabismic eye) when fixating monocularly) [14]
- **Anomalous Correspondence** – is a binocular condition that **links a non-foveal point of the strabismic eye** with the **fovea of the fixating eye**.

## INTERMITTENT

Strabismus can be intermittent or alternating but this type of strabismus leads to amblyopia less frequently than constant strabismus.

### Esotropia (ET)

Esotropia occurs when the eyes are **too convergent** for the object of regard.

### Congenital/Infantile Esotropia

**Congenital (Infantile) esotropia** is a constant large angle esotropia that occurs prior to 6 months of age. Additional clinical features that can be seen include:

1. **Inferior oblique overaction** (70%) – this clinically similar to a superior oblique palsy (hyper deviation during **AD**duction)
2. **Disassociated vertical deviation** (75%) – elevation of the strabismic eye when covered

3. **Latent nystagmus** (50%) – typically a horizontal jerk nystagmus that manifests when either eye is covered, the fast phase will be AWAY from the side of the occluded eye [15]

The large angle of the tropia precludes binocular vision at any distance so surgery is the most common initial treatment.

#### *Accommodative Esotropia*

**Accommodative esotropia** occurs when there is either a **high AC/A ratio** or a significant amount of **hyperopia** (>+2.00). The initial treatment typically includes spectacle prescription with possible bifocal with add to neutralize the near tropia/phoria.

#### *Mechanical Esotropia*

**Mechanical Esotropia** occurs when there is a restriction or obstruction of an extraocular muscle. Causes include:

- Extraocular muscle fibrosis in thyroid orbitopathy
- Blowout fracture
- **Duane syndrome** - is congenital and non-progressive and due to an absence of CN VI and aberrant innervation of a branch of CN III into the lateral rectus [16]. Additionally, globe retraction occurs when both the lateral and medial rectus are stimulated at the same time [17]. The three types include [18]:
  - **Type 1** (75-80%) - esotropia in primary gaze with a compensatory head turn to the involved side
  - **Type 2** (5-10%) - exotropia in primary gaze with a compensatory head turn to the uninvolved side
  - **Type 3** (10-20%) - either an esotropia or exotropia in primary gaze, and will have a compensatory head turn towards the involved side. Additionally, there is no ability to adduct the eye

### BLOWOUT

We typically think of inferior rectus entrapment associated with blowout fractures but we can also see lateral or medial rectus entrapments that lead to esotropia [29] [30].

#### *Microesotropia*

**Microesotropia** has an onset in children under 3 years and is typically a constant, unilateral esotropia with an angle of less than 10 Δ. Since the angle of the tropia is small, it can be challenging to diagnose with a cover test. Patients with microesotropia can have a small central suppression scotoma that leads to no randot stereopsis, additionally, a 4 base out (BO) test can be utilized to aid diagnosis.

- In a patient with normal fixation and no microtropia, we will see two distinct movements on a 4 BO test. These movements include:
  1. Versional movement of **both eyes** toward the apex of the prism
  2. Convergence re-fixation of the **eye that is not covered** by the prism
- In a patient with a right microesotropia and a small central suppression scotoma, we would expect to see the following on a 4 BO test:
  1. Prism placed over right eye – NO movement
  2. Prism placed over the left eye – versional movement of both eyes toward the right, NO convergence re-fixation

## Exotropia (XT)

Exotropia occurs when the eyes are **too divergent** for the object of regard.

### *Congenital Exotropia*

**Congenital exotropia** is typically constant and occurs prior to 6 months of age. Patients with congenital exotropia have an increased incidence of [19]:

- cerebral palsy
- neurologic disorders
- craniofacial disorders
- ocular albinism

### *Sensory Exotropia*

Sensory exotropia occurs in patients with severely reduced VA or a blind eye. In patients who are typically older than 2-4 years old if they become blind or severely low vision can also become exotropic due to an inability to disparate images [20].

### *Intermittent Exotropia*

Intermittent exotropia typically occurs when viewing distance objects when patients are tired, sick or in some way at a lowered mental state (eg. intoxicated) and under brightly illuminated situations. The 3 subtypes of intermittent exotropia are:

1. **Basic Intermittent XT** – distance and near phoria/tropia measurements are within 10  $\Delta$  of each other and convergence is not impacted.
2. **Pseudo-divergence excess** – characterized by an exotropia that is larger at distance but resolves after a period (30-60 minutes) of occlusion of the non-fixating eye. These patients typically compensate by increasing tonic fusional convergence.
3. **Divergence excess** – characterized by an exotropia that is larger at distance than near but does not resolve after occlusion of the non-fixating eye and typically a high AC/A ratio.

