deciphehr™
connecting the dots of rare disease

SUPPORTING SUSPECT PATIENT RECOGNITION FOR FURTHER CLINICAL EVALUATION

Atypical-HUS Program Implementation Guide

atypical-HUS= atypical hemolytic uremic syndrome.

deciphEHR™ provides educational resources to help health systems, hospitals, and specialty practices leverage their electronic health record (EHR) systems. Data from the EHR system may help triage suspect patients for further clinician evaluation.

ALEXION®
AstraZeneca Rare Disease

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Atypical-HUS is a difficult diagnosis to navigate, largely because there is not one definitive diagnostic test, numerous differentials, and a heterogenous disease presentation.[1,2]

Key Sections

Clinical Criteria for Atypical-HUS

1

Atypical hemolytic uremic syndrome (atypical-HUS) is a life-threatening, complement-mediated condition characterized by thrombotic microangiopathy (TMA).[1] Patients with atypical-HUS are at continuous risk of endothelial injury, end-organ damage, and mortality as a consequence of terminal complement overactivation.[3,4]

Atypical-HUS patients most frequently present in the ER or ICU with a complement-triggering condition that can potentially complicate the differential diagnosis such as[1,5,6]:

21.9%
Infections

18.9%
Malignancy

11.7%
Autoimmune disease
(eg, SLE, APS, scleroderma)

11.7%
Transplant
(organ/bone marrow)

8.5%
Malignant hypertension
or hypertensive emergency

1.3%
Certain prescription
medications or illicit drugs

Additional trigger events can include, but are not limited to[3]:

- Pregnancy/postpartum/HELLP/preeclampsia
- Surgery/trauma

ER=emergency room, ICU=intensive care unit, SLE=systemic lupus erythematosus, APS=antiphospholipid syndrome, HELLP=hemolysis, elevated liver enzymes, and low platelets.

1. TMAs manifest as thrombocytopenia, microangiopathic hemolysis, and organ involvement and must be confirmed prior to an atypical-HUS diagnosis.[1,7,8]

Suspect a TMA when a patient presents with:

Thrombocytopenia[3]

- Platelet count of less than 150,000 or a 25% decrease from baseline

Combined with microangiopathic hemolysis[3]

Evidence of one or more of the following:

- Schistocytes* on peripheral blood smear
- Elevated LDH
- Decreased haptoglobin
- Decreased hemoglobin

Combined with one or more of the following[3]

- Renal impairment
- Neurologic symptoms
- Gastrointestinal symptoms
- Cardiovascular symptoms
- Pulmonary symptoms
- Visual symptoms

Additionally, assessing patient and family history of TMA or renal impairment can indicate a possible TMA diagnosis.[1,9]

Disseminated intravascular coagulation (DIC) should be ruled out before TMA consideration based on normal coagulation profile (prothrombin time [PT], activated partial thromboplastin time [aPTT], and D-dimers).[1,3]

*The absence of schistocytes should NOT be used to exclude a TMA diagnosis.[3,10] If schistocytes are not identified in first assessment, peripheral blood smear should continue to be evaluated daily for several days.[3]

2. Once TMA is confirmed, a clinical diagnosis of atypical-HUS requires **exclusion of other TMAs.**[7]

Rule out:

Thrombotic thrombocytopenic purpura (TTP)	» TTP is characterized by a severe deficiency in ADAMTS13 (<5%-10%)[1]* » Accuracy of ADAMTS13 can be negatively impacted by plasma therapy, so it is advised to rapidly take a **peripheral blood sample to test for ADAMTS13** activity **PRIOR TO** intervention to ensure accurate test results[3] » In the absence of accurate ADAMTS13 results, platelet count combined with serum creatinine levels can be used to help differentiate TTP[3] ° Baseline platelet values >30 x 10^9/L OR serum creatinine >1.7 to 2.3 mg/dL, a diagnosis of TTP is almost eliminated[3] » PLASMIC score may also be used in the absence of a reliable ADAMTS13 test (see PLASMIC score section)[11-13]
Shiga toxin-HUS (STEC-HUS)	» Confirm negative for Shiga toxin/enterohemorrhagic *Escherichia coli* (EHEC) using polymerase chain reaction (PCR) assay, serology, or stool culture[1,3,4]
Cobalamin C deficiency	» Confirm normal homocysteine, methionine, methylmalonic acid using blood test to rule out Cobalamin C/Vitamin B12 deficiency[3,14]

*Depending on the assay.

LDH=lactate dehydrogenase, TMA=thrombotic microangiopathy, ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13.

PLASMIC score was developed to rapidly predict the presence of severe ADAMTS13 deficiency (<10%) using 7 commonly available clinical variables.[13,15]

- The presence of each item is given a score of 1 point, for a maximum score of 7[13]
- 0-4 = low risk of TTP, 5 = intermediate risk of TTP, 6-7 = high risk of TTP[13]
- A plasmic score of 0-4 should trigger suspicion of atypical-HUS[13]

Differential	Lab Test(s)
Platelet Count	Less than 30 x 10^9/L[13,15]
Hemo**L**ysis	Retic count >2.5% and/or Haptoglobin undetectable and/or Indirect bilirubin >2.0 mg/dL[13,15]
No **A**ctive Cancer	No evidence of cancer treatment in the past year[13,15]
No **S**tem Cell or Organ Transplant	No evidence of stem cell or solid organ transplant[13,15]
MCV	<90 fL[13,15]
INR	<1.5[13,15]
Creatinine	<2.0 mg/dL[13,15]

3. After atypical-HUS diagnosis you may use genetic testing for prognosis.

While genetics plays an important prognostic role in atypical-HUS, a **negative or inconclusive result does not effectively rule out atypical-HUS.**[1,3]

INR=international normalized ratio, MCV=mean corpuscular volume.

