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# Impact of residual fluid on treatment outcomes in neovascular age-related macular degeneration

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# Objectives

To discuss the presence of residual fluid as a marker of disease activity

To provide an overview of the role of residual fluid on treatment outcomes in nAMD

To introduce an algorithm to guide the management of patients with nAMD according to residual fluid status

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QUESTION

**Do different types of residual fluid affect vision and treatment in different ways?**

nAMD, neovascular age-related macular degeneration.

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# Background

# Fluid as a measure of anti-VEGF treatment efficacy

**Anti-VEGF agents have enhanced the treatment of nAMD as they have the potential to improve vision and restore the macular architecture[1-3]**

**Treatment decisions are individually adapted after assessing disease state (activity, inactivity, and stability)[4]**

**The main marker for disease activity and retreatment with anti-VEGF is the presence of fluid detected on OCT[5]**

- Although VA is often the main outcome measure in RCTs, the absence of fluid on OCT is also a measure of treatment efficacy[3,6,7]
- The evolution of more flexible treatment regimens (e.g., PRN and T&E) has allowed clinicians to tailor treatment decisions to an individual's disease state[7-10]

?

## CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

**How should disease activity state be defined?**

RECOMMENDATION

nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; PRN, *pro re nata* (as needed); RCT, randomized controlled trial; T&E, treat-and-extend; VA, visual acuity; VEGF, vascular endothelial growth factor.

1. Rosenfeld PJ *et al*. *N Engl J Med* 2006; 355 (14): 1419–1431; 2. Brown DM *et al*. *N Engl J Med* 2006; 355 (14): 1432–1444; 3. Heier JS *et al*. *Ophthalmology* 2012; 119 (12): 2537–2548; 4. Shah VP *et al*. *Retina* 2014; 34 (7): 1281–1288; 5. Chakravarthy U *et al*. *Eye* 2020; 34 (12): 2249–2256; 6. Dugel PU *et al*. *Ophthalmology* 2020; 127 (1): 72–84; 7. CATT Research Group. *N Engl J Med* 2011; 364 (20): 1897–1908; 8. Busbee BG *et al*. *Ophthalmology* 2013; 120 (5): 1046–1056; 9. Chakravarthy U *et al*. *Lancet* 2013; 382 (9900): 1258–1267; 10. Wykoff CC *et al*. *Ophthalmology* 2015; 122 (12): 2514–2522.

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# Markers of nAMD disease activity

- **Markers of disease activity include:[1]**
  - A decrease in VA
  - New occurrence of hemorrhage
  - The presence of fluid and subretinal hyper-reflective material on OCT

- **However, the presence of fluid on OCT is often the earliest indicator of disease activity and, as such, is the feature most used to determine disease activity in clinical practice**
- **Therefore, fluid status is taken into consideration when making retreatment management decisions and adjusting treatment intervals[2]**

nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; VA, visual acuity.

1. Shah VP *et al*. *Retina* 2014; 34 (7): 1281–1288; 2. Chakravarthy U *et al*. *Eye* 2020; 34 (12): 2249–2256.

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# Differences in the management of residual fluid

**There is a lack of consistency among trials in the way presence of fluid triggers retreatment:**

- HARBOR[1] and CATT[2] defined fluid in **any compartment** seen on OCT as a criterion for retreatment with a PRN regimen (SRF, IRF, or sub-RPE, as in PED)
- IVAN[3] only used the presence of **SRF** or increasing **IRF**

**There are also complexities in interpreting hyporeflective spaces:**

- **IRF** can result from degenerative cysts, especially over areas of early atrophy[4]
- **SRF** can be caused by non-exudative processes and **does not necessarily imply** the need for anti-VEGF treatment[4]

## CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

**As fluid drives decisions regarding management of patients with nAMD, there is a need for clear consensus on the criteria for retreatment with anti-VEGF according to fluid status**

RECOMMENDATION

IRF, intraretinal fluid; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; PED, pigment epithelial detachment; PRN, *pro re nata* (as needed); RPE, retinal pigment epithelium; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

1. Busbee BG *et al*. *Ophthalmology* 2013; 120 (5): 1046–1056; 2. CATT Research Group. *N Engl J Med* 2011; 364 (20): 1897–1908; 3. IVAN Study Investigators. *Ophthalmology* 2012; 119 (7): 1399–1411; 4. Lek JJ *et al*. *Ophthalmology Retina* 2018; 2 (8): 792–802.

