In patients with atypical-HUS

Thrombotic microangiopathy (TMA) is an ever-present risk[1]

Understand the risks for TMA recurrence

Patients living with atypical-HUS can be at continuous risk of the life-threatening consequences of uncontrolled complement-mediated TMA.[2]

Identify genetic mutations

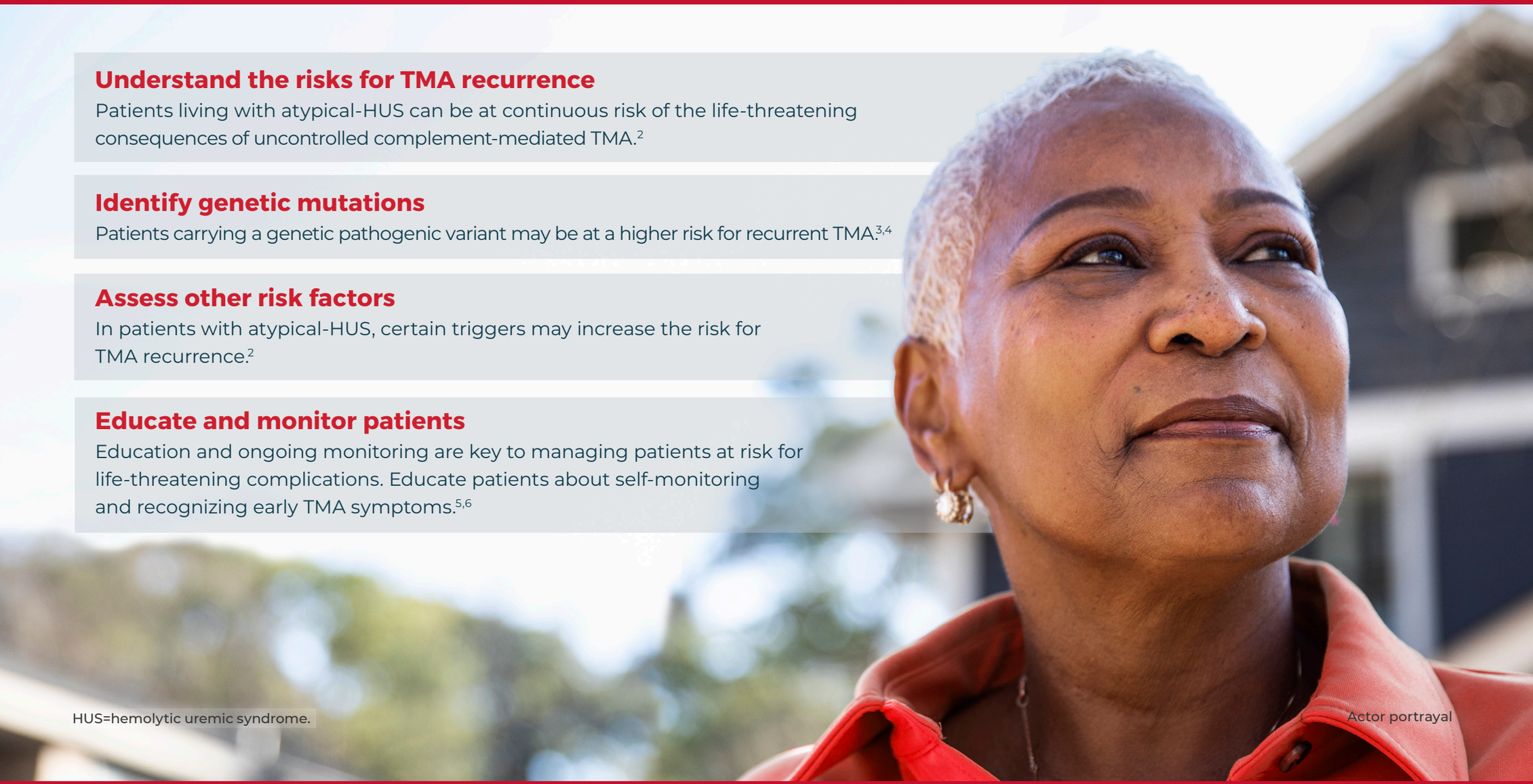
Patients carrying a genetic pathogenic variant may be at a higher risk for recurrent TMA.[3,4]

Assess other risk factors

In patients with atypical-HUS, certain triggers may increase the risk for TMA recurrence.[2]

Educate and monitor patients

Education and ongoing monitoring are key to managing patients at risk for life-threatening complications. Educate patients about self-monitoring and recognizing early TMA symptoms.[5,6]



HUS=hemolytic uremic syndrome.