2

A Guide to Generating Suspect Atypical-HUS Patient Lists

In atypical-HUS, patients being undiagnosed or misdiagnosed can lead to morbidity and mortality.[1] This toolkit may help reduce the incidence of undiagnosed and misdiagnosed patients by utilizing the EHR and evidence-based diagnostic criteria to generate suspect patient lists, which may help increase awareness of suspect patients with atypical-HUS for further evaluation by HCPs.[16]

Suggested Clinical Criteria for Suspect Atypical-HUS Patient List

In an EHR system, a suspect patient list, also referred to as a patient list report, is a list of patients meeting certain clinical criteria. Generating a suspect patient list requires the same clinical criteria used to make an atypical-HUS diagnosis. In addition to creating a list of suspect atypical-HUS patients for further clinical evaluation, a suspect patient list can also be used to flag patient charts with a best practice alert to recommend atypical-HUS testing or clinical referral. Please see the chart below for guidance.

ALL PATIENTS

SIGNS AND SYMPTOMS OF **TMA**

Use the recommended codes listed in Appendix C Table 1 to filter for the following[3]:

- **Thrombocytopenia:**
  Platelet count <150 x 10^9/L or >25% decrease from baseline

Combined with

- **Microangiopathic hemolytic anemia:**
  Evidence of one or more of the following:
  - Schistocytes on peripheral blood smear
  - Elevated LDH
  - Decreased haptoglobin
  - Decreased hemoglobin
- **Ruling out DIC:** coagulation profile results

PATIENTS SUSPECTED OF HAVING TMA

RULE OUT **TTP** AND **STEC-HUS**

Exclude patients based on test results that indicate positive diagnoses of **STEC-HUS** and **TTP** using the recommended codes listed in Appendix C Table 1.[1,3,4,11,17]

PATIENTS SUSPECTED TO HAVE TMA AND TTP AND STEC-HUS ARE RULED OUT

EXCLUDE PATIENTS WITH KNOWN ATYPICAL-HUS DIAGNOSIS

Exclude patients who have already been diagnosed with atypical-HUS using codes from Appendix C Table 3.

PATIENTS SUSPECTED OF HAVING ATYPICAL-HUS

SUSPECT PATIENT LIST

You may consider filtering for codes representing signs and symptoms of organ damage found in Appendix C Table 2. However, including these codes may decrease sensitivity.

IMPORTANT NOTE: While EHR systems may assist providers in generating suspect patient lists, it is the sole responsibility of the HCP to make a diagnosis based on in-person patient evaluation. It is important to indicate that the final suspect list of patients will be sent to the HCP(s) for review. Including criteria for a suspect patient list helps explain to the HCP why the patient is on the report.

HCP=healthcare provider, LDH=lactate dehydrogenase.

For IT Department: High-Level Technical Considerations for Generating Suspect Patient Lists

To leverage EHR codes effectively to build a suspect patient list, you should engage with your healthcare organization's IT department to manage and configure suspect patient lists. See below for an example process and considerations for establishing a suspect patient list in Epic EHR.

In Epic EHR, a suspect patient list is referred to as a **patient list report** (a report that identifies all patients meeting certain clinical criteria).

When configuring a suspect patient list, consider addressing the following questions:

- What will the suspect patient list be named?
- Who will own the suspect patient list? (eg, HCP super user or practice)
- What criteria will be used to determine which patients appear on the suspect patient list?
- What information will be included on the patient list report? (see clinical criteria above, eg, creatinine levels, schistocyte count, cobalamin C, etc)

Additional considerations for creating an effective suspect patient list:

- The suspect patient list should exclude patients who are deceased or have been ruled out as atypical-HUS patients
- Suspect patient lists will be impacted by the data stored in your EHR; for example, any testing that has been conducted and recorded by an outside facility may not be recorded in the EHR, which may lead to a patient being erroneously excluded from the suspect patient list
- Identify and engage with users who have the security privileges and/or technical expertise to configure and monitor suspect patient lists in your EHR
- Consider consulting with epidemiologists to optimize suspect patient list criteria, if available to your institution

Note: The above considerations may not be applicable to all EHR systems. Please consult with your IT department for specific processes and considerations. An example of creating patient lists in other EHR software can be found here:

- **https://support.drchrono.com/hc/en-us/articles/202376054**

Alternatively, your IT department can create patient lists by creating SQL queries allowing near real-time information extraction that can more rapidly account for any changes to suspect patient list criteria.[18,19] This method may be more efficient and can allow for machine learning and rapid patient list requirement updates but will only be applicable if all EHR data is mapped to an existing data warehouse.

SQL=structured query language.

3

Order Sets for Atypical-HUS

Order sets are a clinical decision support tool in EHR systems consisting of groups of related, evidence-based orders for a particular disease state that physicians can order instantly within their EHR system.[20,21]

Order sets are available for use and customization in most EHR systems. Order sets allow for efficient and simultaneous ordering of the necessary components associated with effective clinical care such as lab tests, X-rays, and treatments, etc.[20] Listed below are examples of order sets for TMA and atypical-HUS. **These lists are not exhaustive and should be modified to meet the clinical needs of your healthcare organization and providers.**

TMA diagnostic order sets may include:

- Coombs/direct antiglobulin test (DAT)[22]
- Lactate dehydrogenase (LDH)[3,22]
- Bilirubin total and direct[3,22]
- Haptoglobin[3,22]
- Schistocytes on peripheral blood smear[3,8]
- Platelet count[3,22]
- Hemoglobin[3]
- Reticulocyte[3]
- Complete blood count[23]
- Liver function: alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP)[3,24,25]
- Coagulation screen: aPTT, PT, INR, Fibrinogen[1,3]

Note: DIC should be ruled out prior to diagnosis and treatment for a TMA.[1,3]

Evidence of target organ damage is required for a TMA diagnosis.

