What are the three histological vascular derangements in DBR?

1)
2)
3)
What are the three histological vascular derangements in DBR?

1) **Pericyte loss**

2) **BM thickening** \(\rightarrow\) **\downarrow lumen diameter**

3) **Loss of endothelial barrier function**

*BM = Basement membrane*
What are the three histological vascular derangements in DBR?

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$BM = Basement$ $membrane$
What are the three histological vascular derangements in DBR?

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With respect to the structure of retinal arterioles and capillaries, how are pericytes and endothelial cells related to one another?
What are the three histological vascular derangements in DBR?

1) Pericyte loss
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With respect to the structure of retinal arterioles and capillaries, how are pericytes and endothelial cells related to one another? The cell type cells line the lumen of the vessel. They are surrounded by their BM.
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The endothelial cells line the lumen of the vessel. They are surrounded by their BM.
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*With respect to the structure of retinal arterioles and capillaries, how are pericytes and endothelial cells related to one another?*

The **endothelial** cells line the lumen of the vessel. They are surrounded by their BM. They are **fenestrated or non-**
What are the three histological vascular derangements in DBR?

1) **Pericyte** loss
2) **BM** thickening → ↓ lumen diameter
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*With respect to the structure of retinal arterioles and capillaries, how are pericytes and endothelial cells related to one another?*

The **endothelial** cells line the lumen of the vessel. They are surrounded by their **BM**. They are **nonfenestrated**.
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*With respect to the structure of retinal arterioles and capillaries, how are pericytes and endothelial cells related to one another?*

The **endothelial** cells line the lumen of the vessel. They are surrounded by their **BM**. They are **nonfenestrated**. Tight junctions between cells form the so-called **inner blood-retina barrier**.
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What are the three histological vascular derangements in DBR?

1) Pericyte loss
2) BM thickening → ↓ lumen diameter
3) Loss of endothelial barrier function

Do retinal vessels have an intimal lining?

No

Do they possess a muscular wall?

No

With what nearby vascular bed do they share the lack of these features?

Cerebral vasculature (which makes sense, because the retina is in essence an extension of the CNS).
What are the three histological vascular derangements in DBR?

1) **Pericyte** loss
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***Diabetic Retinopathy: Diabetic Macular Edema***

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**Q**

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That this is known as the inner blood-retina barrier implies the existence of what?
An outer blood-retina barrier

Diabetic Retinopathy: Diabetic Macular Edema

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Yup. What forms the outer blood-retina barrier?

**Inner blood-retina barrier**
What are the three histological vascular derangements in DBR?

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That this is known as the inner blood-retina barrier implies the existence of what?
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Yup. What forms the outer blood-retina barrier?
Tight junctions between retinal pigment epithelium (RPE) cells

inner blood-retina barrier

$\text{three words}$
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*Diabetic Retinopathy: Diabetic Macular Edema*

Which occurs first? *Pericyte loss*
Trypsin mount of normal retina--low and high mag

The dark nuclei belong to pericytes; the lighter, to endothelial cells. 
Note that the ratio between them is roughly 1:1.
Trypsin mount of DBR retina--
low and high mag

But in a retina that with damage 2ndry to diabetes, the ratio of endothelial cells to pericytes is many-to-one.
Trypsin mount of DBR retina--
low and high mag

What are these things?
Trypsin mount of DBR retina--low and high mag

What are these things?
Microaneurysms
What are the three histological vascular derangements in DBR?

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3) **Loss of endothelial barrier function**

*Loss of endothelial barrier function leads to what pathologic event?*
What are the three histological vascular derangements in DBR?

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*Loss of endothelial barrier function leads to what pathologic event?*
Leaching of serum into the retina
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*Loss of endothelial barrier function leads to what pathologic event?*
Leaching of serum into the retina

*Leaching of serum into the retina leads to what pathological state?*
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*Leaching of serum into the retina leads to what pathological state?*
Retinal edema
What are the three histological vascular derangements in DBR?

1) Pericyte loss

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What commonly-prescribed class of PO diabetes medicine is notorious for causing or exacerbating diabetic macular edema?

Retinal edema
What are the three histological vascular derangements in DBR?

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What commonly-prescribed class of PO diabetes medicine is notorious for causing or exacerbating diabetic macular edema?

The thiazolidinediones, AKA the glitazones

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Loss of endothelial barrier function leads to what pathologic event?
Leaching of serum into the retina leads to what pathological state?
Retinal edema

What commonly-prescribed class of PO diabetes medicine is notorious for causing or exacerbating diabetic macular edema?
The thiazolidinediones, AKA the glitazones

Two such meds are commonly prescribed in the US. What are they?
-- Pioglitazone (brand name Actos)
-- Rosiglitazone (brand name Avandia)

Always inquire whether your DME pt is on one of these meds!
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Diabetic Retinopathy: Diabetic Macular Edema

Two systems for classifying DME
Diabetic Retinopathy: Diabetic Macular Edema

Two systems for classifying DME

Primary intervention: Pharmacologic

Primary intervention: Laser surgery
Primary intervention: Pharmacologic

Primary intervention: Laser surgery

Why must the classification of DME be adjusted for the type of primary intervention being contemplated?
Diabetic Retinopathy: Diabetic Macular Edema