## Differential Diagnosis of Amblyopia

In the assessment of patients with amblyopia it is important to consider other conditions that can masquerade as refractive or strabismic amblyopia. Some conditions have obvious clinical findings and others are more subtle. These conditions include [21]:

- Duane's syndrome (XT/ET)
- CN III palsy (XT)
- CN VI palsy (ET)
- Internuclear ophthalmoplegia (XT) – affected eye has limited Adduction and “normal eye” appears to exotropic and exhibits nystagmus on **AB**duction
- Orbital fibrosis/thyroid eye disease (XT/ET) – exotropic eye will not move in on **AD**duction and there will be **resistance to ADduction on forced duction testing**
- Moebius syndrome (XT/ET) – a nonprogressive craniofacial and neurological disorder that manifests as primarily as facial paralysis with lack of lateral eye movements
- Myasthenia gravis (XT/ET)
- Achromatopsia

- Coloboma
- Myelinated nerve fibers
- Retinopathy of prematurity
- Degenerative myopia
- Hypoplastic optic nerve
- Keratoconus
- Media opacities
- Macular, perimacular chorioretinal scar
- Macular pathology (e.g., Stargardt's disease)
- Optic atrophy
- Retrobulbar neuritis
- Nystagmus (congenital, latent, manifest latent)
- Craniopharyngioma

### Traditional Treatment and Management

As discussed above, there are many subsequent sequelae for the visual system that can occur in patients with amblyopia. Traditional treatment options include:

1. Refractive error correction
2. Patching
3. Penalization
4. Vision therapy
5. Surgery

### Update on the Literature – Amblyopia Treatment Studies (ATS)

Because of the above variables, it can make designing a large study challenging to track improvement in each of the areas since improvement could be monitored based on **VA, binocular vision, accommodative accuracy, and even cosmesis**. The advantage of the Amblyopia Treatment Studies is that they are large multi-center prospective studies that **can help guide us on how to improve VA with different treatment options in patients with amblyopia**. The downside with the studies is that they **deal almost exclusively with improvements in VA** and they have had a difficult time, due to many potential factors, evaluating the impact of vision therapy and surgery.

**ATS-1:** In patients with moderate amblyopia is patching or penalization more effective in patients aged 3-7 years old? [22]

- 419 children with amblyopia (20/40 to 20/100) were randomized to:
  - 215 patching (6 hours to full time)
  - 204 atropine (1% QD)
- Baseline mean VA in the amblyopic eye: 20/63
- Baseline mean difference in acuity between eyes: 4.4 lines
- VA Improvement:
  - Six Months Mean VA:
    - Patching: 20/32
    - Atropine: 20/32-2

- Improvement initially was faster in the patching group, but after six months, the difference in acuity between treatment groups was small
- Two Year Mean VA:
  - Patching: **+ 3.7 lines**
  - Atropine: **+ 3.6 lines**

#### Clinical Pearls ATS-1

- Both treatments were well tolerated, although **atropine had a slightly higher degree of acceptability on a parental questionnaire**
- At 6 months it is slightly more likely for patients taking atropine to have reduced acuity in the sound eye at six months but this did not persist with further follow up
- Patching advantage: **more rapid improvement in VA** and possibly a slightly better acuity outcome
- Atropine advantage: **easier administration** and lower cost
- If one treatment doesn't work consider switching to the other
- **Initial choice** of patching or atropine can be made by the **provider and parent**

ATS-2A: In patients with severe amblyopia is 6 hours of patching as effective as full-time patching in patients aged 3-7 years old? [23]

- 175 children with severe amblyopia (20/100 to 20/400) were randomized to either **6 hours per day** or **full-time** daily patching.
- All patients were prescribed **at least one hour** per day of **near visual activities** while patching
- VA Improvement:
  - 6 hours per day of patching: **+ 4.8 lines**
  - Full-time daily patching: **+ 4.7 lines**

#### Clinical Pearls ATS-2A

- For patients with **severe amblyopia**, start with **6 hours** of patching daily

**ATS-2B:** In patients with moderate amblyopia is 2 hours of patching as effective as 6 hours of patching in patients aged 3-7 years old? [24]

- 189 children with severe amblyopia (20/40 to 20/80) were randomized to either **2 hours** or **6 hours** daily patching.
- All patients were prescribed **at least one hour** per day of **near visual activities** while patching
- VA Improvement:
  - 2 hours per day of patching: **+ 2.4 lines**
  - 6 hours per day of patching: **+ 2.4 lines**

#### Clinical Pearls ATS-2B

- For patients with **moderate amblyopia**, start with **2 hours** of patching daily