End-organ damage is a hallmark of TMA and renal involvement may indicate atypical-HUS, however lack of renal involvement does not completely rule out an atypical-HUS diagnosis.[3] Common organ damage diagnostics may include:

- Renal biopsy[3]
- Electrolytes[26]
- Blood urea nitrogen (BUN)[27,28]
- Creatinine[3]
- Amylase[29]
- Lipase[1]
- Troponin[1]
- Urinalysis[3,26]
- Urine Protein Creatinine Ratio (UPCR)[30,31]

Once TMA is confirmed, rule out other TMAs (see also: clinical criteria)

Some orders suggested may include:

Differential	Lab Test(s)
Atypical-HUS	• Requires exclusion of other differential diagnosis[3] • Serum C3 and C4 levels can be measured, but are too variable to exclude a diagnosis of atypical-HUS[3]
TTP	• ADAMTS13 activity[1,3] • If transfusions have already occurred, alternative testing such as plasmic score (<4) and/or platelet values and serum creatinine levels may be used to help differentiate TTP (baseline platelet values >30 x 10^9/L OR serum creatinine >1.7 to 2.3 mg/dL)[3]
STEC-HUS	• Serum PCR for Shiga toxin[3] • Stool sample tested for E. coli-producing Shiga toxin[3]
Cobalamin C disease	• Plasma homocysteine[3] • Plasma methylmalonic acid[3] • Plasma methionine[7] • Genetic testing for MMACHC[32]

Other differentials may include: Pneumococcal HUS, systemic lupus erythematosus, scleroderma renal crisis, complement triggering conditions, autoimmune vasculitis[32]

When bringing an order set build request to your IT department or EHR support person, consider including the following information:

- The name of the order set, for example TMA Diagnostics and Labs
- A list of common and medically appropriate labs, diagnostic orders, and clinical tests to include in the order set
- Any subheadings of the order set and more specific tests
- Clinicians who will have access to the order set, for example Hematology and Nephrology only
- Who will be responsible for adding or removing tests based on clinical need

The use of order sets has been found to promote adherence to evidence-based guidelines, enhance workflow with intuitive instructions, reduce potential for medical errors, and ultimately, improve patient outcomes. However, if standard order sets are not carefully designed, reviewed, and maintained to reflect best practices and ensure clear communication, they may actually contribute to errors.[33,34]

For full Institute for Safe Medication Practices (ISMP) guidelines, see here.

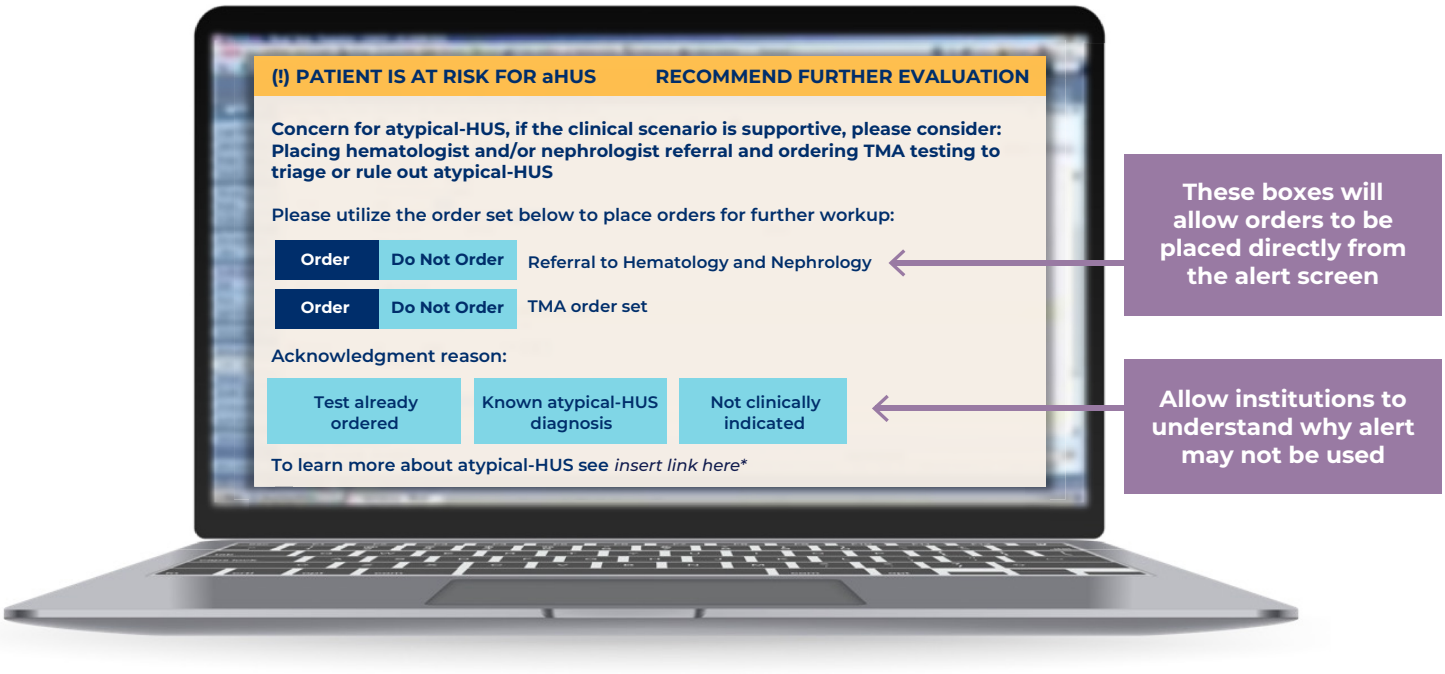
MMACHC=metabolism of cobalamin associated C.

