AMYLOID-TARGETING THERAPIES FOR ALZHEIMER'S DISEASE: A PERSPECTIVE FOR EMERGENCY PHYSICIANS

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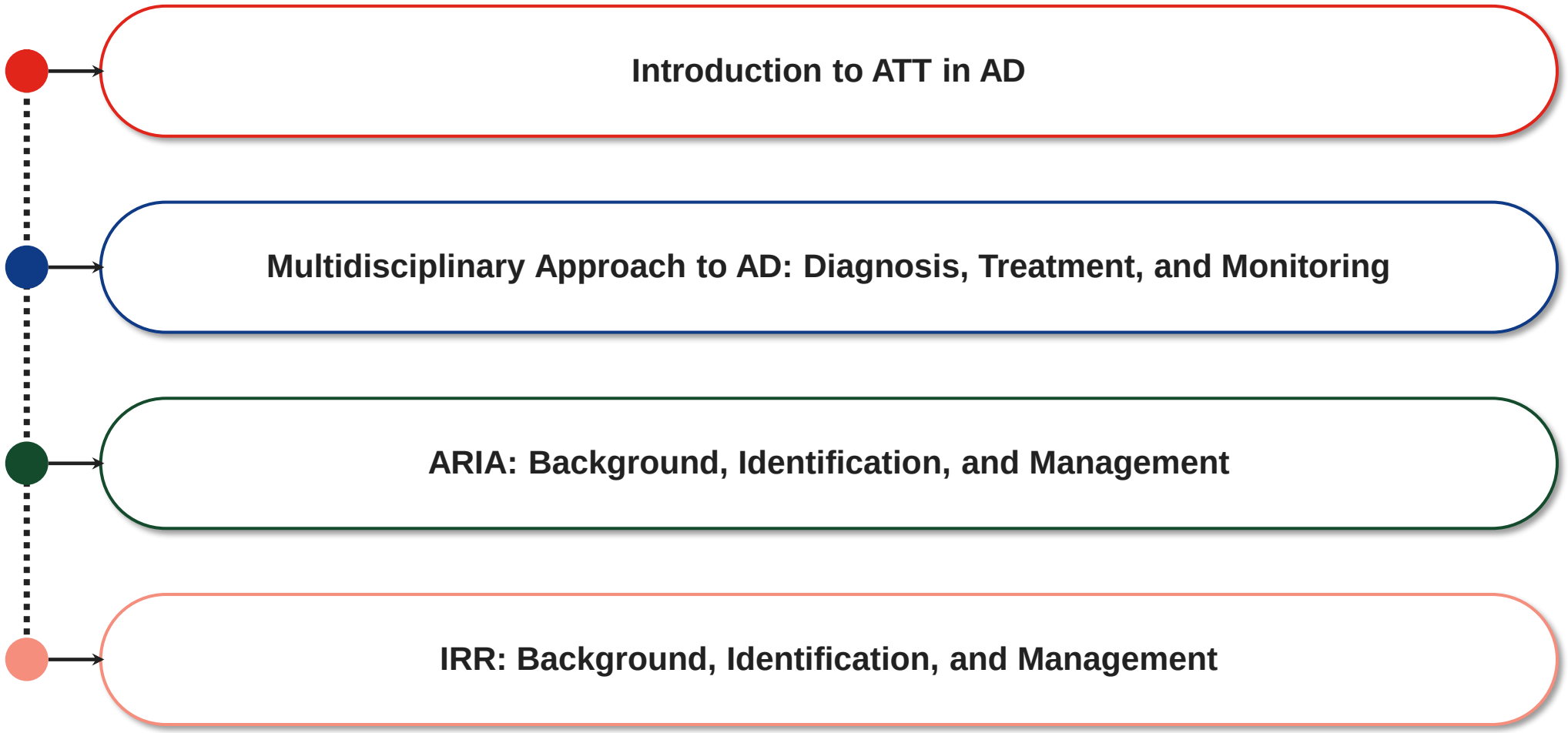
Outline



Note: This is an interactive slide where you can click on the different sections to navigate directly to the respective section.
AD=Alzheimer's Disease; ARIA=Amyloid-Related Imaging Abnormalities; ATT=Amyloid-Targeting Therapies; IRR=Infusion-Related Reactions.

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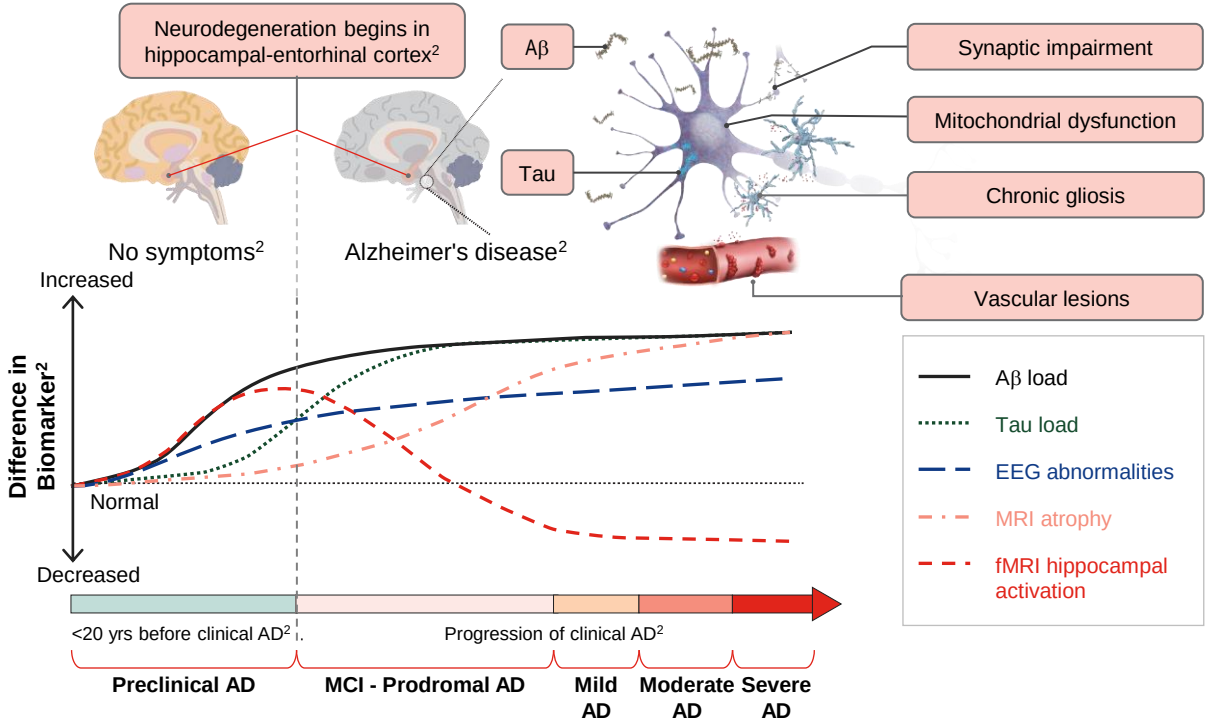
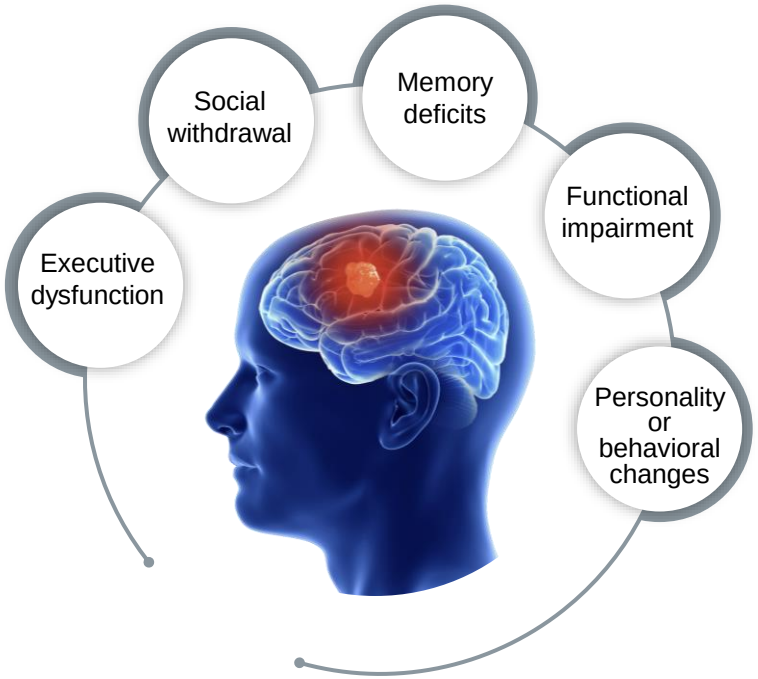
Introduction to Amyloid-Targeting Therapies in Alzheimer's Disease