Two systems for classifying DME

Primary intervention: Pharmacologic

Primary intervention: Laser surgery

Why must the classification of DME be adjusted for the type of primary intervention being contemplated?
Because the factors influencing treatment success differ between the modalities.
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: **Pharmacologic**

Why must the classification of DME be adjusted for the type of primary intervention being contemplated?
Because the factors influencing treatment success differ between the modalities

*In the present context, what is being referred to by the term ‘pharmacologic intervention’?*
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: **Pharmacologic**

- Why must the classification of DME be adjusted for the type of primary intervention being contemplated?
- Because the factors influencing treatment success differ between the modalities

In the present context, what is being referred to by the term ‘pharmacologic intervention’?
- Intravitreal injection of a pharmacologic agent

Primary intervention: **Laser surgery**
Primary intervention: **Pharmacologic**

Why must the classification of DME be adjusted for the type of primary intervention being contemplated?
Because the factors influencing treatment success differ between the modalities

*In the present context, what is being referred to by the term ‘pharmacologic intervention’?*
Intravitreal injection of a pharmacologic agent

*What specific pharmacologic agents are available?*
--?
--?
--?
--?
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: Pharmacologic

Why must the classification of DME be adjusted for the type of primary intervention being contemplated?
Because the factors influencing treatment success differ between the modalities

In the present context, what is being referred to by the term ‘pharmacologic intervention’?
Intravitreal injection of a pharmacologic agent

What specific pharmacologic agents are available?
--Aflibercept
--Ranibizumab
--Bevacizumab
--Triamcinolone

--Pegaptanib (And pegaptanib. But because no one uses it, and the BCSC Retina book barely mentions it, we won’t discuss it further.)
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: Pharmacologic

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In the present context, what is being referred to by the term ‘laser surgery’?
Lasering the edematous regions of the retina

What specific laser procedures are available?
--Focal macular laser (FML)
--Grid macular laser (GML)
**Diabetic Retinopathy: Diabetic Macular Edema**

**Primary intervention:**

*Pharmacologic*

*Primary intervention: Laser surgery*

*Why must the classification of DME be adjusted for the type of primary intervention being contemplated?*

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---

**In the present context, what is being referred to by the term ‘pharmacologic intervention’?**

Intravitreal injection of a pharmacologic agent.

**What specific pharmacologic agents are available?**

--Afiblercept
--Ranibizumab
--Bevacizumab
--Triamcinolone

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**In the present context, what is being referred to by the term ‘laser surgery’?**

Lasering the edematous regions of the retina.
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: 
**Pharmacologic**

Why must the classification of DME be adjusted for the type of primary intervention being contemplated?
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Primary intervention: Pharmacologic

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-- Grid macular laser (GML)
Primary intervention: *Pharmacologic*

In this classification system, there are two types of DME. What are they?
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention:

**Pharmacologic**

- **Center-involved**
- **Non-center-involved**

*In this classification system, there are two types of DME. What are they?*
That which involves the center (foveal) region, and everything else
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: **Pharmacologic**
- Center-involved
- Non-center-involved

Primary intervention: **Laser surgery**

*In this classification system, there are two types of DME. What are they?*
That which involves the center (foveal) region, and everything else

*By what technique is the retina evaluated for the presence of DME?*
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: **Pharmacologic**

- Center-involved
- Non-center-involved

In this classification system, there are two types of DME. What are they?
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By what technique is the retina evaluated for the presence of DME?
By OCT

Primary intervention: Laser surgery
Primary intervention: Pharmacologic

Center-involved
Non-center-involved

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In this system, what findings signal that treatment is indicated?
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: 
*Pharmacologic*

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Center-involving DME + decreased visual acuity
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: Pharmacologic

Center-involved Non-center-involved

In the present context, what is being referred to by the term ‘pharmacologic intervention’? Intravitreal injection of a pharmacologic agent.

What specific pharmacologic agents are available?
- Aflibercept
- Ranibizumab
- Bevacizumab
- Triamcinolone

Broadly, what is the mechanism of action for these meds?

In this system, what findings signal that treatment is indicated? Center-involving DME + decreased visual acuity.
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: Pharmacologic

- Center-involved
- Non-center-involved

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- Aflibercept
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Broadly, what is the mechanism of action for these meds? Interference with VEGF activity

In this system, what findings signal that treatment is indicated?

Center-involving DME + decreased visual acuity
Diabetic Retinopathy: Diabetic Macular Edema

**Primary intervention:**

- **Pharmacologic**
  - Center-involved
  - Non-center-involved

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- Aflibercept
- Ranibizumab
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Broadly, what is the mechanism of action for these meds?

- Interference with VEGF activity

Broadly, what is the mechanism of action for triamcinolone?

- Anti-inflammatory (it's a steroid)

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- Center-involving DME + decreased visual acuity
Primary intervention: \textit{Pharmacologic}

Center-involved

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Broadly, what is the mechanism of action for triamcinolone? Anti-inflammatory (it’s a steroid)
Diabetic Retinopathy: Diabetic Macular Edema

**Primary intervention:**

- **Pharmacologic**
  - Center-involved
  - Non-center-involved

In this classification system, there are two types of DME. What are they?