4

Best Practice Alerts to Help Triage a Suspect Atypical-HUS Patient

Use Suspect Patient Criteria and Diagnostic Best Practices to Create Alerts

Using the data in the EHR to surface information in a patient's health record can be the first step in recognizing a suspect atypical-HUS patient. Best practice alerts (BPAs) can be created using clinical criteria and the data in the EHR to help alert and guide an HCP in further assessing for atypical-HUS. The codes used to triage patients to the suspect patient list may also be used to develop BPAs. An example BPA can be found below.



Illustrative example. BPA should meet institutional guidelines and be specific based on criteria that led to BPA. Consult with clinical and IT teams for effective implementation.

*Further disease state education may be linked to an atypical-HUS page in your institution's EHR system or to an outside resource such as:

- https://ahussource.com/physician/
- https://rarediseases.org/rare-diseases/atypical-hemolytic-uremic-syndrome/
- https://www.uptodate.com/contents/diagnostic-approach-to-suspected-ttp-hus-or-other-thrombotic-microangiopathy-tma

High-Level Technical Considerations for Generating BPAs

Automated BPAs can promote quality care by assisting HCPs in providing timely access to diagnostic best practices, reducing misdiagnosis or delays in diagnosis. BPAs can also reduce inefficiency by decreasing the manual effort for HCPs in the diagnostic process.[35] Each EHR system is unique in how to establish automated BPAs, so you should engage with your healthcare organization's IT department. For example, in Epic EHR, a system is in place called "Best Practice Advisories" that allows organizations to deliver HCPs with messages through storyboard alerts, interruptive/active alerts, or passive alerts.[35,36]* These customized, practice-specific alerts can be programmed by the institution's IT team with assistance from clinical leadership to fire according to predetermined triggers, either individual or in combination, using inclusionary or exclusionary logic.[36] IT staff can be provided the suggested BPAs listed above triggered by patients meeting the suggested clinical criteria.

When making an IT request, clinical leaders should be involved in establishing the clinical criteria for BPAs. Consider including the following information to ensure that the suspect patient list is appropriately configured:

- The name for the alert
- The frequency of the alert based on established clinical guidelines
- Indicate where the alert should be placed
- Identify which providers should see the alert

Additional consideration for creating a BPA:

- Privileges on who can configure a BPA may be selective to specific users with security privileges or technical expertise (eg, data scientists in the IT department); therefore, these stakeholders should be identified and engaged with as early as possible

Optimizing BPAs

Improving the visual design of clinical BPAs may help providers recognize medical conditions faster.[36,37] Five presentation elements that have been suggested for EHR alerts include:

1. Physically organize different information by placing it into bordered blocks
2. Be consistent with visual cues (eg, typeface fonts and colors)
3. Use typeface font size and "weight" to help organize and emphasize information
4. Apply color to the boxes used to organize the information
5. Consider the use of three-dimensional effects (to accommodate users who are color blind)

*It has been found that there is a **7.7x greater likelihood a BPA will be followed** by an HCP if the alert is active rather than passive.[38]

Note: BPAs may require governance oversight, consult with your CMIO/CIO.

For a comprehensive list of suggestions, please see Informatics and interaction: Applying human factors principles to optimize the design of clinical decision support for sepsis.[37]

CIO=chief information officer, CMIO=chief medical information officer.

5

Additional Considerations

There are subtle differences between the various EHR systems. Each has similar functionality, but there may be differences such as the naming conventions of EHR system features. Additionally, organizations may have established protocols or patient portals for communicating sensitive health information identified by a BPA. The following section highlights some of these considerations.

The toolkit is provided for informational purposes only and does not substitute the internal review of your institution. Please coordinate with your institution's approval process before implementing an EHR build.

Naming Conventions

- Generating and maintaining suspect patient lists empower organizations to surface patients who meet certain clinical and demographic criteria. These may also be named "worklists" depending on the system[35,39]
- BPAs allow organizations to notify providers when certain clinical activities should be prioritized for a particular patient. This functionality can account for a variety of clinical variables throughout the patient journey and may also be named "discern alerts"[36,40,41]
- Standardized order sets allow providers to easily understand and order the most relevant tests and management options for patients who meet certain disease criteria or are being seen in a particular department. These may also be known as "power plans" depending on the system[42,43]

Each organization may also have its own vocabulary/terms allowed in drop-down lists, formulary, and lab codes. Engage with IT stakeholders at your organization to align on institution-specific variations.

Patient Communication Considerations

HCPs should follow established communication protocols, especially those related to communicating sensitive information to patients. The BPA can include a link to resources for HCPs to leverage when communicating an atypical-HUS diagnosis/test results (https://ahussource.com/physician/hcp-resources-and-videos).

HCPs may also be provided with resources they can give their patient as they begin to understand their diagnosis, such as: https://ahussource.com/physician/patient-resources and https://rarediseases.org/rare-diseases/atypical-hemolytic-uremic-syndrome/.

Note: EHR systems have patient portals that allow patients to stay in touch with their care teams, review their schedules, access personalized patient educational materials, and be more involved in managing their health. These portals may be one way to communicate the need for a follow-up appointment. Some examples of patient portals include:

- Epic MyChart
- Cerner® HealtheLife℠
- Meditech Health Portal
- Allscripts® FollowMyHealth®

The patient list, order set, and BPA functionality already exist in many EHR systems. Alexion did not sponsor, design, create, or otherwise modify this functionality in any manner. The instructions have not been designed to and are not tools and/or solutions for meeting Meaningful Use, Advancing Care information, and/or any other quality/accreditation requirement.