**ATS-2C:** How often will amblyopia regress after treatment is stopped? [25]

- 156 children (<8 years old) with successfully treated (improvement in VA with patching or atropine) anisometropic or strabismic amblyopia 8 years of age,
- Followed **without treatment for 52 weeks** to assess recurrence of amblyopia,
  - Recurrence defined as either:
    - 2 or more logMAR level reduction of VA from enrollment
    - Treatment is restarted
- Recurrence
  - Patients who were penalized: **21%**
  - Patients who were patched: **25%**
    - If patching is  $\geq 6$  hours and **NO taper**: **42%**
    - If patching is  $\geq 6$  hours and then **taper**: **14%**

#### Clinical Pearls ATS-2C

- ~ **1/4** of successfully-treated amblyopes **will have a recurrence** in the first year of stopping treatment.
- For patients treated with 6+ hours of daily patching, the **risk of recurrence is greater when patching is stopped abruptly** rather than when it is reduced to 2 hours per day prior to cessation.

**ATS-3:** Is treatment (patching or penalization) effective at improving VA in 7-18 year olds with amblyopia? [26]

- 507 patients with amblyopia (20/40 to 20/400) were randomized to be treated with **spectacles only** or **spectacles plus patching/penalization** (2-6 hours/day depending on severity)
- Number of patients who **responded to each treatment** arm are as follows:
  - Patients 7 to <13 years old:
    - Spectacles only: **25%**
    - Spectacles + p/p: **53%**
  - Patients 13 to <18 years old:
    - Spectacles only: **25%**
    - Spectacles + p/p: **23%**
      - Patients **PREVIOUSLY** treated with p/p: **20%**
      - Patients **NOT PREVIOUSLY** treated with p/p: **47%**

#### Clinical Pearls ATS-3

- For patients 7 to <13 years old, **prescribe 2 to 6 hours per day of patching/atropine even if the amblyopia has been previously treated.**
- For patients 13 to <18 years old, **prescribe 2 to 6 hours per day of patching/atropine if amblyopia has not been previously treated and spectacles ONLY if amblyopia was previously treated with p/p.**

**ATS-4:** Is weekend only atropine as effective as daily atropine at treating patients with moderate amblyopia (20/40 to 20/80)? [27]

- 168 children (3 to < 7 years old) with moderate amblyopia (strabismus, anisometropia, or mixed) were randomized to be treated with either **daily atropine** or to **weekend atropine**
- Improvement in VA of the amblyopic eye from baseline to 4 months averaged **2.3 lines in each group.**
- Additionally, VA was either better than 20/25 or better than or equal to the sound eye in:
  - Daily group: **47%**
  - Weekend group: **53%.**
- Stereoacuity outcomes were similar in the two groups.
- Patients were more compliant with the daily dosing

#### Clinical Pearls ATS-4

- In patients with moderate amblyopia when using atropine, **start with daily dosing** to improve compliance and then **taper to weekend dosing** after the initial follow up.



ATS-5: How much effect does spectacle correction have on improving VA in patients with anisometropic amblyopia? [28]

- 84 children (3 to < 7 years old) with previously untreated anisometropic amblyopia (20/40 to 20/250) were evaluated for improvement in BCVA after spectacle correction of their ametropia
- Amblyopia improved with spectacle correction alone by **2 or more lines** in 77% of the patients
- Amblyopia **resolved** with spectacle correction alone in **27% of patients**
- Stabilization of VA took up to 30 weeks but **averaged about 6 months**
- **Follow-up** occurred **every 5 weeks** until stabilization

#### Clinical Pearls ATS-5

- When starting treatment for anisometropic refractive amblyopia, **start with spectacle correction alone** this can make patching or penalization easier (if needed) since the amblyopic eye VA is better.

ATS-6: When patching, does “distance” or “near” activities have an impact on the resolution of amblyopia? [29]

- 425 children (3 to 7 years) with amblyopia (20/40–20/400) that was caused by anisometropia, strabismus, or both, and that persisted after treatment with spectacles were randomized to 2 hours of patching per day with **EITHER** near or distance activities.
- VA improvement at 8 weeks
  - Distance group: averaged **2.6 lines**
  - Near group: averaged **2.5 lines**
- Children with **severe amblyopia** (20/100 to 20/400) improved by a mean of **3.6 lines with 2 hours of daily patching**.

#### Clinical Pearls ATS-6

- When starting patching treatment both distance and near activities are equally effective
- Encourage patients to do activities they enjoy (iPad, Wii, etc.)
- Patients with severe amblyopia will respond with 2 hours of patching

**ATS-7:** How long effective is spectacle correction alone at improving VA in patients with bilateral refractive amblyopia and what is the time frame for VA improvement? [30]

- 113 children (age 3 to <10) with untreated bilateral refractive amblyopia (20/40 to 20/320) were prescribed optimal spectacle correction.
- After 1 year of treatment VA improvement was:
  - Initial binocular acuity of 20/40 to 20/80 was **3.4 lines**
  - Initial binocular acuity of 20/100 to 20/320 was **6.3 lines**
- Cumulative probability of binocular acuity of 20/25 or better was
  - 21% at 5 weeks
  - 46% at 13 weeks
  - 59% at 26 weeks
  - 74% at 52 weeks

#### Clinical Pearls ATS-7

- Within 1 year 3/4 of patients with bilateral refractive amblyopia will have binocular VA improve to 20/25 or better with spectacle correction alone.