AD is a Progressive Neurodegenerative Disease[1]

Pathophysiological changes associated with AD, as indicated by multiple biomarkers, can appear well before a patient presents with cognitive symptoms.[2,3] **Accumulation of Aβ plaques in the brain is one of the defining pathophysiological features of AD.**[4] Increase in amyloid load, along with tau load elevation, may induce neuronal hyperexcitability, cell death, and network dysfunction in AD progression.[2]



Summarized clinical presentation of AD*[5,6]



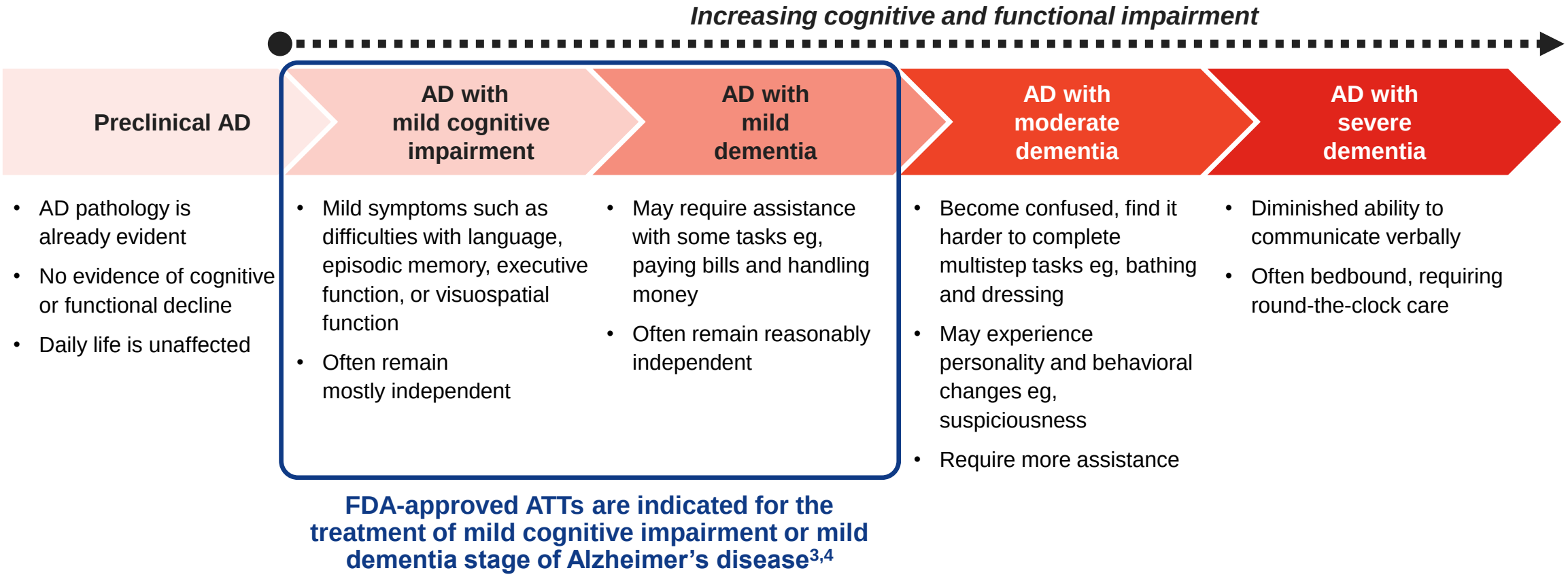
Models are not to scale and are for illustration purposes only.

*This is an abbreviated list of clinical signs and symptoms of AD. Enlisted signs and symptoms may or may not present in every AD patient and may vary depending upon the clinical stage of AD. Please refer to "NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease" for details about clinical staging of AD.[5] Aβ=Amyloid Beta; AD=Alzheimer's Disease; EEG=Electroencephalogram; fMRI=Functional Magnetic Resonance Imaging; MCI=Mild Cognitive Impairment; MRI=Magnetic Resonance Imaging; NIA-AA=National Institute on Aging and Alzheimer's Association; yrs=Years.

1. DeTure MA, Dickson DW. *Mol Neurodegener*. 2019;14:32. 2. Jeremic D, et al. *Ageing Res Rev*. 2021;72:101496. 3. Jack CR Jr, et al. *Lancet Neurol*. 2013;12(2):207-216. 4. Mintun MA, et al. *N Engl J Med*. 2021;384(18):1691-1704. 5. Jack CR Jr, et al. *Alzheimers Dement*. 2018;14(4):535-562. 6. https://www.alz.org/getmedia/76e51bb6-c003-4d84-8019-e0779d8c4e8d/alzheimers-facts-and-figures.pdf (Accessed February 15, 2025).

Progression of Symptoms Through the AD Continuum

Signs and symptoms across the AD continuum[1,2]



FDA-approved ATTs are indicated for the treatment of mild cognitive impairment or mild dementia stage of Alzheimer's disease[3,4]

AD=Alzheimer's Disease; ATT=Amyloid-Targeting Therapy; FDA=Food and Drug Administration.

1. https://www.alz.org/getmedia/76e51bb6-c003-4d84-8019-e0779d8c4e8d/alzheimers-facts-and-figures.pdf (Accessed February 15, 2025). 2. Porsteinsson AP, et al. J *Prev Alz Dis.* 2021;3(8):371-386.
3. Lecanemab [US PI]. Nutley, NJ, USA: Eisai Inc and Biogen, 2025. 4. Donanemab [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 2024.

Treatment Options for AD

Non-Pharmacologic or Behavioral Interventions

Non-pharmacologic interventions that may help to improve or maintain cognition/function, help to support independence in usual activities of daily living, or address behavioral symptoms (eg, cognitive therapy, physical exercise, nutrition)[1]

Disease-Modifying Therapy

Pharmacotherapy that modifies the clinical course of disease but does not stop or reverse the disease (eg, amyloid-targeting therapy)[2]

Symptomatic Therapy

Pharmacotherapy that may improve cognitive and behavioral symptoms, but does not alter the course of the disease[3]

- **Treatment of cognitive symptoms:** ChEIs (donepezil, rivastigmine, galantamine), glutamate regulators (memantine), and ChEI + glutamate regulator (donepezil + memantine)[4]
- **Treatment of non-cognitive symptoms:** Orexin receptor antagonists (suvorexant)[4]

AD=Alzheimer's Disease; ChEI=Cholinesterase Inhibitor.

1. Li X, et al. *Neurol Ther.* 2023;12(1):39-72. 2. Huang LK, et al. *J Biomed Sci*. 2023;30(1):83. 3. Cummings J. *Mol Neurodegener.* 2021;16(1):2. 4. https://www.alz.org/getmedia/4f4ca289-a2c6-4df9-8cdf-390365bd477e/alzheimers-dementia-fda-approved-treatments-for-alzheimers-ts.pdf (Accessed February 15, 2025).

Treatment Options for AD: ATTs

ATTs act on the underlying pathophysiology of AD and can slow clinical decline[1-3]

They are indicated for the treatment of AD. Treatment with ATTs should be initiated in patients with mild cognitive impairment (MCI) or mild dementia stage of the disease[4,5]:

	 **Lecanemab-irmb[4]**	 **Donanemab-azbt[5]**
Antibody target	Aggregated soluble and insoluble forms of Aβ	Aggregated insoluble forms of Aβ
AD stage	MCI or mild dementia	MCI or mild dementia

Aβ=Amyloid Beta; AD=Alzheimer's Disease; ATT=Amyloid-Targeting Therapy; MCI=Mild Cognitive Impairment.

1. Yiannopoulou KG, et al. *J CNS Dis*. 2020;12:1-12. 2. Van Dyck CH, et al. *N Engl J Med*. 2023;388(1):9-21. 3. Self WK, Holtzman DM. *Nat Med*. 2023;29(9):2187-2199. 4. Lecanemab [US PI]. Nutley, NJ, USA: Eisai Inc. and Biogen, 2025. 5. Donanemab [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 2024.