6

Implementing, Monitoring, and Maintaining a Program

The following section provides further guidance on how to implement the deciphEHR™ program in your healthcare organization as well as how to monitor and maintain the program. To assess the program, including surfaced suspect patients, you will need to monitor it on an ongoing basis. Remember, it will be essential to be clear about what you want to achieve and how you will measure it.

Step 1:

Establish a Clinical Program Lead

- It is important to establish a Clinical Program Lead for the project (a medical specialist with EHR experience and expertise in atypical-HUS, most likely a hematologist or nephrologist) who can answer questions and help direct and oversee successful program implementation.
- The Clinical Program Lead can communicate the value of the program to stakeholders throughout the healthcare organization by sharing the deciphEHR™ atypical-HUS Disease Overview and the Rare Disease Overview.
- The Clinical Program Lead can provide ongoing support, including monitoring the program and continuing to champion the use of EHR across multiple specialties for rapid triage of suspect atypical-HUS patients.
- Clinical Program Leads provide support to establish a diagnostic plan based on the clinical criteria for atypical-HUS, suggestions for developing suspect patient lists, order sets, and BPAs to help HCPs triage suspected atypical-HUS patients.

Step 2:

Identify, engage, and communicate with organizational stakeholders*

- Identify and collaborate with relevant stakeholders within your healthcare organizations who are important in implementing the deciphEHR™ program and encouraging sustainable success.
- Stakeholders may vary depending on the organization but may include:

Clinical Leadership

» Pathology and Specialty Medical Staff*
» Laboratory
» Pharmacy

Administrative Leadership

» IT/EHR Resource(s)
» Data Scientist (if available)
» Quality Director

*You may consider inviting input from representative medical staff during the initiation, implementation, and maintenance of this program.

- For stakeholder involvement see here.

Step 3:

Establish an implementation and support team

- Consider including the following members on your implementation and support team*:

  - » Clinical Program Lead†
  - » Specialty/Physician Representative(s)‡
  - » Implementation/Project Manager
  - » Super User
  - » EHR Analyst (EHR Builder, Suspect Patient List, BPA Builder)
  - » Workflow Redesign/ Process Engineer
  - » Report Writer/ Measurement and Tracking Lead

*Depending on the size and type of your organization, your organization may assign employees to more than one role.
†You may consider an additional stakeholder who has experience leading the implementation of BPAs.
‡For most applicable physicians see here.

Step 4:

Develop and execute the implementation plan

- Engage relevant stakeholders and implementation team to establish the adoption, scope, implementation, and rollout of the program
- Leverage the clinical criteria for atypical-HUS (see Section 1) to create suspect patient list for future clinical evaluation by (see Section 2 for technical considerations):
  - » Including recommended medical codes in the Appendix C
  - » Engaging clinical leadership and Super User with IT departments for most effective implementation
- Establish BPAs for HCPs based on clinical criteria (see Section 4 for technical considerations)
  - » Provide atypical-HUS education within the clinical alert using web links such as: https://rarediseases.info.nih.gov/diseases/8702/atypical-hemolytic-uremic-syndrome or https://rarediseases.org/rare-diseases/atypical-hemolytic-uremic-syndrome/
  - » Provide atypical-HUS resources for HCPs with suspect or confirmed atypical-HUS patients such as: https://ahussource.com/physician/ahus-overview
  - » Engage clinical leadership and Super User with IT departments for most effective implementation

Note: While EHR systems may assist providers in generating suspect lists, it is the sole responsibility of the HCP to make a diagnosis based on in-person patient evaluation.

Step 5:

Develop a monitoring and evaluation framework[44-46]

- The Measurement and Tracking Lead may be in charge of continuing to monitor and evaluate suspect atypical-HUS patient lists on a routine (eg, monthly, bimonthly) basis to assess the effectiveness of the program (the Super User may be engaged in this process)
- Effectiveness of the program should be measured based on defined metrics for success (for examples see Step 6)
- The Clinical Program Lead and Super User can monitor and evaluate the BPA program to assess its usefulness and effectiveness in assisting HCPs (eg, through HCP interview)

Step 6:

Measure success[44]

- Metrics for success should be determined at the start of implementation and should be continually measured to assess the success of the program. Metrics for success may include:
  - » Amount of time from suspect patient alert or on a report to the HCP for evaluation to rule in or rule out atypical-HUS
  - » Number of times an HCP acts on a BPA
  - » Number of patients for which an alert helps the HCP to confirm an atypical-HUS diagnosis

Step 7:

Ongoing improvement[44]