- That which involves the center (foveal) region,
- And everything else

By what technique is the retina evaluated for the presence of DME?

- By OCT

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Let’s drill down on VEGF...

**Pharmacologic intervention**

- Intravitreal injection of a pharmacologic agent

What specific pharmacologic agents are available?

- Aflibercept
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What does VEGF stand for?

VEGF-A_165
What does VEGF stand for?
Vascular endothelial growth factor

VEGF-A_{165}
What does VEGF stand for?
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Broadly speaking, what is it?
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Broadly speaking, what is it?
An extracellular signaling protein involved in vascular development

VEGF-A$^{165}$
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Does VEGF do anything besides grow new blood vessels?

\textbf{VEGF-A}_{165}
What does VEGF stand for?
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Broadly speaking, what is it?
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Does VEGF do anything besides grow new blood vessels?
Yes, it also is a potent vasodilator (it was known originally as vascular permeability factor)

VEGF-A165
What does VEGF stand for? Vascular endothelial growth factor

**Broadly speaking, what is it?**
An extracellular signaling protein involved in **vascular development**

Does VEGF do anything besides grow new blood vessels? Yes, it also is a potent vasodilator (it was known originally as **vascular permeability factor**)

How potent?

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Vascular endothelial growth factor

Broadly speaking, what is it?
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Does VEGF do anything besides grow new blood vessels?
Yes, it also is a potent vasodilator (it was known originally as vascular permeability factor)

How potent?
About 10,000x more potent than histamine!
What does VEGF stand for?
Vascular endothelial growth factor

Broadly speaking, what is it?
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Does VEGF do anything besides grow new blood vessels?
Yes, it also is a potent vasodilator (it was known originally as vascular permeability factor)

How potent?
About 10,000x more potent than histamine!

VEGF-A_{165}

This property accounts for VEGF’s role in the development of diabetic macular edema, and explains why anti-VEGF meds can treat this condition!
What does VEGF stand for?
Vascular endothelial growth factor

Broadly speaking, what is it?
An extracellular signaling protein involved in vascular development

How does VEGF work?

VEGF-A$_{165}$
What does VEGF stand for?
Vascular endothelial growth factor

Broadly speaking, what is it?
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How does VEGF work?
Extracellular VEGF binds to VEGF receptors (VEGFR), which are transmembrane receptor tyrosine kinase (RTK) structures.
What does VEGF stand for?
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Broadly speaking, what is it?
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How does VEGF work?
Extracellular VEGF binds to VEGF receptors (VEGFR), which are transmembrane receptor tyrosine kinase (RTK) structures.

What does the A signify?
VEGF-A_{165}
What does VEGF stand for? Vascular endothelial growth factor

Broadly speaking, what is it? An extracellular signaling protein involved in vascular development

How does VEGF work? Extracellular VEGF binds to VEGF receptors (VEGFR), which are transmembrane receptor tyrosine kinase (RTK) structures.

What does the A signify? VEGF is not a single entity—a number of similar-but-different proteins comprise the ‘VEGF family.’ These are differentiated as VEGF-A through VEGF-F. (One family member, placental growth factor [PlGF], is the exception to the naming rule.) When the term VEGF is used in the ophthalmology literature without a subfamily designation, it is understood to mean VEGF-A.
What does VEGF stand for?
Vascular endothelial growth factor

Broadly speaking, what is it?
An extracellular signaling protein involved in vascular development

How does VEGF work?
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VEGF-A

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What does the 165 signify?

Diabetic Retinopathy: Diabetic Macular Edema
**What does VEGF stand for?**
Vascular endothelial growth factor

**Broadly speaking, what is it?**
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**What does 165 signify?**
VEGF-A is not a single entity either. At least 4 isoforms exist; these differ in the number of peptides they contain, and that number is used as a subscript to identify specific isoforms.
What does VEGF stand for?
Vascular endothelial growth factor

Broadly speaking, what is it?
An extracellular signaling protein involved in vascular development

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What does the A signify?
VEGF is not a single entity—a number of similar-but-different proteins comprise the ‘VEGF family.’ These are differentiated as VEGF-A through VEGF-F. (One family member, placental growth factor [PIGF], is the exception to the naming rule.) When the term VEGF is used in the ophthalmology literature without a subfamily designation, it is understood to mean VEGF-A.

What does 165 signify?
VEGF-A is not a single entity either. At least 4 isoforms exist; these differ in the number of peptides they contain, and that number is used as a subscript to identify specific isoforms.

Why focus on isoform 165?
**Diabetic Retinopathy: Diabetic Macular Edema**

*What does VEGF stand for?*
Vascular endothelial growth factor

*Broadly speaking, what is it?*
An extracellular signaling protein involved in vascular development

*How does VEGF work?*
Extracellular VEGF binds to VEGF receptors (VEGFR), which are transmembrane receptor tyrosine kinase (RTK) structures.

**VEGF-A**

*What does the A signify?*
VEGF is not a single entity—a number of similar-but-different proteins comprise the ‘VEGF family.’ These are differentiated as VEGF-A through VEGF-F. (One family member, *placental growth factor* [PlGF], is the exception to the naming rule.) When the term *VEGF* is used in the ophthalmology literature without a subfamily designation, it is understood to mean VEGF-A.