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Treatment Risks Associated with ATTs[1,2]

WARNING: AMYLOID-RELATED IMAGING ABNORMALITIES (ARIA)
See full prescribing information for complete boxed warning

Monoclonal antibodies directed against aggregated forms of beta amyloid, can cause amyloid related imaging abnormalities (ARIA) characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). Incidence and timing of ARIA vary among treatments.

ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages, some of which have been fatal, have been observed in patients treated with this class of medications. Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with an ATT.

ApoE ε4 Homozygotes

Patients who are apolipoprotein E ε4 (*ApoE* ε4) homozygotes (approximately 15% of Alzheimer's disease patients) treated with this class of medications have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers.

Testing for *ApoE* ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed, they can still be treated with an ATT; however, it cannot be determined if they are *ApoE* ε4 homozygotes and at higher risk for ARIA.

Consider the benefit of ATTs for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with an ATT.

APOE ε4=Apolipoprotein E Allele 4; ARIA=Amyloid-Related Imaging Abnormalities; ATT=Amyloid-Targeting Therapy.

1. Donanemab [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 2024. 2. Lecanemab [US PI]. Nutley, NJ, USA: Eisai Inc. and Biogen, 2025.

Considerations for Treatment Initiation With ATTs

Initiating and monitoring treatment with ATTs requires patient education and multidisciplinary collaboration[1]

Patients must meet eligibility criteria: Amyloid-positive and a diagnosis of AD (MCI or mild dementia stage)[1]

Treatment risks[1-3]:

Amyloid-related imaging abnormalities (ARIA) and infusion-related reactions (IRR) represent key safety events associated with ATT use that can be serious and potentially life-threatening

Presence of *APOE* ε4 allele is associated with higher rates of ARIA (especially among *APOE* ε4 homozygotes)

- *APOE* ε4 allele testing should be offered prior to ATT treatment so that risk of ARIA can be appropriately considered

Treatment benefits/aims[1]:

- Treats early symptomatic AD
- Reduces brain amyloid plaques
- Slows disease-related cognitive and functional decline
- Slows functional decline

Patient considerations[1]:

- High test and visit burden
- Potentially high financial costs
- Ability to undergo MRIs due to need for regular safety monitoring and urgent imaging in case of symptoms

AD=Alzheimer's Disease; *APOE* ε4=Apolipoprotein E Allele 4; ATT=Amyloid-Targeting Therapy; MCI=Mild Cognitive Impairment; MRI=Magnetic Resonance Imaging.

1. Ramanan VK, et al. Neurology. 2023;101(19):842-852. 2. Lecanemab [US PI]. Nutley, NJ 07110, USA: Eisai Inc. and Biogen, 2025. 3. Donanemab [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 2024.

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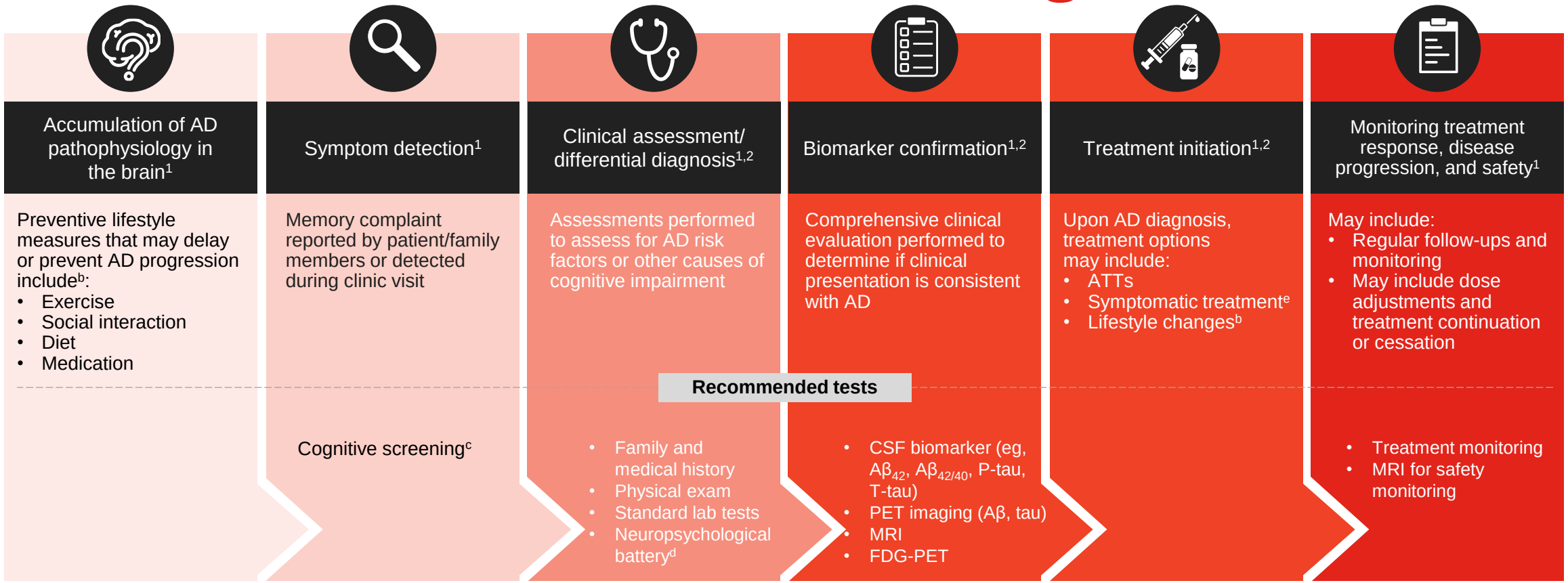
Multidisciplinary Approach to Alzheimer’s Disease: Diagnosis, Treatment, and Monitoring

Overview of Typical Patient Care Journey[a] for ATTs: Treatment Initiation and Monitoring

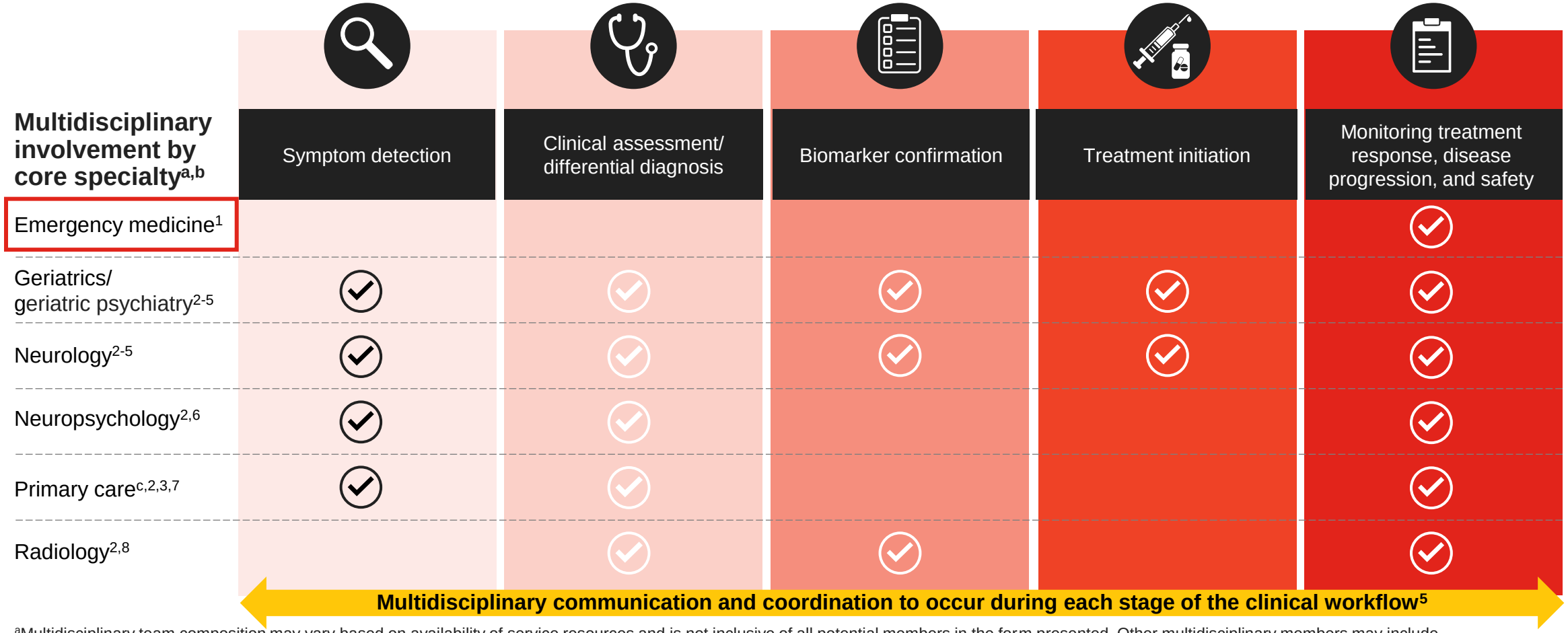


[a]Example of a clinical workflow shown; process may vary. [b]May help to maintain cognition/function; evidence linking lifestyle changes directly to AD disease modification is currently limited.[5,6] [c]eg, MMSE or MoCA.[2] [d]May include cognitive tests (eg, AD8, IQCODE, MMSE, MoCA, Mini-Cog, QDRS, PQH9), functional tests (eg, A-IADL-Q, FAST, FAQ), and/or behavioral tests (eg, GDS, NPI-Q).[2,7] [e]May improve cognitive and behavioral symptoms, but does not alter the course of the disease.[8] See speaker notes for abbreviations.