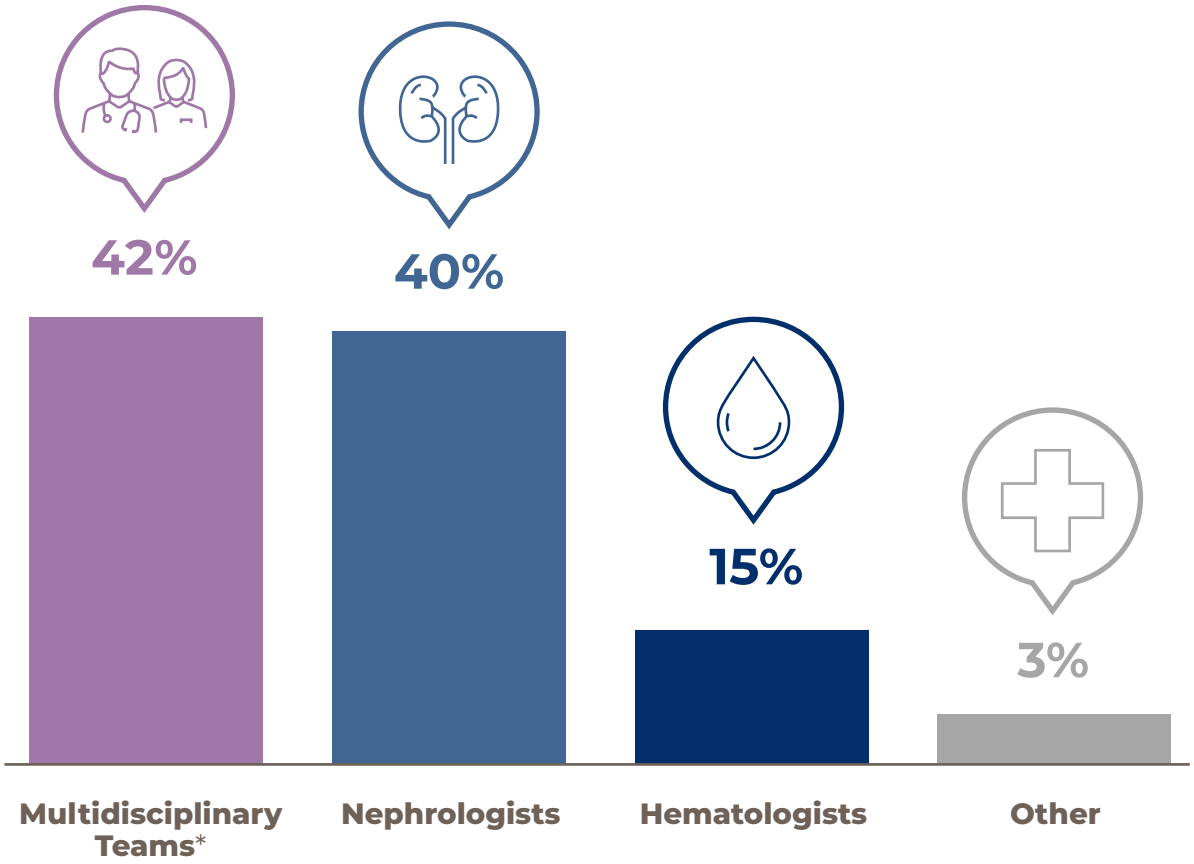
- Engage with Clinical Program Lead to assess atypical-HUS diagnostic criteria to ensure they are current
  - » Determine the appropriate timeframe for reassessment based on institutional standards (eg, annually)
  - » Check deciphEHRrare.com for updates
- Evaluate the effectiveness of atypical-HUS suspect patient lists and BPAs to triage suspect patients to confirm or rule out atypical-HUS
- In case of clinical concerns, reference your implementation and support team
- For EHR implementation troubleshooting and support, consider contacting your EHR provider

7

Appendix A: Medical Staff Considerations

Identify and collaborate with relevant stakeholders within your healthcare organizations who may see undiagnosed patients with atypical-HUS. See the list of possible specialists below. Learn, understand, and comply with your institution's requirements for implementing.

Patients presenting atypical-HUS symptoms are most likely to visit the following HCPs on the path to diagnosis[47]:



*Multidisciplinary teams may include: nephrologist, hematologist, rheumatologist, transfusion medicine physicians, transplant teams, critical care physicians.

Appendix B: Additional Clinical Considerations

Quick Guide for Differential Diagnosis of TMAs: Atypical-HUS, TTP, and STEC-HUS[1,3,7,48]

Thrombocytopenia
Platelet count <150 x 10^9/L or >25% decrease from baseline

and

Microangiopathic hemolysis: Schistocytes and/or Elevated LDH and/or Decreased haptoglobin and/or Decreased hemoglobin

plus 1 or more of the following

COMMON SIGNS AND SYMPTOMS

Renal impairment
- Elevated creatinine level *and/or*
- Decreased eGFR *and/or*
- Elevated blood pressure *and/or*
- Abnormal urinalysis results

Neurological symptoms
- Confusion *and/or*
- Seizures *and/or*
- Stroke *and/or*
- Other cerebral abnormalities

GI symptoms
- Diarrhea ± blood *and/or*
- Nausea/vomiting *and/or*
- Abdominal pain *and/or*
- Gastroenteritis/pancreatitis

OTHER SIGNS AND SYMPTOMS

CV symptoms
- MI *and/or*
- Hypertension *and/or*
- Arterial stenosis *and/or*
- Peripheral gangrene

Pulmonary symptoms
- Dyspnea *and/or*
- Pulmonary hemorrhage *and/or*
- Pulmonary edema

Visual symptoms
- Pain and blurred vision *and/or*
- Retinal vessel occlusion *and/or*
- Ocular hemorrhage

Evaluate ADAMTS13 activity and Shiga toxin/EHEC test*†

While ADAMTS13 results are awaited, a platelet count >30 x 10^9/L and/or sCr >1.7 to 2.3 mg/dL almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)

≤5%† ADAMTS13 activity	>5% ADAMTS13 activity	Shiga toxin/EHEC positive
TTP	Atypical-HUS	STEC-HUS

Plasmic score of 0-4 and/or continued persistence of TMA despite treatment of triggers should increase suspicion of atypical-HUS.[3,13]

*Shiga toxin/EHEC test is warranted with history/presence of GI symptoms.
†Range found in published literature is <5%-10%.

CV=cardiovascular, eGFR=estimated glomerular filtration rate, GI=gastrointestinal, MI=myocardial infarction, sCr=serum creatinine.