*What does 165 signify?*
VEGF-A is not a single entity either. At least 4 isoforms exist; these differ in the number of peptides they contain, and that number is used as a subscript to identify specific isoforms.

*Why focus on isoform 165?*
It seems to be the most important with respect to pathologic angiogenesis in the human eye.
Primary intervention: **Pharmacologic**

**Center-involved**

**Non-center-involved**

In this classification system, there are two types of DME. What are they?

- That which involves the center (foveal) region, and everything else

By what technique is the retina evaluated for the presence of DME?

- By OCT

In this system, what findings signal that treatment is indicated?

- Center-involving DME + decreased visual acuity

In the present context, what is being referred to by the term ‘pharmacologic intervention’?

- Intravitreal injection of a pharmacologic agent

What specific pharmacologic agents are available?

- Aflibercept
- Ranibizumab
- Bevacizumab
- Triamcinolone

Does good clinical trial data exist justifying the use of these anti-VEGF agents in treating DME?

In this system, what findings signal that treatment is indicated?

- Center-involving DME + decreased visual acuity
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: **Pharmacologic**

- Center-involved
- Non-center-involved

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In the present context, what is being referred to by the term ‘pharmacologic intervention’?
Intravitreal injection of a pharmacologic agent

What specific pharmacologic agents are available?
- Aflibercept
- Ranibizumab
- Bevacizumab
- Triamcinolone

Does good clinical trial data exist justifying the use of these anti-VEGF agents in treating DME?
Yes, multiple studies have established them to be safe and effective

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In this system, what findings signal that treatment is indicated?
Center-involving DME + decreased visual acuity
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: **Pharmacologic**

Center-involved  Non-center-involved

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In this classification system, there are two types of DME. What are they?

- That which involves the center (foveal) region
- And everything else

By what technique is the retina evaluated for the presence of DME?

By OCT

In this system, what findings signal that treatment is indicated?

- Center-involving DME + decreased visual acuity

In the present context, what is being referred to by the term ‘pharmacologic intervention’?

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What specific pharmacologic agents are available?

- Aflibercept
- Ranibizumab
- Bevacizumab
- Triamcinolone

Does good clinical trial data exist justifying the use of intravitreal steroids in treating DME?

- Yes, although they are less effective, and have a worse side-effect profile
### Diabetic Retinopathy: Diabetic Macular Edema

**Primary intervention:**

- **Pharmacologic**
  - Center-involved
  - Non-center-involved

**Laser surgery**

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**Center-involved**

**Non-center-involved**

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- In this classification system, there are two types of DME. What are they?
  - That which involves the center (foveal) region, and everything else.

- By what technique is the retina evaluated for the presence of DME?
  - By OCT

- In this system, what findings signal that treatment is indicated?
  - Center-involving DME + decreased visual acuity

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**Pharmacologic Intervention**

- In the present context, what is being referred to by the term ‘pharmacologic intervention’?
  - Intravitreal injection of a pharmacologic agent

- What specific pharmacologic agents are available?
  - --Aflibercept
  - --Ranibizumab
  - --Bevacizumab
  - --Triamcinolone

- Does good clinical trial data exist justifying the use of intravitreal steroids in treating DME?
  - Yes, although they are less effective, and have a worse side-effect profile
**Diabetic Retinopathy: Diabetic Macular Edema**

**Primary intervention:**
- **Pharmacologic**
  - Center-involved
  - Non-center-involved

**Primary intervention:**
- **Laser surgery**

*In this classification system, there are two types of DME. What are they?*
That which involves the center (foveal) region, and everything else

*By what technique is the retina evaluated for the presence of DME?*
By OCT

*In this system, what findings signal that treatment is indicated?*
Center-involving DME + decreased visual acuity
Primary intervention: Pharmacologic

Primary intervention: Laser surgery

In this classification system, there are two types of DME. What are they?
That which involves the center (foveal) region, and everything else

By what technique is the retina evaluated for the presence of DME?
By OCT

In this system, what findings signal that treatment is indicated?
Center-involving DME + decreased visual acuity
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention:
- **Pharmacologic**
  - Center-involved
  - Non-center-involved
- **Laser surgery**
  - Clinically significant
  - Not clinically significant

In this classification system, there are two types of DME. What are they?
That which involves the center (foveal) region, and everything else

By what technique is the retina evaluated for the presence of DME?
By OCT

In this system, what findings signal that treatment is indicated?
Center-involving DME + decreased visual acuity
**Diabetic Retinopathy: Diabetic Macular Edema**

**Primary intervention:**
- **Pharmacologic**
  - Center-involved
  - Non-center-involved

**Primary intervention:**
- **Laser surgery**
  - Clinically significant
  - Not clinically significant

---

*In this classification system, there are two types of DME. What are they?*
That which involves the center (foveal) region, and everything else

*By what technique is the retina evaluated for the presence of DME?*
By OCT

*In this system, what findings signal that treatment is indicated?*
Center-involving DME + decreased visual acuity
**Diabetic Retinopathy: Diabetic Macular Edema**

**Primary intervention:**
- **Pharmacologic**
- **Laser surgery**

**Center-involved**
**Non-center-involved**

In this classification system, there are two types of DME. What are they?
That which involves the center (foveal) region, and everything else

By what technique is the retina evaluated for the presence of DME?
By OCT

By what technique is the retina evaluated for the presence of DME?
By DFE

In this system, what findings signal that treatment is indicated?
Center-involving DME + decreased visual acuity

In this classification system, there are two types of DME. What are they?
That which qualifies as ‘clinically significant,’ and that which does not
In this classification system, there are two types of DME. What are they? That which involves the center (foveal) region, and everything else.