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# Assessment of fluid

# Does presence of fluid always suggest ongoing VEGF activity?

**RCTs have shown a clear correlation between anti-VEGF injection frequency and absence of fluid[1,2]**

**Presence of fluid has historically implied ongoing VEGF activity, so the goal of treatment has been resolution of fluid[3-5]:**

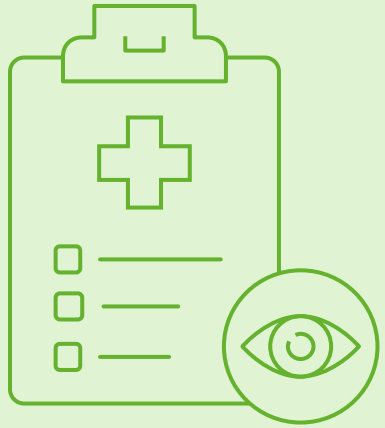
- The American Academy of Ophthalmology, Royal College of Ophthalmologists, and EURETINA state that fluid on OCT is an indication of active disease and recommend retreatment when fluid is present[6-8]
- In contrast, a “dry” retina is believed to be a marker of absence of exudative activity[1,2]

OCT, optical coherence tomography; RCT, randomized controlled trial; VEGF, vascular endothelial growth factor.

1. Simader C *et al*. *Ophthalmology* 2014; 121 (6): 1237–1245; 2. Waldstein SM *et al*. *Ophthalmology* 2016; 123 (7): 1521–1529; 3. Heier JS *et al*. *Ophthalmology* 2012; 119 (12): 2537–2548; 4. CATT Research Group. *N Engl J Med* 2011; 364 (20): 1897–1908; 5. Wykoff CC *et al*. *Ophthalmology* 2015; 122 (12): 2514–2522; 6. Schmidt-Erfurth U *et al*. *Br J Ophthalmol* 2014; 98 (9): 1144–1167; 7. Flaxel CJ *et al*. *Ophthalmology* 2020; 127 (1): 1–65; 8. Chakravarthy U *et al*. *Eye* 2013; 27 (12): 1429–1431.

# Differential diagnosis in the event of persistent fluid

- The concept that any fluid in any retinal location is equivalent to ongoing VEGF activity requiring retreatment needs to be reconsidered[1]
- When using an individualized protocol, if it has been impossible to resolve fluid despite adequate treatment with an anti-VEGF agent, the original diagnosis should be re-evaluated and a differential diagnosis for SRF should be considered. For example[2]:
  - Adult vitelliform macular dystrophy
  - Central serous chorioretinopathy
  - Optic disc pit maculopathy
  - Best disease



SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

1. Zur D *et al. Br J Ophthalmol* 2024 [epub ahead of print]. doi: 10.1136/bjo-2024-325640; 2. Iglicki M *et al*. *Retina* 2019; 39 (11): 2161–2166.

# Novel ways of assessing the presence and quantity of fluid

**Fluid status is defined not only by the presence or absence of fluid but also by its location**

- OCT central retinal macular thickness has only a weak correlation to fluid presence due to the spatial distribution of fluid in different retinal compartments: IRF is predominantly located beyond this central area[1]

**Subjectivity in the interpretations of scans can lead to different treatment decisions among clinicians:**

- In CATT, a review of OCT scans by the reading center showed that decisions by ophthalmologists were consistent with the retreatment protocol in only 72–74% of cases[2]
- Similar discrepancies were seen in the FLUID[3] trial

**Discrepancies likely arise from clinicians adding their own interpretations to residual fluid assessments, leading to varied treatment decisions and outcomes**