1. Hampel H, et al. *Nat Aging*. 2022;2(8):692-703. 2. Porsteinsson AP, et al. *J Prev Alzheimers Dis.* 2021;8(3):371-386. 3. Cummings J, et al. *J Prev Alzheimers Dis*. 2023;10(3):362-377. 4. Limpahan LP, et al. *Am J Emerg Med*. 2013;31(9):1297-1301. 5. Li X, et al. *Neurol Ther.* 2023;12(1):39-72. 6. Barbera M, et al. *J Prev Alzheimers Dis*. 2023;10(4):718-728. 7. Kroenke K, et al. *J Gen Intern Med*. 2001;16(9):606-613. 8. Cummings J. *Mol Neurodegener*. 2021;16(1):2.

Patient may seek ED services for ATT-associated AEs.[3] The physician prescribing the ATT and the PCP should receive communication about the patient's ER visit (and associated clinical outcomes) upon discharge.[4]

Overview of Typical Patient Care Journey for ATTs: HCP Roles



[a]Multidisciplinary team composition may vary based on availability of service resources and is not inclusive of all potential members in the form presented. Other multidisciplinary members may include physical/occupational therapists, nutritionists, social workers, and/or pharmacists.[6,9] [b]Each specialty may include physicians and NPs/PAs.[4,9] [c]May include any PCP in regular contact with the patient.[5] See speaker notes for abbreviations.

1. Lo AX, et al. *J Am Geriatr Soc.* 2024;72(12):3945-3949. 2 https://www.alz.org/getmedia/76e51bb6-c003-4d84-8019-e0779d8c4e8d/alzheimers-facts-and-figures.pdf (Accessed February 15, 2025). 3. Hampel H, et al. *Neuron*. 2023;111(18):2781-2799. 4. https://www.alz.org/getmedia/12127c15-bc6b-4410-b1ba-a6402cccfe17/alzheimers-facts-and-figures-special-report-2023.pdf (Accessed February 15, 2025). 5. Galvin JE, et al. *Front Neurol*. 2021;11:592302. 6. Galvin JE, *Neurodegener Dis Manag.* 2014;4(6):455-469. 7. de Levante Raphael D. *Medicina (Kaunas).* 2022;58(7):906. 8. Teipel S, et al. *J Nucl Med.* 2022;63(7):981-985. 9. Grand JH, et al. *J Multidiscip Healthc*. 2011;4:125-147.

Overview of Typical Patient Care Journey for ATTs: Communication Strategies Relevant to the ED

- Patients may present to the ED with medical alert identification (eg, a bracelet, wallet card, or key ring)[1]; clinicians to consider checking or directly asking the patient
- EMR automated warnings communicate essential patient information to clinicians, and may inform patient management and safety[2]
- The discharge of a patient from the ED to their PCP, neurologist, or ATT prescribing provider represents an important transition of care; coordination between clinicians directly impacts care quality and patient safety[3]
- To ensure high-quality care and continuity, appropriate information must be provided to the PCP or prescribing provider within a reasonable time frame after patient discharge[3-5]
- Effective communication is key in reducing the risk of errors during follow-up, helping ensure patient safety and minimizing medication complications[3,6]

AE=Adverse Event; ATT=Amyloid-Targeting Therapy; ED=Emergency Department; EMR=Electronic Medical Record; EP=Emergency Practitioner; PCP=Primary Care Provider.

1. Rahman S, et al. *Anaesthesia*. 2017;72(9):1139-1145. 2. Todd B, et al. *J Emerg Med*. 2021;60(3):390-395. 3. Rider AC, et al. *West J Emerg Med*. 2018;19(2):245-253.
4. https://www.jointcommission.org/resources/news-and-multimedia/newsletters/newsletters/quick-safety/quick-safety-issue-26-transitions-of-care-managing-medications/transitions-of-care-managing-medications/ (Accessed February 18, 2025). 5. Greenwald JL, et al. *J Patient Saf.* 2007;3:97-106. 6. Marsall M, et al. *BMC Health Serv Res*. 2024;24(1):576.

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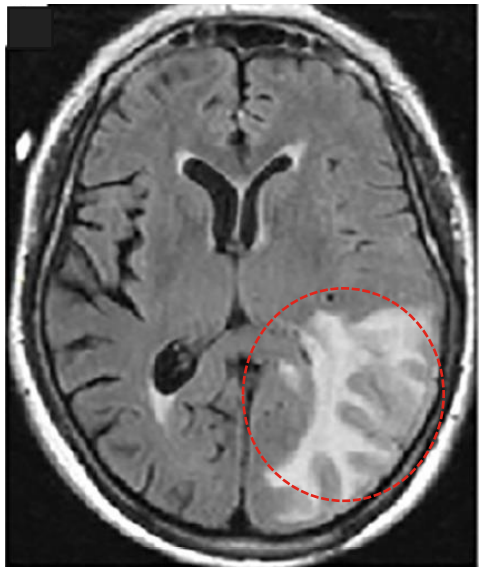
Amyloid-Related Imaging Abnormalities: Background, Identification, and Management

Amyloid-Related Imaging Abnormalities (ARIA)

- ARIA are a **spectrum of MRI signal abnormalities** associated with **Aβ clearance**[1-3]
- ARIA can occur spontaneously in AD/CAA without ATT intervention and are also associated with the use of **monoclonal antibodies directed against Aβ**[1,3]
- **ARIA type** is determined by the **nature of leakage product and location**[2,4] and the two types may be observed on the same scan[4]

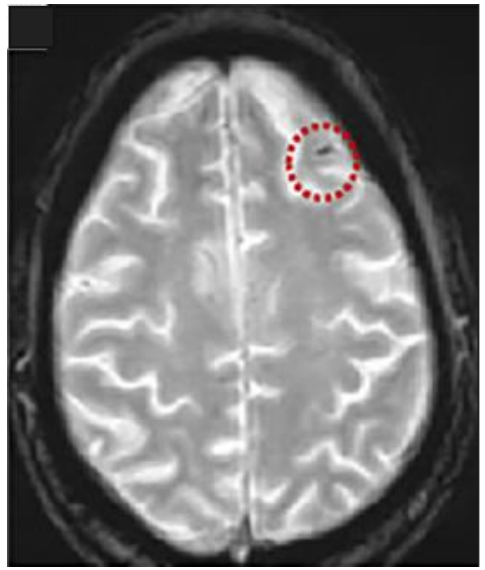
Types of ARIA

ARIA-E
(Vasogenic edema and/or sulcal effusion)[2,3,5]



Left parieto-occipital lobe (T2-FLAIR)[5]

ARIA-H
(Microhemorrhages/localized superficial siderosis/hemosiderin deposits)[1,5]



Left frontal lobe sulcus (GRE/T2*)[5]

Aβ=Amyloid Beta; AD=Alzheimer's Disease; ARIA-E=Amyloid-Related Imaging Abnormalities-Edema; ARIA-H=Amyloid-Related Imaging Abnormalities-Hemosiderin Deposition; ATT=Amyloid-Targeting Therapy; CAA=Cerebral Amyloid Angiopathy; FLAIR=Fluid-Attenuated Inversion Recovery; GRE=Gradient Recalled Echo; MRI=Magnetic Resonance Imaging.