Actor portrayal

aHUS Source

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For many patients with atypical-HUS, the risks of severe and life-threatening TMA recurrence are potentially lifelong[1,2]

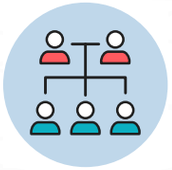
Certain factors may increase the risk for TMA recurrence

Identified genetic mutation

Mutations in complement genes have been associated with higher risk of TMA[3,4,7]

Clinical history of TMA

Multiple TMA manifestations suggest high risk for subsequent TMA in the presence of complement-triggering conditions[3,7]



Family history of TMA or renal disease

Patients with a family history of TMA or renal disease have a higher rate of disease progression; the rate of ESRD or death has been reported to be between 50% and 80%[4,8]

History of renal transplant

Patients with certain genetic mutations are at a higher risk for TMA recurrence following renal transplantation[9]

Pediatric onset

Children are considered to be at high risk due to the increased frequency of complement-activating events such as infections and vaccinations; TMA recurrence was reported to be high in untreated pediatric-onset patients[7,10]

Complement biomarkers/levels

Increased serum C5b-9 plasma levels in unmanaged patients with atypical-HUS has been associated with a higher risk of relapse[11]

Susceptibility or exposure to triggers

Patients who experience triggers such as malignant hypertension or complications from pregnancy, including miscarriages, preeclampsia, HELLP syndrome, and others, are at increased risk for recurrent TMA[12,13]

Following diagnosis, patients remain at risk for severe TMA recurrence

Consider genetic testing

Genetic testing can aid in providing guidance around disease management. Approximately 60% to 70% of patients with atypical-HUS have an identified genetic mutation[2,14-17]

Assess other risks

Triggers such as the ones mentioned above may put patients at a higher risk for severe TMA recurrence[2,14]

Understanding TMA in atypical-HUS

- Atypical-HUS is a life-threatening condition driven by overactivation of the complement system[2,14]
- Patients with atypical-HUS can be at continuous risk for the severe and life-threatening consequences of TMA[2]
- Approximately 50% of patients with atypical-HUS progress to ESRD within a year; 25% die during the acute stage of the disease despite extensive PE[14]
- Approximately 25% to 30% of unmanaged patients who have had a TMA manifestation will experience relapse; there are other risk factors that increase that probability[7,10]
- Therefore, understanding patients' risk of TMA recurrence will help in assessing prognosis

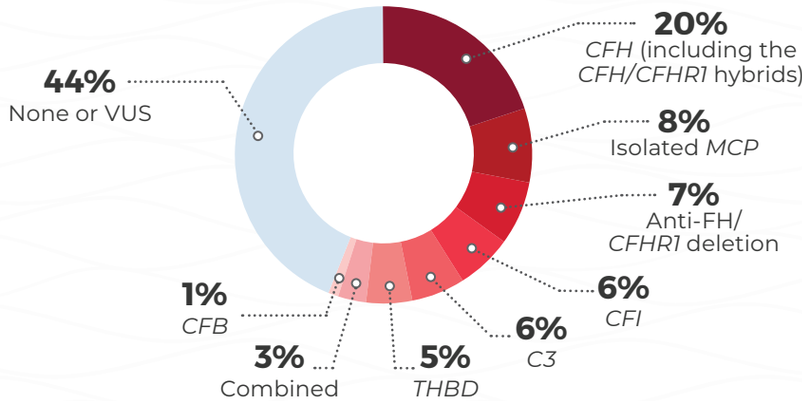
ESRD=end-stage renal disease; HELLP=hemolysis, elevated liver enzymes, low platelet counts; HUS=hemolytic uremic syndrome; PE=plasma exchange; TMA=thrombotic microangiopathy.