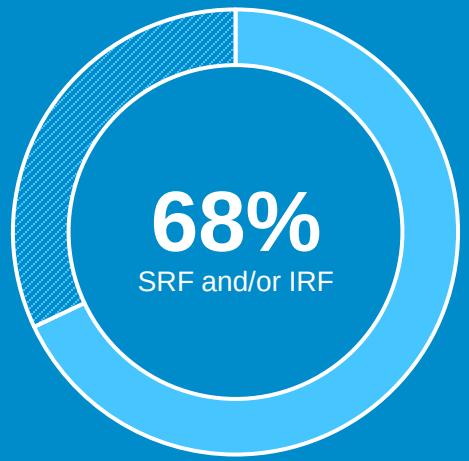
- AI-based algorithms may have great potential in this field, having been proven to be highly accurate in identifying different fluid compartments and providing quantitative topographic volumetric information[1,4,5]

AI, artificial intelligence; IRF, intraretinal fluid; OCT, optical coherence tomography.

1. Reiter GS *et al*. *Retina* 2021; 41 (6): 1318–1328; 2. CATT Research Group. *N Engl J Med* 2011; 364 (20): 1897–1908; 3. Guymer RH *et al*. *Ophthalmology* 2019; 126 (5): 723–734; 4. Klimscha S *et al*. *Invest Ophthalmol Vis Sci* 2017; 58 (10): 4039–4048; 5. Chakravarthy U *et al*. *Ophthalmology* 2016; 123 (8): 1731–1736.

# Change in fluid status under anti-VEGF treatment

**Despite intensive injection protocols, most patients still show retinal fluid over time: in the SEVEN-UP study, 68% of eyes showed SRF and/or IRF after 7 years[1]**




**Analysis of fluid by type should therefore be viewed in the larger context of time and its dynamic under treatment:**

- In a retrospective study of nAMD, eyes with isolated SRF at baseline had a smaller chance of achieving complete resolution of fluid after 3 induction doses, compared with eyes that had IRF or a combination of SRF and IRF at baseline (22% vs. 33% and 31%, respectively)[2]
- A *post hoc* analysis of the HARBOR data showed that patients with residual SRF without IRF at months 12 and 24 gained the greatest amount of vision compared with patients who experienced complete resolution of SRF. This group was followed by patients with both SRF and IRF resolved, and then by patients with residual SRF and IRF[3]

**Stability of fluid is also important:**

- In a T&E setting, new occurrence of any fluid on OCT was shown to be likely to lead to vision loss, but small amounts of persistent fluid were tolerated without a compromise in vision[4]
- Greater fluctuations in retinal fluid volumes during the maintenance phase of anti-VEGF treatment are associated with worse VA after 2 years[5]

IRF, intraretinal fluid; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; SRF, subretinal fluid; T&E, treat-and-extend; VA, visual acuity; VEGF, vascular endothelial growth factor.

1. Rofagha S *et al*. *Ophthalmology* 2013; 120 (11): 2292–2299; 2. Ebneter A *et al*. *Ophthalmologica* 2015; 234 (2): 61–66; 3. Holekamp NM *et al*. *Am J Ophthalmol* 2022; 233: 8–17; 4. Wickremasinghe SS *et al*. *Retina* 2016; 36 (7): 1331–1339; 5. Chakravarthy U *et al*. *Eye* 2021; 35 (11): 2983–2990.

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# Is the presence of fluid in different compartments predictive of visual outcome?

- Although RCTs have shown a clear correlation between anti-VEGF injection frequency and absence of fluid,[1,2] it is important to assess different compartments for the presence of fluid throughout the entire treatment period, as analysis of anatomic location of fluid compartments reveals significant differences:

| | At baseline | In the early phase (1–3 months) | During long-term follow-up |
|---|---|---|---|
| **SRF** | Predictive factor for greater visual gains[3] | VIEW[5] found that persistent SRF had little impact on visual outcome | Despite intensive injection protocols, most patients still show retinal fluid over time. Impact on visual outcomes can be contradictory:<br>• In the CATT[2] and VIEW[6] trials, different proportions of patients achieved a dry retina in different treatment arms, but there was no significant difference in improvement of BCVA and prevention of vision loss over 2 years<br>• Long-term, persistent IRF can negatively affect visual outcomes, while persistent SRF may be tolerated without worsening vision[3,7,8] |
| **IRF** | Predictive factor for worse baseline VA and worse visual outcomes[4] | Patients with persistent IRF at 1 or 3 months experienced a reduction in VA after 1 year[5] | |

BCVA, best-corrected visual acuity; IRF, intraretinal fluid; RCT, randomized controlled trial; SRF, subretinal fluid; VA, visual acuity; VEGF, vascular endothelial growth factor.