By what technique is the retina evaluated for the presence of DME? By OCT.

In this system, what findings signal that treatment is indicated? Center-involving DME + decreased visual acuity.

In this classification system, there are two types of DME. What are they? That which qualifies as ‘clinically significant,’ and that which does not.

By what technique is the retina evaluated for the presence of DME? By DFE.

In this system, what findings signal that treatment is indicated? The presence of CSME.
Diabetic Retinopathy: Diabetic Macular Edema

**Primary intervention:** Laser surgery

**Pharmacologic**

- Center-involved
- Non-center-involved

In this classification system, there are two types of DME. What are they?
That which involves the center (foveal) region, and everything else

By what technique is the retina evaluated for the presence of DME?
By OCT

In this system, what findings signal that treatment is indicated?
Center-involving DME + decreased visual acuity

What does CSME stand for?
'Clinically significant macular edema'
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention:
- Pharmacologic
  - Center-involved
  - Non-center-involved

Primary intervention:
- Laser surgery

Clinically significant
Not clinically significant

In this classification system, there are two types of DME. What are they?
That which involves the center (foveal) region, and everything else
That which qualifies as ‘clinically significant,’ and that which does not

By what technique is the retina evaluated for the presence of DME?
By OCT
By DFE

What does CSME stand for?
‘Clinically significant macular edema’

In this system, what findings signal that treatment is indicated?
Center-involving DME + decreased visual acuity
The presence of CSME
**Diabetic Retinopathy: Diabetic Macular Edema**

**Primary intervention:**
- **Pharmacologic**
  - Center-involved
  - Non-center-involved

**Primary intervention:**
- **Laser surgery**
  - Clinically significant
  - Not clinically significant

**Of the two approaches to treating DME, which is considered first-line?**
- Pharmacologic, but not in every case (we'll revisit this issue shortly)

**By what technique is the retina evaluated for the presence of DME?**
- By OCT

**In this system, what findings signal that treatment is indicated?**
- Center-involving DME + decreased visual acuity

**In this system, what findings signal that treatment is indicated?**
- The presence of CSME
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: 

- **Pharmacologic**
  - Center-involved
  - Non-center-involved

Primary intervention: 

- **Laser surgery**
  - Clinically significant
  - Not clinically significant

In this classification system, there are two types of DME. What are they?

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By what technique is the retina evaluated for the presence of DME?

- By OCT

In this system, what findings signal that treatment is indicated?

- Center-involving DME + decreased visual acuity

Of the two approaches to treating DME, which is considered first-line?

- Pharmacologic, but not in every case (we'll revisit this issue later)
Primary intervention: *Pharmacologic*

Center-involved

Non-center-involved

Primary intervention: *Laser surgery*

Clinically significant

Not clinically significant

In this classification system, there are two types of DME. What are they?

- That which qualifies as ‘clinically significant,’ and that which does not

By what technique is the retina evaluated for the presence of DME?

- By DFE
- By OCT

In this system, what findings signal that treatment is indicated?

- Center-involving DME + decreased visual acuity
- The presence of CSME

Why is pharmacologic first-line?

Because it beat laser head-to-head in several clinical trials

Beat it how, ie, what outcome measure was used?

Visual acuity at 1- and/or 2-years post-tx
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: **Pharmacologic**

- Center-involved
- Non-center-involved

Primary intervention: **Laser surgery**

- Clinically significant
- Not clinically significant

In this classification system, there are two types of DME. What are they?

That which qualifies as ‘clinically significant,’ and that which does not

By what technique is the retina evaluated for the presence of DME?

By OCT

In this system, what findings signal that treatment is indicated?

Center-involving DME + decreased visual acuity

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Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: **Pharmacologic**

- Center-involved
- Non-center-involved

Primary intervention: **Laser surgery**

- Clinically significant
- Not clinically significant

In this classification system, there are two types of DME. What are they?
- That which qualifies as ‘clinically significant,’
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By what technique is the retina evaluated for the presence of DME?
- By OCT

In this system, what findings signal that treatment is indicated?
- Center-involving DME + decreased visual acuity

Of the two approaches to treating DME, which is considered first-line?
- **Pharmacologic**, but not in every case (we’ll revisit this issue later)

Why is pharmacologic first-line?
- Because it beat laser head-to-head in several clinical trials

What outcome measure was used?
- Visual acuity at 1- and/or 2-years post-tx

Why is pharmacologic first-line?
- Because it beat laser head-to-head in several clinical trials

What outcome measure was used?
- Visual acuity at 1- and/or 2-years post-tx
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: **Pharmacologic**

- Center-involved
- Non-center-involved

Primary intervention: **Laser surgery**

- Clinically significant
- Not clinically significant

Of the two approaches to treating DME, which is considered first-line? **Pharmacologic**

Why is pharmacologic first-line? Because it beat laser head-to-head in several clinical trials