1. Salloway S, et al. *JAMA Neurol*. 2022;79(1):13-21. 2. Filippi M, et al. *JAMA Neurol*. 2022;79(3):291-304. 3. Sperling RA, et al. *Alzheimers Dement*. 2011;7(4):367-385.
4. Cogswell PM, et al. *Am J Neuroradiol*. 2022;43(9):E19-E35. 5. Barakos J, et al. *J Prev Alzheimers Dis*. 2022;9(2):211-220.

ARIA: Biological Mechanisms and Risk Factors

The exact mechanism of ARIA is unknown. Hypotheses include[1]:

- Amyloid-targeting monoclonal antibody binds to deposited Aβ in cerebral vessels
- Perivascular drainage system becomes overwhelmed, leading to leakage of fluid and RBCs from cerebral vasculature

Carriership of the *APOE* ε4 allele is one of the strongest risk factors for ARIA development[2]

Use of anti-thrombotic medication in combination with amyloid-targeting mAb therapies has been observed to increase the risk of ARIA-H in select clinical trials[3]

The greatest risk for ARIA occurs earlier in the treatment course across the ATT class[2]

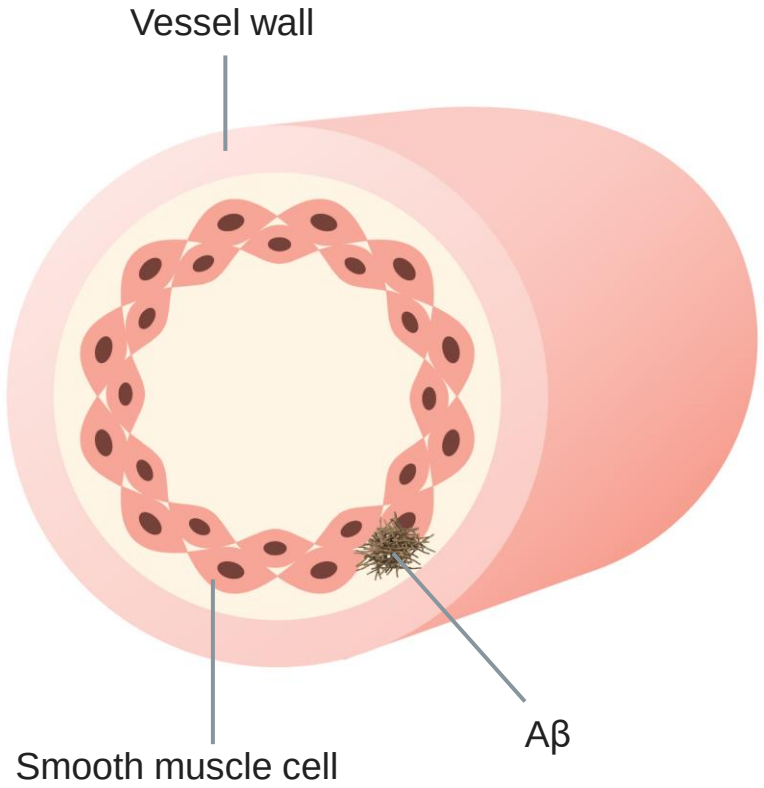
Neuroimaging findings that may indicate CAA include evidence of intracerebral hemorrhage, cerebral microhemorrhage, and cortical superficial siderosis. CAA has an increased risk for intracerebral hemorrhage[1,4]

Aβ=Amyloid Beta; *APOE* ε4=Apolipoprotein E Allele 4; ARIA=Amyloid-Related Imaging Abnormalities; ARIA-H=Amyloid-Related Imaging Abnormalities-Hemosiderin Deposition; ATT=Amyloid-Targeting Therapy; CAA=Cerebral Amyloid Angiopathy; mAb=Monoclonal Antibody; RBC=Red Blood Cell.

1. Greenberg SM, et al. *Nat Rev Neurol*. 2020;16(1):30-42. 2. Cogswell PM, et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19-E35. 3. Barakos J, et al. *J Prev Alzheimers Dis*. 2022;9(2):211-220.
4. Pinho J, et al. *Cerebrovasc Dis Extra*. 2021;11(1):15-21.

Cerebral Amyloid Angiopathy (CAA)

Physiological Perivascular Aβ Clearance

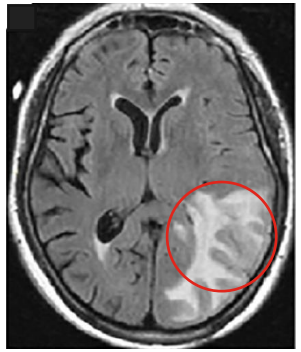
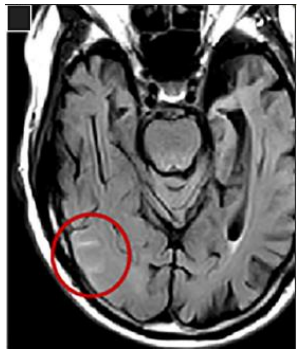
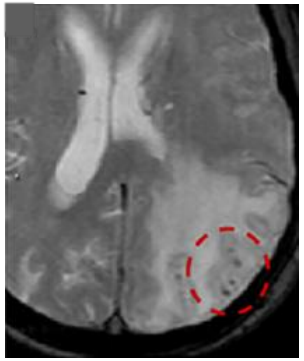
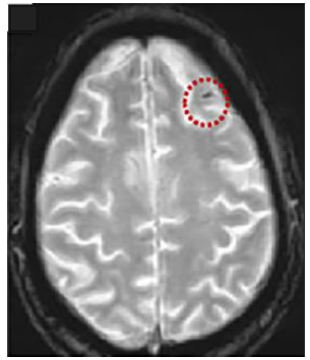


- CAA is the **pathogenic deposition of amyloid in cerebral microvasculature**[1]
- Although CAA is a major cause of intracerebral hemorrhage in the elderly and an independent cause of cognitive impairment and dementia, it is a comorbid condition, that may occur alongside AD and other dementias like DLB[2-4]
- CAA-related inflammation (CAA-ri) is a rare autoimmune encephalopathy associated with[2]:
  - Elevated CSF concentrations of spontaneous anti-Aβ autoantibodies
  - Transient focal areas of swelling (ie, ARIA-E)
  - CAA-related microhemorrhage (ie, ARIA-H)
- Evidence suggests that drug-induced ARIA may represent the iatrogenic form of CAA-ri[2]

Aβ=Amyloid Beta; AD= Alzheimer's Disease; ARIA-E=Amyloid-Related Imaging Abnormalities-Edema; ARIA-H=Amyloid-Related Imaging Abnormalities-Hemosiderin Deposition; CAA=Cerebral Amyloid Angiopathy; CSF=Cerebrospinal Fluid; DLB= Dementia with Lewy Bodies.

1. Greenberg SM, et al. *Nat Rev Neurol*. 2020;16(1):30-42. 2. Zedde M, et al. *Am J Neuroradiol.* 2023;44(2):E13-E14. 3. Bruce SS, Parikh NS. *Current Treatment Options in Neurology*. 2023;25(7):187-197. 4. Walker L, et al. *Acta Neuropathol Commun*. 2024;12(1):28.

Main Characteristics of ARIA

	ARIA-E[1-3]		ARIA-H[1-3]	
Leakage product	Proteinaceous fluids		Blood-degradation products	
Imaging[a]	T2 FLAIR		T2*GRE and/or SWI	
Location	**Parenchyma**	**Leptomeninges**	**Parenchyma**	**Leptomeninges**
	 Example of vasogenic edema	 Example of sulcal effusion	 Example of microhemorrhages	 Example of superficial siderosis

[a]Primary diagnostic imaging sequence.[1]

ARIA=Amyloid-Related Imaging Abnormalities; ARIA-E=Amyloid-Related Imaging Abnormalities-Edema; ARIA-H=Amyloid-Related Imaging Abnormalities-Hemosiderin Deposition; FLAIR=Fluid-Attenuated Inversion Recovery; GRE=Gradient-Recalled Echo; SWI=Susceptibility-Weighted Imaging.

1. Barakos J, et al. *Am J Neuroradiol.* 2013;34(10):1958-1965. 2. Barakos J, et al. *J Prev Alzheimers Dis*. 2022;9(2):211-220. 3. Cogswell PM, et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19-E35.