1. Simader C *et al*. *Ophthalmology* 2014; 121 (6): 1237–1245; 2. CATT Research Group. *N Engl J Med* 2011; 364 (20): 1897–1908; 3. Waldstein SM *et al*. *Ophthalmology* 2016; 123 (1): 60–69; 4. Ritter M *et al*. *Br J Ophthalmol* 2014; 98 (12): 1629–1635; 5. Schmidt-Erfurth U *et al*. *Ophthalmology* 2015; 122 (4): 822–832; 6. Heier JS *et al*. *Ophthalmology* 2012; 119 (12): 2537–2548; 7. Reiter GS *et al*. *Retina* 2021; 41 (6): 1318–1328; 8. Sharma S *et al*. *Ophthalmology* 2016; 123 (4): 865–875.

# Macular atrophy and fluid status

- Treatment regimens aiming to completely dry the macula result in more frequent injections,[1] but the relationship between treatment and macular atrophy remains unclear:
  - The CATT[2] study reported an association between more frequent injections and macular atrophy, while the HARBOR[3] and IVAN[4] studies found no association
- Poor visual outcomes are associated more with the development of atrophy and scarring than with the incomplete treatment of MNV activity[5]
- The role of fluid in different compartments has been investigated in relation to macular atrophy development:
  - In CATT[6] and HARBOR,[3] baseline IRF was associated with macular atrophy development, but the presence of baseline SRF was linked to a lower risk of developing macular atrophy
  - It is thought that fluid in the subretinal space may provide a protective barrier between the outer segments of photoreceptors and the pathologic RPE as there is correspondence between presence of SRF and ellipsoid zone integrity and intact photoreceptors[7]

IRF, intraretinal fluid; MNV, macular neovascularization; RPE, retinal pigment epithelium; SRF, subretinal fluid.

1. Guymer RH *et al*. *Ophthalmology* 2019; 126 (5): 723–734; 2. Grunwald JE *et al*. Ophthalmology 2014; 121 (1): 150–161; 3. Sadda SR *et al*. *Ophthalmology* 2018; 125 (6): 878–886; 4. Bailey C *et al*. *Ophthalmology* 2019; 126 (1): 75–86; 5. Rofagha S *et al*. *Ophthalmology* 2013; 120 (11): 2292–2299; 6. Grunwald JE *et al*. *Ophthalmology* 2017; 124 (1): 97–104; 7. Riedl S *et al*. *Retina* 2020; 40 (11): 2148–2157.

# Deliberate toleration of fluid

- To maintain initial gains from treatment while reducing treatment burden, retreatment intervals can be re-adjusted according to individual MNV activity[1]

T&E regimens aim to gradually extend the treatment interval while maintaining a dry retina.[2] However, if SRF persists despite maximal treatment intensity (i.e., monthly treatments), clinicians might consider extending the intervals if there is no further reduction in SRF or IRF on OCT for ≥2 consecutive clinic visits, provided there is no new retinal hemorrhage[3]

- In the FLUID study, tolerance of residual SRF <200 µm led to visual outcomes comparable with intensive treatment intolerant to any residual fluid and resulted in fewer injections over 2 years[4]

IRF has a negative impact on visual outcomes[1,5] and therefore all treatment algorithms aim to achieve complete resolution of exudative intraretinal cysts

IRF, intraretinal fluid; MNV, macular neovascularization; OCT, optical coherence tomography; SRF, subretinal fluid; T&E, treat-and-extend.