What outcome measure was used? Visual acuity (VA) at 1- and/or 2-years post-tx

In this classification system, there are two types of DME. What are they? That which qualifies as 'clinically significant,' and that which does not

By what technique is the retina evaluated for the presence of DME? By OCT

In this system, what findings signal that treatment is indicated? Center-involving DME + decreased visual acuity

In this system, what findings signal that treatment is indicated? The presence of CSME
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: **Pharmacologic**
- Center-involved
- Non-center-involved

Primary intervention: **Laser surgery**
- Clinically significant
- Not clinically significant

In this classification system, there are two types of DME. What are they?
- That which qualifies as 'clinically significant,'
- And that which does not

By what technique is the retina evaluated for the presence of DME?
- By OCT

In this system, what findings signal that treatment is indicated?
- Center-involving DME + decreased visual acuity

Of the two approaches to treating DME, which is considered first-line?
**Pharmacologic**, but not in every case (we'll revisit this issue later)

Why is pharmacologic first-line?
Because it beat laser head-to-head in several clinical trials

What outcome measure was used for the treatment of DME?
Visual acuity (VA) at 1-and/or 2-years post-tx

Three important studies demonstrated the superiority of anti-VEGF tx—what are they?
- One study: Intravitreal ranibizumab > laser for center-involved DME
- Two studies: Intravitreal aflibercept > laser for center-involved DME

Protocol I: Intravitreal ranibizumab > laser for center-involved DME
VIVID & VISTA: Intravitreal aflibercept > laser for center-involved DME

one study: Intravitreal ranibizumab > laser for center-involved DME
two studies: Intravitreal aflibercept > laser for center-involved DME
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: **Pharmacologic**

- Center-involved
- Non-center-involved

Primary intervention: **Laser surgery**

- Clinically significant
- Not clinically significant

---

**Primary intervention:**

- **Pharmacologic**
- **Laser surgery**

---

**Protocol I:** Intravitreal ranibizumab > laser for center-involved DME

**VIVID & VISTA:** Intravitreal aflibercept > laser for center-involved DME

---

Of the two approaches to treating DME, which is considered first-line? Why is pharmacologic first-line? Because it beat laser head-to-head in several clinical trials.

What outcome measure was used? Visual acuity (VA) at 1- and/or 2-years post-tx.

Three important studies demonstrated the superiority of anti-VEGF tx—what are they? Protocol I and VIVID & VISTA.

---

In this classification system, there are two types of DME. What are they? That which qualifies as ‘clinically significant,’ and that which does not.

By what technique is the retina evaluated for the presence of DME? By OCT.

---

In this system, what findings signal that treatment is indicated? Center-involving DME + decreased visual acuity.

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Why is pharmacologic first-line? Because it beat laser head-to-head in several clinical trials.

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By what technique is the retina evaluated for the presence of DME? By DME.

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What are the findings that signal treatment is indicated? The presence of CSME.
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: **Pharmacologic**

- Center-involved
- Non-center-involved

Primary intervention: **Laser surgery**

- Clinically significant
- Not clinically significant

In this classification system, there are two types of DME. What are they?

- That which qualifies as ‘clinically significant,’
- That which does not

By what technique is the retina evaluated for the presence of DME?

- By OCT

In this system, what findings signal that treatment is indicated?

- Center-involving DME + decreased visual acuity

Of the two approaches to treating DME, which is considered first-line?

- Pharmacologic

Why is pharmacologic first-line?

Because it beat laser head-to-head in several clinical trials

What outcome measure was used?

- Visual acuity (VA) at 1- and/or 2-years post-tx

**Protocol I**

- Intravitreal ranibizumab > laser for center-involved DME

**VIVID & VISTA**

- Intravitreal aflibercept > laser for center-involved DME

**tl;dr it for me, bro—what did the studies show?**

- Laser was effective for maintaining VA, but intravitreal anti-VEGF tx improved VA
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: **Pharmacologic**
- Center-involved
- Non-center-involved

Primary intervention: **Laser surgery**
- Clinically significant
- Not clinically significant

---

In this classification system, there are two types of DME. What are they?
- That which qualifies as ‘clinically significant,’
- And that which does not

By what technique is the retina evaluated for the presence of DME?
- OCT

In this system, what findings signal that treatment is indicated?
- Center-involving DME + decreased visual acuity

---

Of the two approaches to treating DME, which is considered first-line?

**Pharmacologic**, but not in every case (we’ll revisit this issue later)

Why is pharmacologic first-line?
- Because it beat laser head-to-head in several clinical trials

What outcome measure was used?
- Visual acuity (VA) at 1-and/or 2-years post-tx

---

Protocol I: Intravitreal ranibizumab > laser for center-involved DME

**tl;dr it for me, bro**—what did the studies show?
- That laser was effective for maintaining VA,
- But intravitreal anti-VEGF tx improved VA

**VIVID & VISTA** : Intravitreal aflibercept > laser for center-involved DME
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention:
*Pharmacologic*

- Center-involved
- Non-center-involved

Primary intervention:
*Laser surgery*

Clinically significant
Not clinically significant

In this classification system, there are two types of DME. What are they?
That which involves the center (foveal) region, and everything else
That which qualifies as ‘clinically significant,’ and that which does not

By what technique is the retina evaluated for the presence of DME?
By OCT

In this system, what findings signal that treatment is indicated?
Center-involving DME + decreased visual acuity

By the way: How is CSME defined?