7

Appendix C: Medical Codes to Support Suspect Patient Lists, Order Sets, and BPAs

The clinical criteria for atypical-HUS that are required for a patient to appear on the suspect patient list are consistent across all age groups. The medical codes that represent these criteria and suggestions for how to best use these codes are found here.

EHR Code Types

The EHR system contains multiple code types, each containing unique information. These codes can be used in combination to triage suspect atypical-HUS patients. Below are examples of code types that can be found in the EHR:

- **ICD-10:** International Classification of Diseases tenth revision, a globally used diagnostic code for epidemiology, health management, and clinical purposes[49]
- **SNOMED:** Systematized Nomenclature of Medicine Clinical Terms, a common language for systems to adopt for indexing, storing, retrieving, and aggregating clinical data[50]
- **LOINC:** Logical Observation Identifiers Names and Codes, a database and universal standard for identifying medical laboratory observations[51]
- **CPT:** Current Procedural Terminology, a uniform language for coding medical services and procedures such as surgeries, diagnostic tests, evaluation, and management services[52]
- **HCPCS:** Healthcare Common Procedure Coding System, a collection of standardized codes that represent basic medical procedures, supplies, products, and services[53]

Suggestions for Leveraging EHR Codes

All codes are listed at the parent level. Determining level of specificity (eg, specific codes within parent trees) is at the discretion of the institution. The institution is responsible for selection of codes based on the specific situation and patient needs and condition.

No one code has been found to have high specificity and sensitivity for atypical-HUS; therefore, it is suggested codes be used in combination to develop suspect patient lists

- Codes may be used as **inclusionary**, indicating a patient **should** be flagged to the suspect patient list, or **exclusionary**, indicating a patient **should not** be flagged to the suspect patient list
- Codes may change over time; please visit the respective code sites for up-to-date codes
  - » An Excel spreadsheet version is also available on the web page for your convenience
- The codes used to triage patients to the suspect patient list may also be used to develop BPAs

Suggested Codes for the Suspect Patient List Indicated in Section 2

Table 1: Recommended codes for patients at risk for atypical-HUS

It is suggested that any code, or set of codes, that indicate TMA or a potential misdiagnosis of TTP should immediately be triaged for further clinical evaluation of atypical-HUS. The codes used to triage patients to the suspect patient list may also be used to develop BPAs and suggest order sets.

For a visual representation of this suspect patient list, see Appendix B.

Code Type	Code	Code Description	Suggestions for Implementation
TMA Diagnostic Codes (inclusionary)			
SNOMED	126729006	Thrombotic microangiopathy	High-priority code
ICD-9	446.6	Thrombotic microangiopathy	High-priority code
ICD-10	M31.1	Thrombotic microangiopathy	High-priority code
Codes That Indicate TMA (inclusionary)			
Thrombocytopenia			
SNOMED	2897005	Immune thrombocytopenia (disorder)	High-priority code in combination with microangiopathic hemolysis OR elevated LDH
ICD-10	D69.6	Thrombocytopenia (unspecified)	High-priority code in combination with microangiopathic hemolysis OR elevated LDH
SNOMED	302215000	Thrombocytopenic disorder (disorder)	High-priority code in combination with microangiopathic hemolysis OR elevated LDH
SNOMED	415116008	Platelet count below reference range (finding)	High-priority code in combination with microangiopathic hemolysis OR elevated LDH
LOINC	49497-1	Platelets [#/volume] in Blood by Estimate	High-priority code in combination with microangiopathic hemolysis OR elevated LDH
LOINC	777-3	Platelets [#/volume] in Blood by Automated count	High-priority code in combination with microangiopathic hemolysis OR elevated LDH
Hemolysis			
ICD-10	D59.4	Other non-autoimmune hemolytic anemias (including microangiopathic hemolytic anemia)	High-priority code in combination with thrombocytopenia OR platelet count below reference range
SNOMED	73320003	Hemolysis (finding)	High-priority code in combination with Coombs-negative test (evidence for microangiopathic hemolysis) and in combination with thrombocytopenia OR platelet count below reference range
LOINC	800-3	Schistocytes in blood by light microscopy	Lab observation from a complete blood count order
Coombs test			
LOINC	1007-4	Direct antiglobulin test - polyspecific reagent	Negative Coombs test used in combination with hemolysis finding to indicate microangiopathic hemolysis
LOINC	51006-5	Direct antiglobulin test - unspecified reagent	Negative Coombs test used in combination with hemolysis finding to indicate microangiopathic hemolysis
LDH			
ICD-10	R74.0	Elevation of levels of transaminase and lactate dehydrogenase [LDH]	High-priority code in combination with thrombocytopenia OR platelet count below reference range
LOINC	42929-0	Lactate dehydrogenase panel - Serum or Plasma	High-priority code when elevated in combination with thrombocytopenia
TTP Diagnosis Codes (inclusionary)			
SNOMED	78129009	Thrombotic thrombocytopenic purpura (disorder)	High-priority code for potential misdiagnosis
ICD-10	D69.3	Idiopathic thrombocytopenic purpura	High-priority code for potential misdiagnosis
ICD-10	M31.10	Thrombotic microangiopathy, unspecified	High-priority code for potential misdiagnosis

The above codes and suggested use cases for codes are illustrative. Any code implementation should be aligned with Clinical Leadership at your institution.