Detecting ARIA: MRI Protocol Recommended by the ASNR

Imaging protocol standardization is necessary to ensure consistent accuracy for diagnosing ARIA, and specific parameters are needed to achieve cross-platform standardization[1]

3T scanner (recommended); 1.5T scanner (minimal)[2,3]	High-field scanners have greater sensitivity but limited availability. The use of 1.5T is endorsed as a minimum standard
Slice thickness: ≤5 mm[2]	Thinner slices increase resolution but should be balanced against the loss in signal-to-noise ratio
TE: ≥20 ms[2,3]	Longer TE increases sensitivity to detection
2D T2*GRE or SWI (for ARIA-H)[2-4]	T2*GRE and SWI MRI sequences are used to improve detection and visualization of superficial siderosis and microhemorrages
T2 FLAIR (for ARIA-E)[2,4]	To monitor brain edema or sulcal effusion (ARIA-E)
DWI[3]	Recommended for differential diagnosis
T1-weighted 3D[4]	Allows hippocampal volumetric calculations

ARIA=Amyloid-Related Imaging Abnormalities; ARIA-E= Amyloid-Related Imaging Abnormalities-Edema; ARIA-H= Amyloid-Related Imaging Abnormalities-Hemosiderin Deposition; ASNR=American Society of Neuroradiology; DWI=Diffusion-Weighted Imaging; FLAIR=Fluid-Attenuated Inversion Recovery; GRE=Gradient-Recalled Echo; MRI=Magnetic Resonance Imaging; SWI=Susceptibility-Weighted Imaging; TE=Time to Echo.

1. Pinter NK, et al. *Alzheimers Dement*. 2022;18(Suppl. 1):e065618. 2. Sperling RA, et al. *Alzheimer's Dement.* 2011;7:367-385. 3. Cogswell PM, et al. *AJNR Am J Neurol.* 2022;43:e19-35. 4. Barakos J, et al. *AJNR Am J Neuroradiol*. 2013;34(10):1958-1965.

ARIA MRI Radiographic Severity Classification Criteria

ARIA Type		Radiographic Severity[a]		
		Mild	Moderate	Severe
ARIA-E	Sulcal and/or cortical/subcortical FLAIR hyperintensity	1 location <5 cm	1 location 5-10 cm OR >1 location each <10 cm	≥1 location >10 cm
ARIA-H	Microhemorrhage[b]	≤4	5-9	≥10
	Superficial siderosis	1 focal area	2 focal areas	>2 focal areas

Note: Lobar macrohemorrhage (focus of hemorrhage identifiable on T1- or T2-weighted imaging, and usually >10 mm in diameter on GRE) rarely occurs with anti-amyloid agents, and when it does, it may be the result of an underlying disease process such as CAA.

[a]ARIA is graded on the basis of treatment-emergent events. For ARIA-H, this count includes cumulative new microhemorrhages/regions of superficial siderosis compared with the baseline, pre-treatment examination.

[b]Microhemorrhages are punctate, rounded, and markedly hypointense foci in the brain parenchyma on T2* sequences, measuring <10 mm in diameter.

ARIA=Amyloid-Related Imaging Abnormalities; ARIA-E= Amyloid-Related Imaging Abnormalities-Edema; ARIA-H= Amyloid-Related Imaging Abnormalities-Hemosiderin Deposition; CAA=Cerebral Amyloid Angiopathy; FLAIR=Fluid-Attenuated Inversion Recovery; GRE= Gradient-Recalled Echo; MRI=Magnetic Resonance Imaging.

Cogswell PM, et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19-E35.

Clinical Manifestations and Outcomes of ARIA-E and -H

ARIA-E and -H are most frequently detected on protocol-specified, surveillance MRI scans in patients who are clinically asymptomatic[1]

Symptoms of ARIA may include[2-4]:

Headache

Confusion/ dizziness

Nausea

Less frequent

Gait disturbance

Visual symptoms/ blurred vision

Rare

Seizure, status epilepticus, encephalopathy, stupor, focal neurological deficits

ARIA-E typically resolves over time with treatment pause or withdrawal[1]

ARIA-H hemosiderin deposition typically does not resolve[1]

ARIA=Amyloid-Related Imaging Abnormalities-Edema; ARIA-E=Amyloid-Related Imaging Abnormalities-Edema; ARIA-H=Amyloid-Related Imaging Abnormalities-Hemosiderin Deposition; MRI=Magnetic Resonance Imaging.

1. Cogswell PM, et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19-E35. 2. Cummings J, et al. *J Prev Alzheimers Dis.* 2021;8(4):398-410. 3. Cummings J, et al. *J Prev Alzheimers Dis*. 2022;9(2):221-230.
4. Cummings J, et al. *J Prev Alzheimers Dis*. 2023;10(3):362-377.

Timeframe of ARIA Across the Treatment Course

ARIA tends to be asymptomatic, **occur early in the treatment course**, and resolve following dose adjustment or treatment discontinuation, although serious and life-threatening events rarely can occur[1-4]

- Serious intracerebral hemorrhages >1 cm, some of which have been fatal, and observed in patients treated with this class of medications[3,4]
- Treatment may be continued if the ARIA case is mild on MRI and asymptomatic; radiographically moderate or severe ARIA may warrant treatment suspension[3-5]

Occurrence of ARIA appears to **decrease** with ongoing amyloid-targeting mAb treatment but may occur at anytime during the treatment[1]

Approximately **80%** of ARIA-E cases have been observed to have resolved within **16-20 weeks**[4-6]

The long-term impact of ARIA is yet to be elucidated, and no formal decision-making guidelines currently exist for the management and treatment of ARIA[3,6,7]

Note: Refer to product prescribing information for specific dosing recommendations for ARIA.
ARIA=Amyloid-Related Imaging Abnormalities; ARIA-E=Amyloid-Related Imaging Abnormalities-Edema; ARIA-H=Amyloid-Related Imaging Abnormalities-Hemosiderin Deposition; mAb=Monoclonal Antibody; MRI=Magnetic Resonance Imaging.

1. Barakos J, et al. *J Prev Alzheimers Dis*. 2022;9(2):211-220. 2. Filippi M, et al. *JAMA Neurol*. 2022;79(3):291-304. 3. Lecanemab [US PI]. Nutley, NJ, USA: Eisai Inc. and Biogen, 2025. 4. Donanemab [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 2024. 5. Withington CG, Turner RS. *Front Neurol*. 2022;13:862369. 6. Salloway S, et al. *JAMA Neurol*. 2022;79(1):13-21. 7. Sperling RA, et al. *Alzheimers Dement*. 2011;7(4):367-385.

Management of Severe ARIA

If severe ARIA is identified, recommendations include:

Prompt MRI to identify ARIA changes

DWI sequences should be included to rule out ischemic stroke

Admission to the hospital or a critical care unit with access to clinicians experienced in the management of ARIA

Early initiation of high-dose glucocorticoids may be considered

Monitoring for seizures and treatment if needed

ARIA=Amyloid-Related Imaging Abnormalities; DWI=Diffusion-Weighted Imaging; MRI=Magnetic Resonance Imaging.

Cummings J, et al. *J Prev Alzheimers Dis*. 2023;10(3):362-377.

Differential Diagnosis of ARIA: Acute Ischemic Stroke

Signs/symptoms

Acute onset, unilateral weakness, speech disturbance, headache, paresis, dysphasia/dysarthria, gait abnormalities[1]

Imaging

Parenchymal FLAIR hyperintensity of ischemic stroke may resemble ARIA-E[2]

- Diffusion-weighted imaging can differentiate between ARIA-E and ischemic stroke[2]

Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with an ATT[3]

ARIA should be considered a highly likely diagnosis when[2]:

- MRI signal abnormalities suggestive of ARIA-E or ARIA-H are evident
- The patient has recently been exposed to an ATT
- No evidence of any other underlying cause or lesion can be identified

Note: Information presented constitutes a general diagnostic approach to be considered. Individual clinicians' judgment and results of other clinical, laboratory, or radiographic assessments may be indicated as part of the differential diagnosis process. Consultation with neurology specialists for a multidisciplinary evaluation is advised.

ARIA=Amyloid-Related Imaging Abnormalities; ARIA-E=Amyloid-Related Imaging Abnormalities-Edema; ARIA-H=Amyloid-Related Imaging Abnormalities-Hemosiderin Deposition; ATT=Amyloid-Targeting Therapy; FLAIR=Fluid-Attenuated Inversion Recovery.

1. Yew KS, Cheng EM. *Am Fam Physician*. 2015;91(8):528-536. 2. Barakos J, et al. *AJNR Am J Neuroradiol*. 2013;34(10):1958-1965. 3. Donanemab [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 2024.