By the way: How is CSME defined?
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention:

Pharmacologic

Laser surgery

Primary intervention:

Center-involved

Non-center-involved

Clinically significant

Not clinically significant

In this classification system, there are two types of DME. What are they?
That which involves the center (foveal) region, and everything else
That which qualifies as ‘clinically significant,’ and that which does not

By what technique is the retina evaluated for the presence of DME?
By OCT

In this system, what findings signal that treatment is indicated?
Center-involving DME + decreased visual acuity

By the way: How is CSME defined?
That’s the subject of the next section…
CSME

Acronym for *clinically significant macular edema*

Definition has three components:

- Any retinal thickening within...
Diabetic Retinopathy: Diabetic Macular Edema

CSME

- Acronym for *clinically significant macular edema*
- Definition has three components:
  - Any retinal thickening within 1/3 DD of the foveal center
Diabetic Retinopathy: Diabetic Macular Edema

CSME: Any retinal thickening within 1/3 DD of the foveal center
Diabetic Retinopathy: Diabetic Macular Edema

CSME
- Acronym for *clinically significant macular edema*
- Definition has three components:
  - Any retinal thickening within \( \frac{1}{3} \) DD of the foveal center

What does DD stand for?
CSME

Acronym for *clinically significant macular edema*

Definition has three components:

- Any retinal thickening within $1/3 \text{DD}$ of the foveal center

*What does DD stand for?*

Disc diameter
CSME

- Acronym for *clinically significant macular edema*
- Definition has three components:
  - Any retinal thickening within $\frac{1}{3}$ DD of the foveal center

What does DD stand for?
Disc diameter

How big is $\frac{1}{3}$ DD in microns?
CSME

- Acronym for *clinically significant macular edema*
- Definition has three components:
  - Any retinal thickening within 1/3 DD of the foveal center

**What does DD stand for?**
Disc diameter

**How big is 1/3 DD in microns?**
500
CSME

Acronym for *clinically significant macular edema*

Definition has three components:

- Any retinal thickening within 1/3 DD of the foveal center;
- Hard exudates within 1/3 DD of the foveal center that are associated with adjacent retinal thickening.
CSME

- Acronym for **clinically significant macular edema**
- Definition has three components:
  - Any retinal thickening within **1/3 DD of the foveal center**; or
  - **Hard exudates within 1/3 DD of the foveal center** that are associated with adjacent retinal thickening.
Diabetic Retinopathy: Diabetic Macular Edema

HE within 1/3 DD of the foveal center that are associated with adjacent retinal thickening
CSME

- Acronym for *clinically significant macular edema*

- Definition has three components:
  - Any retinal thickening within 1/3 DD of the foveal center;
  - Hard exudates within 1/3 DD of the foveal center that are associated with adjacent retinal thickening;
  - An area of retinal thickening in size, any part of which is within 1 DD of the foveal center.
CSME

- Acronym for  *clinically significant macular edema*  
- Definition has three components:
  - Any retinal thickening within 1/3 DD of the foveal center;  
    - *or*
  - Hard exudates within 1/3 DD of the foveal center that are associated with adjacent retinal thickening;  
    - *or*
  - An area of retinal thickening 1 DD or larger in size, any part of which is within 1 DD of the foveal center.
Retinal thickening $\geq 1$DD in area, any portion of which is w/in 1DD of the foveal center
In this case, the area is too far away to qualify under the ‘any thickening w/in 500µm’ rule, and too small to qualify under the ‘1DD area w/in 1DD of the central fovea’ rule. This is DME, but *not* CSME.
Diabetic Retinopathy: Diabetic Macular Edema

CSME
Diabetic Retinopathy: Diabetic Macular Edema

CSME
Diabetic Retinopathy: Diabetic Macular Edema

CSME
Diabetic Retinopathy: Diabetic Macular Edema

CSME
CSME

- Acronym for *clinically significant macular edema*
- Definition has three components:
  - Any retinal thickening within 1/3 DD of the foveal center; *or*
  - Hard exudates within 1/3 DD of the foveal center that are associated with adjacent retinal thickening; *or*
  - An area of retinal thickening 1 DD or larger in size, any part of which is within 1 DD of the foveal center

What landmark clinical trial provided this definition of CSME?
**CSME**

- Acronym for *clinically significant macular edema*

- Definition has three components:
  - Any retinal thickening within **1/3 DD of the foveal center**;  
    *or*  
  - **Hard exudates within 1/3 DD of the foveal center** that are associated with adjacent retinal thickening;  
    *or*  
  - An area of retinal thickening **1 DD or larger in size**, any part of which is within **1 DD of the foveal center**

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*What landmark clinical trial provided this definition of CSME?*

The **Early Treatment of Diabetic Retinopathy Study (ETDRS)**
**CSME**

- Acronym for *clinically significant macular edema*

- Definition has three components:
  - Any retinal thickening within **1/3 DD of the foveal center**;  
  - **Hard exudates within 1/3 DD of the foveal center** that are associated with adjacent retinal thickening;  
  - An area of retinal thickening **1 DD or larger** in size, any part of which is within **1 DD of the foveal center**