1. Holekamp NM *et al*. *Am J Ophthalmol* 2022; 233: 8–17; 2. Wykoff CC *et al*. *Ophthalmology* 2015; 122 (12): 2514–2522; 3. Freund KB *et al*. *Retina* 2015; 35 (8): 1489–1506; 4. Guymer RH *et al*. *Ophthalmology* 2019; 126 (5): 723–734; 5. Waldstein SM *et al*. *Ophthalmology* 2016; 123 (1): 60–69.

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# Clinical challenges

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# Clinical challenges requiring guidance

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**Defining disease state**

What criteria are used to define disease activity, inactivity, and stability?

**Monitoring**

What are the most important considerations when assessing fluid status?

**Treatment**

How should patients be managed according to status of residual fluid?

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# Vision Academy recommendations

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# Diagnosis and assessment of fluid status

## A definitive diagnosis of MNV should be made before initiating treatment

- Non-exudative MNV (i.e., a neovascular membrane identified on OCT-A, fluorescein angiography, or indocyanine green angiography in the absence of IRF or SRF exudation) should not be treated until there are signs of retinal fluid exudation
- The MNV lesion type, size, and location in relation to the fovea should be established
- The presence and localization of fluid as seen on OCT should also be recorded at baseline:
  - SRF
  - IRF
  - Sub-RPE fluid

General consensus

IRF, intraretinal fluid; MNV, macular neovascularization; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; RPE, retinal pigment epithelium; SRF, subretinal fluid.

BACK TO CHALLENGES

# Definition of disease activity state: activity, inactivity, and stability

**It is important to define the disease activity state in order to make treatment decisions; therefore, the activity of the disease should be evaluated at each visit, based on clinical examination and review of OCT images**

- Disease inactivity is achieved when there is:
  - Absence of IRF and SRF attributable to VEGF activity
  - Absence of deterioration in vision attributable to MNV activity
  - Absence of new retinal hemorrhage attributable to MNV activity
- Disease stability is achieved when there is:
  - No fluid or a small amount of persistent residual SRF without a further decrease despite monthly injections being performed until maximal anatomical effect (with at least an initial 3 monthly injections during the induction phase)
    - In this case, and only in the absence of any other signs of disease activity, we suggest the disease might be considered stable and the treatment interval maintained or cautiously increased

**Disease is considered active when the above states are not achieved**

General consensus

IRF, intraretinal fluid; MNV, macular neovascularization; OCT, optical coherence tomography; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

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# Management: induction phase

**Treatment should be given monthly through the induction phase and continued until maximal anatomical effect is achieved**

- Patients should be monitored for disease activity using a multimodal approach:
  - BCVA
  - Clinical examinations for retinal hemorrhage
  - OCT
- Fluid compartments should be assessed individually, and fluid status should be evaluated to determine the appropriate treatment decisions:
  - If IRF and/or SRF levels are reducing, monthly treatment should continue until disease inactivity or stability is achieved
  - If there is no change in the amount of SRF or IRF initially, the diagnosis should be re-evaluated, including fluorescein or indocyanine green angiography
  - Hyporeflective cystoid spaces not responsive to anti-VEGF treatment should be re-evaluated for atrophic spaces, loss of tissue, and outer retinal tubulations

Masquerading diagnoses for nAMD should be considered for SRF that does not change with initial treatments

General consensus

BCVA, best-corrected visual acuity; IRF, intraretinal fluid; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

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# Management: maintenance phase

## Patients should be examined at the first visit following the final induction dose of anti-VEGF therapy for the presence of disease activity

- T&E is the treatment regimen of choice
- If the disease is active, monthly treatment should be continued
- In cases of disease inactivity or stability, the treatment interval should be adjusted on an individual basis*
  - The treatment interval can be extended by 2-week or possibly up to 4-week increments, according to the physician's discretion
- Upon recurrence of MNV activity in any of the parameters (i.e., new retinal hemorrhage, drop in vision, or new and/or increased IRF, SRF, or sub-RPE fluid), injection intervals should be shortened by ≥2 weeks, to a minimum of a 4-week interval, depending on the severity of the recurrence
- Persistent VEGF-driven IRF is considered a biomarker of disease activity and should never be tolerated
  - The injection interval should be shortened by ≥2 weeks, to a minimum of a 4-week interval
- A small amount of stable, residual SRF is considered compatible with favorable visual outcomes and can be tolerated
  - Treatment intervals can be cautiously extended in the absence of any other signs of disease activity