Other Differential Diagnoses of ARIA

Subarachnoid Hemorrhage

Signs/symptoms	Acute, sudden onset headache, neck pain/stiffness, altered consciousness[1]
Imaging	Leptomeningeal FLAIR hyperintensity of subarachnoid hemorrhage may resemble ARIA-E effusion[2]

Posterior Reversible Encephalopathy Syndrome (PRES)/Reversible Cerebral Vasoconstriction Syndrome (RCVS)

Signs/symptoms	PRES: Visual disturbance, headache, seizures, impaired consciousness[3] RCVS: Nausea, photophobia, and phonophobia[4]
Imaging	PRES closely resembles ARIA-E due to parenchymal and leptomeningeal involvement[2] Imaging of patients with RCVS may look healthy or show lesions[4]

Cerebral Amyloid Angiopathy-Related Inflammation (CAA-ri)

Signs/symptoms	From mild cognitive disturbances and headache to rapidly progressive decline and seizures[5]
Imaging	Unifocal/multifocal areas of subcortical vasogenic edema with mild mass effect; background of cerebral amyloid angiopathy (microhemorrhages, siderosis, and chronic parenchymal hematoma)[5]

Note: Information presented constitutes a general diagnostic approach to be considered. Individual clinicians' judgment and results of other clinical, laboratory, or radiographic assessments may be indicated as part of the differential diagnosis process. Consultation with neurology specialists for a multidisciplinary evaluation is advised.

ARIA=Amyloid-Related Imaging Abnormalities; ARIA-E= Amyloid-Related Imaging Abnormalities-Edema; FLAIR=Fluid-Attenuated Inversion Recovery; PRES=Posterior Reversible Encephalopathy Syndrome; RCVS=Reversible Cerebral Vasoconstriction Syndrome.

1. Patel S, et al. *Int J Emerg Med*. 2021;14(1):31. 2. Barakos J, et al. *AJNR Am J Neuroradiol.* 2013;34(10):1958-1965. 3. Triplett JD, et al. *Pract Neurol*. 2022;22(3):183-189. 4. Ducros A. *Lancet Neurol*. 2012;11(10):906-917. 5. Agarwal A, et al. *Radiographics*. 2023;43(9):e230009.

Roles of Emergency Care in the ATT Clinical Workflow

Key challenge

There are currently **no evidence-based clinical policies or care guidelines for pre-hospital and ED management of ARIA**. Collaboration between emergency physicians and specialists in the patient journey is needed for the development and implementation of protocols to identify and manage suspected ARIA[1]

	Before a patient presents with ARIA	When a patient presents with ARIA
Patient screening and assessment	Implement a plan to accurately identify patients receiving ATTs[1]	Ensure patients receive timely and appropriate assessments and consultations[1]
Imaging considerations	Develop a plan together with MDT regarding[1-3]: • Appropriate and consistent imaging protocols for patients on ATTs • What to do if MRI is not readily available	When determining ARIA on neuroimaging consider the following, if available[1,2]: • History of ATT use or previous episodes of ARIA • Access to pre-treatment imaging results, if available • Differential diagnosis of ARIA-E vs. ischemic stroke
Treatment considerations	Develop a protocol for patients who present with signs of stroke[1]	Discuss the risk vs. benefit of thrombolytics and make a decision on whether to administer[1]
Plan	**ARIA admission plan:** Develop protocols to address emergency concerns and triage patients who develop neurologic signs and symptoms while on treatment, including when and where to seek ED evaluation[1]	**ARIA follow-up:** Communicate any ARIA findings to referring physicians to ensure optimal patient management[3]

ARIA=Amyloid-Related Imaging Abnormalities; ARIA-E= Amyloid-Related Imaging Abnormalities-Edema; ATT=Amyloid-Targeting Therapy; ED=Emergency Department; MDT=Multidisciplinary Team; MRI=Magnetic Resonance Imaging.

1. Lo AX, et al. *J Am Geriatr Soc.* 2024;72(12):3945-3949. 2. Barakos J, et al. *J Prev Alzheimers Dis*. 2022;9(2):211-220. 3. Cogswell PM, et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19-E35.

Back to Home

Infusion-Related Reactions: Background, Identification, and Management

What Are Infusion-Related Reactions?

Infusion-related reactions (IRRs) are immune responses to a drug infusion (eg, during treatment with ATTs or chemotherapy)[1-4]

IRRs caused by ATTs **usually occur during a patient's first session** but can occur at any time during the course of treatment[2-4]

IRR symptoms typically occur **during** or **within 24 hours** of the infusion[1]

In general, the **risk** of an IRR **declines with each infusion**[5]

ATTs can trigger the production of IgGs, which may cause serious adverse immune reactions[6]

In severe cases, such as anaphylaxis, IRRs can be life-threatening, so knowing how to quickly recognize and respond is critical for patient safety[1,2]

Note: Hypersensitivity reactions to individual ATTs represent a contraindication to treatment.[3,4] Please refer to product prescribing information for additional information.
ATT=Amyloid-Targeting Therapy; Ig=Immunoglobulin; IRR=Infusion-Related Reactions; IV=Intravenous.

1. Doessegger L, Banholzer ML. *Clin Transl Immunol.* 2015;4(7):e39. 2. Lenz HJ. *Oncologist*. 2007;12(5):601-609. 3. Lecanemab [US PI]. Nutley, NJ, USA: Eisai Inc. and Biogen, 2025. 4. Donanemab [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 2024. 5. https://www.uptodate.com/contents/infusion-related-reactions-to-therapeutic-monoclonal-antibodies-used-for-cancer-therapy (Accessed February 21, 2025). 6. Vaisman-Mentesh A, et al. *Front Immunol*. 2020;11:1951.

Signs and Symptoms of an IRR in the Context of ATT

The symptoms of IRRs can be diverse, including, but not limited to:

Cardiovascular issues

- Tachycardia
- Hypo/hypertension

Skin changes

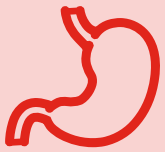
- Urticaria
- Rash
- Erythema
- Pruritus

Respiratory difficulties

- Bronchospasm
- Shortness of breath

Pain

- Headache
- Myalgia
- Chest pain



Gastrointestinal upset

- Nausea
- Vomiting

Other abnormalities

(eg, fever, fatigue)

ATT=Amyloid-Targeting Therapy; IRR=Infusion-Related Reaction.

Doessegger L, Banholzer ML. *Clin Transl Immunol.* 2015;4(7):e39.

Example Algorithm for IRR Management

1 Prior to the infusion[1]

- **Assess history for risk factors**
- Ensure appropriate pre-medications taken/given at the specified time periods
- Updated IRR protocol (including standing orders) and medical equipment/ supplies needed for resuscitation must be available
- Educate patient and caregiver about signs and symptoms of IRRs

2 Upon recognition of reaction and assessment of reaction severity[1]

Mild or moderate reactions

- **Stop or slow infusion**

Severe or life-threatening reactions

- **Stop infusion and assess for anaphylaxis** – follow anaphylaxis guidelines

- Have someone call for medical assistance
- Maintain IV line with normal saline or other appropriate solution
- Assess vitals and level of consciousness regularly
- Position patient appropriately
- Administer oxygen, if required
- Administer PRN medications

3 Symptom treatment[1]

- Apply symptomatic treatment (eg, antipyretic for fever, saline for hypotension, etc.)

4 After symptom resolution[1]

Mild or moderate reactions

- **Consider restart and re-challenge at a reduced rate with pre-medications**

Severe or life-threatening reactions

- **Restarting treatment with ATTs after anaphylaxis or serious hypersensitivity reactions is contraindicated[2,3]**

Note: Please refer to product prescribing information for additional information. **This algorithm for the acute management of IRRs is an example built for educational purposes only. Organization's treatment-specific standing orders for the monitoring and management of IRRs should be followed.** Severity grading according to the NCI Common Terminology Criteria for Adverse Events version 5.0 (November 2017).[4] AE=Adverse Event; ATT-Amyloid-Targeting Therapy; Ig=Immunoglobulin; IRR=Infusion-Related Reaction; PRN=Pro Re Nata (ie, As Needed).

1.https://canadacommons.ca/artifacts/4816352/management-of-cancer-medication-related-infusion-reactions/5652995/ (Accessed February 18, 2025). 2. Lecanemab [US PI]. Nutley, NJ, USA: Eisai Inc. and Biogen, 2025. 3. Donanemab [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 2024. 4. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf (Accessed February 18, 2025).