*What landmark clinical trial provided this definition of CSME?*  
The *Early Treatment of Diabetic Retinopathy Study (ETDRS)*

*What 3 questions did this study seek to answer?*  
1)  
2)  
3)
CSME

- Acronym for \textit{clinically significant macular edema}

- Definition has three components:
  - Any retinal thickening within \textit{1/3 DD of the foveal center};
  - \textbf{or}
  - \textbf{Hard exudates within \textit{1/3 DD of the foveal center} that are associated with adjacent retinal thickening};
  - \textbf{or}
  - An area of retinal thickening \textit{1 DD or larger} in size, any part of which is within \textit{1 DD of the foveal center}

\textbf{What landmark clinical trial provided this definition of CSME?} The \textbf{Early Treatment of Diabetic Retinopathy Study (ETDRS)}

\textbf{What 3 questions did this study seek to answer?}

1) Is laser effective in treating diabetic macular edema?
2) Is \textbf{PRP} effective for treating early \textbf{NPDR}?
3) Is \textbf{ASA} effective in preventing the progression of \textbf{DBR}?

\textbf{PRP} = Pan-retinal photocoagulation
\textbf{ASA} = aspirin
\textbf{NPDR} = Non-proliferative diabetic retinopathy
CSME

Acronym for *clinically significant macular edema*

Definition has three components:

- Any retinal thickening within 1/3 DD of the foveal center; or
- Hard exudates within 1/3 DD of the foveal center that are associated with adjacent retinal thickening; or
- An area of retinal thickening 1 DD or larger in size, any part of which is within 1 DD of the foveal center.

What landmark clinical trial provided this definition of CSME?

The *Early Treatment of Diabetic Retinopathy Study (ETDRS)*

What 3 questions did this study seek to answer?

1) Is laser effective in treating diabetic macular edema?
2) Is PRP effective for treating early NPDR?
3) Is ASA effective in preventing the progression of DBR?

What modality of laser (ie, type of energy) was employed in the ETDRS?

Argon

What two approaches/strategies for laser application were employed?

Focal macular laser (FML) and grid macular laser (GML)

FML: Energy applied directly to individual leaking microaneurysms (MAs)

GML: Energy applied to areas of diffuse leakage when offending MAs are not readily identifiable.
CSME

Acronym for *clinically significant macular edema*.

Definition has three components:

- Any retinal thickening within 1/3 DD of the foveal center;
- Hard exudates within 1/3 DD of the foveal center that are associated with adjacent retinal thickening;
- An area of retinal thickening 1 DD or larger in size, any part of which is within 1 DD of the foveal center.

What landmark clinical trial provided this definition of CSME?

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**What landmark clinical trial provided this definition of CSME?**
The *Early Treatment of Diabetic Retinopathy Study (ETDRS)*

**What 3 questions did this study seek to answer?**
1) Is laser effective in treating diabetic macular edema?
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Argon

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- **Focal macular laser (FML):** Energy applied directly to individual leaking microaneurysms (MAs)
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**Diabetic Retinopathy: Diabetic Macular Edema**

### CSME

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Yes; it cut the risk of moderate vision loss (MVL) by 50%, as well as increased the likelihood of gaining vision.

What is the definition of MVL?
Doubling of the baseline visual angle (e.g., 20/40 → 20/80)

Is there a qualifier on the effectiveness of laser for diabetic macular edema?
Yes. It was effective only if the edema met CSME criteria (that's why the criteria are what they are).
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**Take note of this!** The byzantine definition of CSME is what it is because it delineates the sort of DME that will respond favorably to laser treatment. The point being, if a pt’s DME fails to meet the ETDRS definition of CSME, don’t laser it!

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What does NPDR stand for in this context?
Nonproliferative diabetic retinopathy

So, what was the answer to the question?
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So, what was the answer to the question?
PRP reduced the risk of severe vision loss in pts with severe NPDR, but not with mild or moderate NPDR.

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What was the answer to this question? No. However, it didn’t worsen it either; therefore, DBR is not a contraindication for ASA use.
Diabetic Retinopathy: Diabetic Macular Edema

Primary intervention: Pharmacologic
- Center-involved
- Non-center-involved

Primary intervention: Laser surgery
- Clinically significant
- Not clinically significant

In this classification system, there are two types of DME. What are they?
- That which involves the center (foveal) region, and everything else
- That which qualifies as 'clinically significant,' and that which does not

By what technique is the retina evaluated for the presence of DME?
- OCT

In this system, what findings signal that treatment is indicated?
- Center-involving DME + decreased visual acuity

Of the two approaches to treating DME, which is considered first-line? Pharmacologic, but not in every case (we’ll revisit this issue later)

Time to revisit this issue. Under what circumstances might laser by the preferred treatment modality?
- If there is an obvious, easily-lased microaneurysm that is the source of the edema (that meets CSME criteria of course);
- If there is reason to doubt the pt will comply with the demands imposed by a pharmacologic treatment regimen (eg, monthly visits).

Additionally, some clinicians opt for laser if a pt presents with DME but has good VA (recall from the 'anti-VEGF-vs-laser trials' tl;dr that laser is effective for maintaining VA)
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