**Treatment intervals should be decreased if fluid volumes appear to increase**

General consensus

***T&E is the regimen of choice. Treatment options should be discussed with the patient and an individualized treatment regimen offered.**

IRF, intraretinal fluid; MNV, macular neovascularization; RPE, retinal pigment epithelium; SRF, subretinal fluid; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

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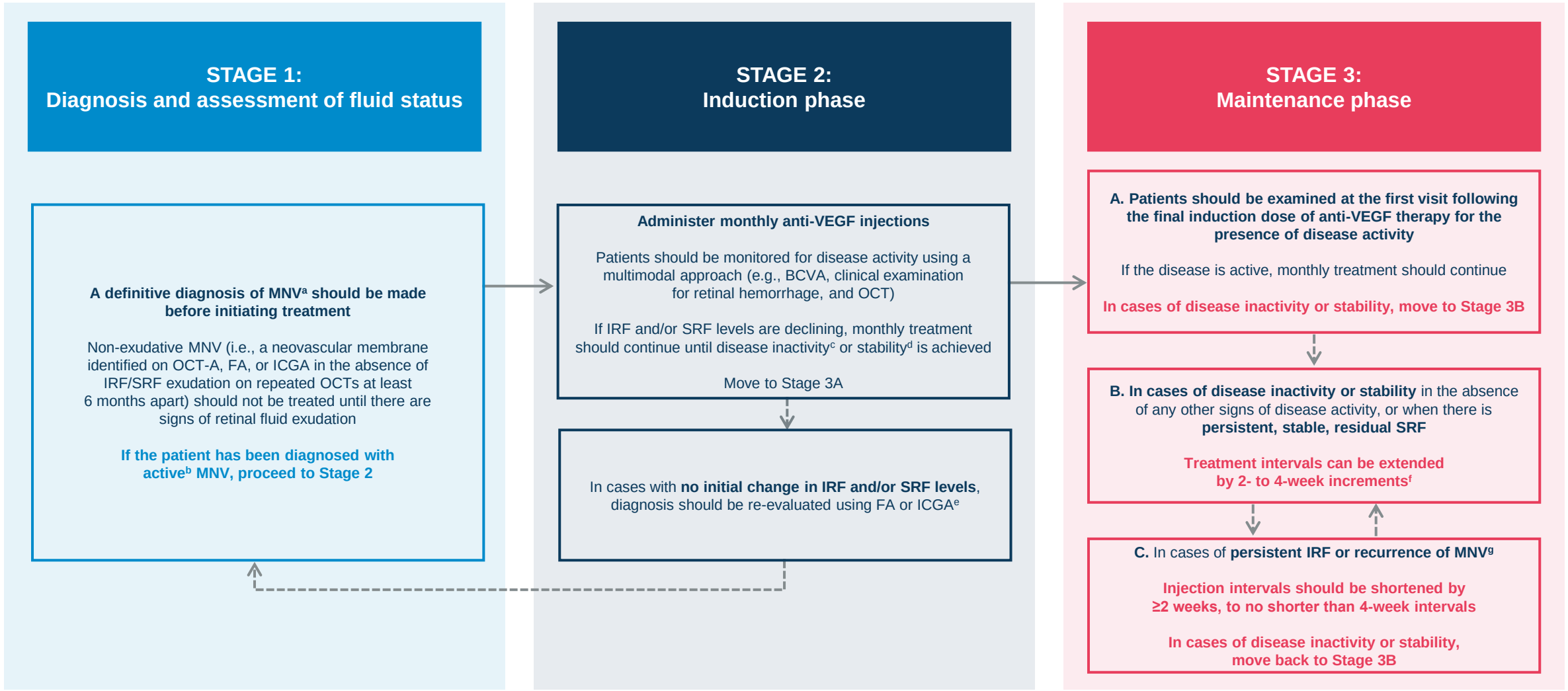