Difference Between an IRR and a Delayed Hypersensitivity Reaction

- Most adverse reactions to mAb infusions occur within the first 24h[1]
- Some of the commonly reported IRR and hypersensitive reactions with mAb infusions in ATT are[2,3]:
  - **IRR:** Chills, generalized aches, headaches, chest pain, hypertension, difficulty breathing, nausea/vomiting, and skin reactions
  - **Hypersensitive reactions:** Angioedema, bronchospasm, and anaphylaxis
- Delayed hypersensitivity reactions (typically arising from 12h to several weeks after mAb infusion) have been reported after approximately 3%[a] of first infusions[4]
  - They may also occur at subsequent infusions (reported during 4%[a] of desensitization protocols)[4]
  - These can be severe, and therefore it is important for patients to monitor themselves and remain vigilant for several weeks after infusion[4]

Hypersensitivity – an **exaggerated** response of the **immune system** to an antigen[6]

IRR – any immune response to a drug infusion, which typically occurs **during** or **within 24h** of the infusion[5]

Immediate hypersensitivity reaction[b]: occurs **within 24h** of exposure[6] (**an IRR**)

Delayed hypersensitivity reaction[c]: Usually occurs **more than 12h after** exposure, with a maximal reaction time between 48h and 72h[6] (**not an IRR**)

[a]Retrospective study of hypersensitivity reactions to 16 mAbs in 104 patients who received mAb desensitization as part of standard of care.[4] [b]Coombs and Gell Types I-III reactions, mediated by IgE, IgG, IgM, or immune complexes.[6] [c]Coombs and Gell Type IV reactions, mediated by T-cells.[6]

ATT=Amyloid-Targeting Therapy; Ig=Immunoglobulin; IRR=Infusion-Related Reaction; mAb=Monoclonal Antibody.

1. Galateanu B, et al. *Int J Mol Sci.* 2023;24(4):3886. 2. Donanemab [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 2024. 3. Lecanemab [US PI]. Nutley, NJ, USA: Eisai Inc. and Biogen, 2025 4. Isabwe GAC, et al. *J Allergy Clin Immunol*. 2018;142(1):159-170. 5. Doessegger L, Banholzer ML. *Clin Transl Immunol.* 2015;4(7):e39. 6. Marwa K, Kondamudi NP. StatPearls. Treasure Island (FL): StatPearls Publishing. 2023.

Anaphylaxis can be an IRR

IRRs

- Any immune response to a drug infusion, which typically occurs **during** or **within 24 hours** of the infusion

Anaphylaxis

- **Severe**, systemic hypersensitivity reaction, characterized by being **rapid in onset (minutes to several hours)** with **life-threatening airway, breathing, or circulatory problems**
- Usually associated with skin and mucosal changes (~80% of cases)
- Allergic in nature (ie, mediated by IgE)

Sampson criteria

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:

- **Acute onset of an illness** (minutes to several hours) with **involvement of the skin, mucosal tissue, or both** (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
  - Respiratory compromise
  - Reduced BP or associated symptoms of end-organ dysfunction
- Two or more of the following that occur rapidly after **exposure to a likely allergen** for that patient (minutes to several hours):
  - Involvement of the skin-mucosal tissue
  - Respiratory compromise
  - Reduced BP or associated symptoms
  - Persistent gastrointestinal symptoms
- Reduced BP[a] after **exposure to known allergen** for that patient (minutes to several hours)

[a]Low SBP (age-specific values) or >30% SBP decrease from baseline.
BP=Blood Pressure; IgE=Immunoglobulin E; IRR=Infusion-Related Reaction; SBP=Systolic Blood Pressure.
Doessegger L, Banholzer ML. *Clin Transl Immunol.* 2015;4(7):e39.

Summary (1 of 3)

Alzheimer's Disease (AD) and Amyloid-Targeting Therapies (ATTs)

- **AD is a progressive neurodegenerative disease** characterized by amyloid plaques, neurofibrillary tangles, neuroinflammation, and neurodegeneration[1,2]

- **Treatment options for AD include** non-pharmacologic/behavioral interventions, symptomatic therapy, and **disease-modifying treatments (including ATTs)**[3-5]

- **Several healthcare providers** comprise the core multidisciplinary team within the **ATT clinical workflow**[6-13]

  – **Patients may seek emergency department services for ATT-related adverse events** such as amyloid-related imaging abnormalities and other adverse treatment reactions[14]

1. Jack CR Jr, et al. *Lancet Neurol*. 2010;9(1):119-128. 2. Koper MJ, et al. *Acta Neuropathologica*. 2020;139:463-484. 3. Li X, et al. *Neurol Ther*. 2023;12(1):39-72. 4. Huang LK, et al. *J Biomed Sci*. 2023;30(1):83. 5. Cummings J. *Mol Neurodegener*. 2021;16(1):2. 6. de Levante Raphael D. *Medicina (Kaunas)*. 2022;58(7):906. 7. https://www.alz.org/getmedia/76e51bb6-c003-4d84-8019-e0779d8c4e8d/alzheimers-facts-and-figures.pdf (Accessed February 18, 2025). 8. Hampel H, et al. *Neuron*. 2023;111(18):2781-2799. 9. https://alz.org/media/Documents/alzheimers-facts-and-figures-special-report-2023.pdf (Accessed February 15, 2025). 10. Galvin JE, et al. *Front Neurol.* 2021;11:592302. 11. Grand JH, et al. *J Multidiscip Healthc.* 2011;4:125-147. 12. Galvin JE, et al. *Neurodegener Dis Manag*. 2014;4(6):455-469. 13. Teipel S, et al. *J Nucl Med.* 2022;63(7):981-985. 14. Lo AX, et al. *J Am Geriatr Soc.* 2024;72(12):3945-3949.

Summary (2 of 3)

Amyloid-Related Imaging Abnormalities (ARIA)

- **ARIA are a spectrum of MRI signal abnormalities** associated with amyloid clearance in the brain[1-3]
  - **ATTs carry a boxed warning for ARIA**[4,5]
  - ARIA usually occur **early in treatment** and are **usually asymptomatic**, although **serious and life-threatening events rarely can occur**[4,5]
- **Ongoing monitoring** for ARIA via MRI is crucial during treatment with ATTs.[6] ARIA is best visualized on MRI[7]
- CT is not sufficient for differential diagnosis of ARIA as its use is limited to detection of milder forms of ARIA-E and insensitive to the detection of ARIA-H[8]
- **ARIA-E** can cause focal neurologic deficits that **can mimic an ischemic stroke**[5]
  - Clinicians should **consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy** in a patient being treated with an ATT[5]

ARIA=Amyloid-Related Imaging Abnormalities; ARIA-E=Amyloid-Related Imaging Abnormalities-Edema; ARIA-H=Amyloid-Related Imaging Abnormalities-Hemosiderin Deposition; ATT=Amyloid-Targeting Therapy; MRI=Magnetic Resonance Imaging.

1. Salloway S, et al. *JAMA Neurol*. 2022;79(1):13-21. 2. Filippi M, et al. *JAMA Neurol.* 2022;79(3):291-304. 3. Sperling RA, et al. *Alzheimers Dement.* 2011;7(4):367-385. 4. Lecanemab [US PI]. Nutley, NJ 07110, USA: Eisai Inc. and Biogen, 2025. 5. Donanemab [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 2024. 6. Cogswell PM, et al. *AJNR Am J Neuroradiol.* 2022;43(9):E19-E35. 7. Salloway S, et al. *JAMA Neurol*. 2025;82(1):19-29. 8. Barakos J, et al. *J Prev Alzheimers Dis*. 2022;9(2):211-220.

Summary (3 of 3)

Infusion-Related Reactions (IRRs)

- **IRRs typically occur within 24 hours of monoclonal antibody infusion** and may happen during any treatment session[1,2]
- **Risk of IRRs generally declines with each infusion**[3]
- In severe cases, **IRRs can be life-threatening**; knowing how to quickly **recognize and respond is critical for patient safety**[1,2]

1. Doessegger L, et al. *Clin Transl Immunol*. 2015;4(7):e39. 2. Lenz HJ. *Oncologist*. 2007;12(5):601-609. 3. https://www.uptodate.com/contents/infusion-related-reactions-to-therapeutic-monoclonal-antibodies-used-for-cancer-therapy (Accessed February 21, 2025).