**ATS-8:** Does weekend atropine with a plano lens in the sound eye help improve amblyopia better than weekend atropine alone? [31]

- 180 children with moderate amblyopia (20/40 to 20/100) were randomized to **weekend atropine plus plano lens over the sound eye** or **weekend atropine use alone**.
- Sound eye had to be hyperopic of +1.50 or more
- VA improvement
  - Atropine **ONLY:** **2.4 lines**
  - Atropine **PLUS:** **2.8 lines**
- Amblyopic eye VA of 20/25 or better
  - Atropine **ONLY:** **29%**
  - Atropine **PLUS:** **40%**
- Patients in the atropine plus group were more likely to have reduced VA in the sound eye at 18 weeks, however, this effect resolved after ceasing treatment.

#### Clinical Pearls ATS-8

- Augmenting atropine treatment with a plano lens over the sound eye **does not** significantly improve amblyopic eye VA

**ATS-9:** Is patching or atropine more effective at improving amblyopia in patients who are 7 to <13? [32]

- 193 children with amblyopia (20/40-20/100) were assigned to **receive weekend atropine or patching of the sound eye 2 hours per day** and followed for 17 weeks
- VA improvement:
  - Atropine: **7.6 letters**
  - Patching: **8.6 letters**
- VA of 20/25 or better:
  - Atropine: **17%**
  - Patching: **24%**

#### Clinical Pearls ATS-9

- Treatment with atropine or patching led to similar degrees of improvement among 7- to < 13year-olds with moderate amblyopia
- ~20% achieved VA of 20/25 or better in the amblyopic eye

**ATS-10:** How effective are Bangerter filters over the sound eye at improving VA in patients with amblyopia? [33]

- 186 children (3 to <10 years old) with moderate amblyopia (20/40-20/80) were randomized to receive **2 hours of daily patching** or a **Bangerter filter** (blur to BVA in amblyopic eye) over the spectacle lens of the sound eye and followed every 6 weeks for 24 weeks.
- Average VA improvement:
  - Bangerter group: **1.9 lines**
  - Patching group: **2.3 lines**
- Percentage of patients with 3 or more lines of VA improvement:
  - Bangerter group: **38%**
  - Patching group: **35%**
- Percentage of patients with 20/25 VA or better in amblyopic eye acuity
  - Bangerter group: **36%**
  - Patching group: **31%,**
- There was a lower treatment burden in the Bangerter group

#### Clinical Pearls ATS-10

- With a **small average difference** in VA improvement between patching and Bangerter filters and **lower treatment burden**, Bangerter filter treatment is a reasonable treatment option for patients with moderate amblyopia.

**ATS-13:** How much effect does spectacle correction have on improving VA in patients with strabismic or combined mechanism amblyopia? [34]

- 146 children (3 to <7 years old) with previously untreated strabismic (S) amblyopia (n = 52) or combined-mechanism (CM) amblyopia (n = 94) were treated with spectacle lenses only
- Average VA improvement: **2.6 lines**
  - S: **3.2 lines**
  - CM: **2.3 lines**
- VA improvement of  $\geq 2$  lines: **75%**
- VA improvement of  $\geq 3$  lines: **54%**
- Resolution of amblyopia: **32%**

#### Clinical Pearls ATS-13

- Optical treatment alone of S and CM amblyopia results in clinically significant improvement in amblyopic eye VA
- Amblyopia will resolve in ~33% of patients with S or CM amblyopia with spectacles alone
- Spectacle correction alone should be strongly considered as the initial treatment for patients with S/or CM amblyopia

**ATS-15:** In patients whose VA plateaued when patching as per ATS-2B have further improved VA if patching time is increased? [35]

- 169 children (3 to <8 years) with stable residual amblyopia (20/32-20/160) after 2 hours of daily patching for at least 12 weeks were randomized to either **continue 2 hours of daily patching** or **increase patching time to an average of 6 hours/day**.
- Average VA improvement:
  - 2-hour group: **0.6 lines**
  - 6-hour group: **1.2 lines**
- Percentage of patients with 2 or more lines of VA improvement:
  - 2-hour group: **40%**
  - 6-hour group: **18%**

#### Clinical Pearls ATS-15

- When amblyopic eye VA stops improving with 2 hours of daily patching, consider increasing the daily patching dosage to 6 hours

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