[a]The MNV lesion type, size, and location in relation to the fovea should be established and recorded, and the presence and localization of fluid as seen on OCT should be recorded at baseline; [b]Disease is considered active when the disease stability or disease inactivity states are not achieved, defined as: the presence of IRF and/or SRF attributable to VEGF activity, deterioration in vision attributable to MNV activity, presence of new retinal hemorrhage attributable to MNV activity, increasing amounts of SRF/IRF despite regular injections; [c]Disease inactivity is achieved when there is absence of IRF and SRF attributable to VEGF activity, absence of deterioration in vision attributable to MNV activity, or absence of new retinal hemorrhage attributable to MNV activity; [d]Disease stability is achieved when there is no fluid or a small amount of persistent residual SRF without a further decrease, despite adequate regular injections being performed until maximal anatomic effect (with at least an initial 3 monthly injections during the induction phase), in the absence of any other signs of disease activity; [e]Hyporeflective cystoid spaces that are not responsive to anti-VEGF treatment should be re-evaluated for atrophic spaces, loss of tissue, and outer retinal tubulations; [f]T&E is the regimen of choice. Treatment options should be discussed with the patient and an individualized treatment regimen offered. Treatment intervals should be extended at the physician's discretion; [g]Signs of MNV recurrence include any of the following: new retinal hemorrhage, visual deterioration, or new and/or increased IRF, SRF, or sub-RPE fluid. BCVA, best-corrected visual acuity; FA, fluorescein angiography; ICGA, indocyanine green angiography; IRF, intraretinal fluid; MNV, macular neovascularization; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; SRF, subretinal fluid; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

Figure reproduced from Zur D *et al. Br J Ophthalmol* 2024 [epub ahead of print]. doi: 10.1136/bjo-2024-325640. 

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# Vision Academy recommendations on the impact of residual fluid on treatment outcomes in nAMD

- A definitive diagnosis of MNV should be made before initiating treatment. The presence and location of fluid on OCT, as well as the MNV lesion type, should be recorded at baseline
- Disease activity state should be assessed at each visit using a multimodal approach (BCVA, clinical examinations for retinal hemorrhage, and OCT) and classified as active, inactive, or stable
- During the induction phase, fluid compartments should be assessed individually, and fluid status should be evaluated to determine appropriate treatment decisions. Monthly treatment should continue until disease inactivity or stability is achieved
- Patients should be examined at the first visit following the final induction dose of anti-VEGF therapy for the presence of disease activity
- During the maintenance phase, an individualized approach should be used to treat patients with inactive or stable disease, with a decrease in treatment intervals in the event of disease recurrence

BCVA, best-corrected visual acuity; MNV, macular neovascularization; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor.

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# Further considerations

- Morphological retinal parameters on OCT are predictive of functional outcomes in nAMD, and RCTs have demonstrated a strong relationship between VEGF suppression and a reduction in retinal fluid
- However, the use of fluid-related signs and their interpretation as disease activity remains ambiguous, highlighting the need for improved markers of neovascular activity
- Despite intensive anti-VEGF treatment, a residual subretinal space may be seen after active exudation has ceased:[1]
  - Recent data indicate that vision outcomes when treatment intervals are extended, while tolerating a small amount of SRF, are non-inferior to those achieved when no SRF is permitted. These data show that residual SRF does not negatively impact visual outcomes
  - In contrast, IRF, which is exudative and not degenerative cysts, can be considered a biomarker of disease activity; the presence of IRF at baseline and its persistence under VEGF suppression are correlated with worse visual outcomes
- Large-scale, long-term prospective studies using volumetric quantification of fluid and the documentation of atrophic regions would provide greater clarity on the role of residual fluid in the treatment algorithm for nAMD

IRF, intraretinal fluid; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; RCT, randomized controlled trial; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

1. Arnold JJ *et al*. *BMC Ophthalmol* 2016; 16: 31.