In atypical-HUS, certain genetic mutations may impact patients' prognoses

Understand the role of genetics in atypical-HUS

- Atypical-HUS develops because of a **predisposition for complement dysregulation** and/or exposure to **factors that trigger complement activation**[2,14,18,19]
- Pathologic gene mutations or autoantibodies contributing to the underlying complement dysregulation are identified in **approximately 60% to 70% of patients with atypical-HUS**[1,15-17,20,21]
- In **approximately 40% of patients with atypical-HUS**, no underlying genetic mutations have been identified[16]
- However, as **mutations continue to be discovered**, some of these individuals may prove to have a genetic component[22,23]

Percentages of genetic mutations identified in patients with atypical-HUS[13,20,21]



Adapted from Noris M, et al. *Clin J Am Soc Nephrol.* 2010;5(10):1844-1859 and Bresin E, et al. *J Am Soc Nephrol.* 2013;24(3):475-486.

Patients with atypical-HUS carrying certain genetic mutations experience poorer prognoses[9,24]

- **Patients with identified mutations are associated with a higher risk** of TMA recurrence, ESRD progression, and death within the next year after the first episode[9,24]
- **The risk of TMA recurrence is increased after a renal transplant** in certain mutations[9,24]

Clinical outcomes of patients with atypical-HUS carrying identified genetic mutations[9,24]

Gene	Risk of death or ESRD within the next year after first episode	Risk of TMA recurrence	Risk of TMA recurrence after renal transplant
CFH	50%-70%	50%	75%-90%
MCP	0%-6%	70%-90%	<20%
Anti-FH	30%-40%	40%-60%	Higher with increased antibody titers
CFI	50%	10%-30%	45%-80%
C3	60%	50%	40%-70%
THBD	50%	30%	1 patient
CFB	50%	3/3 without ESRD	100%

Adapted from Abbas F, et al. *World J Transplant*. 2018;8(5):122-141 and Campistol JM, et al. *Nefrologia*. 2015;35(5):421-447.

Genetic testing may be a valuable prognostic tool for managing patients with atypical-HUS.[2,13] However, as **about 40% of patients with atypical-HUS** do not have an identified genetic mutation, genetic testing for diagnosis can have limitations.[2,14]

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; anti-FH=anti-complement factor H antibodies; *C3*=complement component 3; *CFB*=complement factor B; *CFH*=complement factor H; *CFHR1*=complement factor H-related protein 1; *CFI*=complement factor I; ESRD=end-stage renal disease; HUS=hemolytic uremic syndrome; *MCP*=membrane cofactor protein; *THBD*=thrombomodulin; TMA=thrombotic microangiopathy; VUS=variants of unknown significance.

Monitoring is crucial for managing TMA recurrence in patients with atypical-HUS

Patients with atypical-HUS are at continuous risk for TMA relapse

- Approximately 25% to 30% of patients with untreated atypical-HUS experience recurrent TMA[7,10]
- The risk is approximately 2 to 3 times higher in patients with a genetic pathogenic variant[3,7,10,11,25]
- Molecular genetic testing such as a sequence analysis or a gene-targeted deletion/duplication analysis can inform patients of the mode of inheritance and aid clinicians in disease management[15,16]

Assess biomarkers to evaluate level of risk

Increased serum C5b-9 plasma levels in unmanaged patients with atypical-HUS has been associated with a higher risk of relapse[11]

Ongoing follow-up is necessary for all patients with atypical-HUS

- Assess patients' genetic mutations, family history of TMA, renal impairment, and other risk factors such as pediatric onset or pregnancy[7,10]
- Educate patients on early TMA symptoms and regular monitoring of proteinuria using urine dipsticks[4-6]
- In patients with atypical-HUS, monitor TMA complications such as thrombosis, angina, seizures, dyspnea, or increasing blood pressure[7]
- Monitor any change of ≥25% from baseline in 2 or more of the following lab values: increase and > ULN in serum LDH or in sCr levels, and decrease and < LLN in platelet count[4,7]

Education and ongoing monitoring are key to managing patients at risk for life-threatening complications of TMA.[4]

Speak to your Alexion representative to learn more. If you are unsure who your Alexion representative is, you can call **1-833-551-2539,** or visit **aHUSSource.com/physician** to learn more about atypical-HUS.

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The information in this presentation is intended as educational information for healthcare professionals. It does not replace a healthcare professional's judgment or clinical diagnosis.

HUS=hemolytic uremic syndrome; LDH=lactate dehydrogenase; LLN=lower limit of normal; sCr=serum creatinine; TMA=thrombotic microangiopathy; ULN=upper limit of normal.

Actor portrayal

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