Code Type	Code	Code Description	Suggestions for Implementation
Ordered ADAMTS13 Codes (inclusionary)			
CPT/HCPCS	85397	The lab analyst performs a test for functional activity of a specific biochemical compound related to coagulation or fibrinolysis that does not have a separate, specific procedure code	An order of an ADAMTS13 is a high-priority code indicating TMA
LOINC	53622-7	von Willebrand factor (vWf) cleaving protease actual/normal in platelet poor plasma by chromogenic method	An order of an ADAMTS13 is a high-priority code indicating TMA
ADAMTS13 Codes with Results <5%-10% (exclusionary)			
LOINC	53622-7	von Willebrand factor (vWf) cleaving protease actual/normal in platelet poor plasma by chromogenic method	ADAMTS13 < 5% may be used as exclusionary criteria as this is evidence of confirmed TTP
STEC-HUS Codes (exclusionary)			
ICD-10	B96.21	Shiga toxin-producing Escherichia coli	Positive Shiga toxin may be used as exclusionary criteria as this is evidence of confirmed STEC-HUS
CPT/HCPCS	87427	Shiga toxin/enterohemorrhagic E. coli positive	Positive Shiga toxin may be used as exclusionary criteria as this is evidence of confirmed STEC-HUS

Table 2: Other codes for patients at risk for atypical-HUS

Additional codes that may be useful in identifying atypical-HUS patients are listed below. These codes may not have high specificity for atypical-HUS, but may still indicate a suspect atypical-HUS patient when used in combination with the codes from Table 1. The decision on if/how to implement these codes should be aligned with your institution's Clinical Leadership.

Code Type	Code	Code Description	Suggestions for Implementation
Signs and Symptoms of TMA Codes (inclusionary)			
Renal impairment			
SNOMED	14669001	Acute renal failure syndrome (disorder)	Renal impairment sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	N17.0	Acute renal failure with tubular necrosis	Renal impairment sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	42399005	Renal failure syndrome (disorder)	Renal impairment sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	310647000	Anemia secondary to renal failure (disorder)	Renal impairment sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	46177005	End-stage renal disease (disorder)	Renal impairment sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	166717003	Serum creatinine raised (finding)	Renal impairment sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	167222005	Abnormal urinalysis (finding)	Renal impairment sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
Neurological impairment			
SNOMED	40917007	Clouded consciousness (finding)	Neurological sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	419045004	Loss of consciousness (finding)	Neurological sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	32834005	Brief loss of consciousness (finding)	Neurological sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1

The above codes and suggested use cases for codes are illustrative. Any code implementation should be aligned with Clinical Leadership at your institution.

Code Type	Code	Code Description	Suggestions for Implementation
Signs and Symptoms of TMA Codes (inclusionary) (continued)			
Neurological impairment (continued)			
ICD-10	R55	Syncope and collapse	Neurological sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	91175000	Seizure (finding)	Neurological sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
GI impairment			
SNOMED	62315008	Diarrhea (finding)	GI sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	75694006	Pancreatitis (disorder)	GI sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	9991008	Abdominal colic (finding)	GI sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
Pulmonary impairment			
SNOMED	78144005	Pulmonary hemorrhage	Pulmonary sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	70995007	Pulmonary hypertension (disorder)	Pulmonary sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	I27.20	Secondary pulmonary hypertension, unspecified	Pulmonary sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	I27.0	Primary pulmonary hypertension	Pulmonary sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	19242006	Pulmonary edema (disorder)	Pulmonary sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	I27.29	Other secondary pulmonary hypertension	Pulmonary sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	I27.24	Chronic thromboembolic pulmonary hypertension	Pulmonary sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	267036007	Dyspnea (finding)	Pulmonary sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
Cardiovascular impairment			
SNOMED	85898001	Cardiomyopathy (disorder)	Cardiovascular sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	50920009	Myocarditis (disorder)	Cardiovascular sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	70272006	Malignant hypertension (disorder)	Cardiovascular sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
SNOMED	84114007	Heart failure (disorder)	Cardiovascular sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	O11.3	Preexisting hypertension with preeclampsia, third trimester	Cardiovascular sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	O11.4	Preexisting hypertension with preeclampsia, complicating childbirth	Cardiovascular sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	O14.90	Unspecified preeclampsia, unspecified trimester	Cardiovascular sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	O14.93	Unspecified preeclampsia, third trimester	Cardiovascular sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	O14.03	Mild to moderate preeclampsia, third trimester	Cardiovascular sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1

The above codes and suggested use cases for codes are illustrative. Any code implementation should be aligned with Clinical Leadership at your institution.

Code Type	Code	Code Description	Suggestions for Implementation
Signs and Symptoms of TMA Codes (inclusionary) (continued)			
Cardiovascular impairment (continued)			
ICD-10	O14.24	HELLP syndrome, complicating childbirth	Cardiovascular sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	O14.23	HELLP syndrome (HELLP), third trimester	Cardiovascular sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	O14.15	Severe preeclampsia, complicating the puerperium	Cardiovascular sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	O14.13	Severe preeclampsia, third trimester	Cardiovascular sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	O14.14	Severe preeclampsia complicating childbirth	Cardiovascular sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
Visual impairment			
SNOMED	28998008	Retinal hemorrhage	Visual sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
Thrombosis			
SNOMED	439127006	Thrombosis (disorder)	Sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
ICD-10	I82.0	Budd-Chiari syndrome	Sign/symptom of TMA, may consider implementing this code in addition to other more specific codes from Table 1
Lab Tests and Procedures Codes (inclusionary)			
LOINC	34555-3	Creatinine clearance: renal panel	Lab test (inclusionary) indicating possible renal impairment, may consider implementing this code in addition to other more specific codes from Table 1
LOINC	45066-8	Creatinine & Glomerular filtration rate.predicted panel:-:Serum, Plasma or Blood	Lab test indicating possible renal impairment, may consider implementing this code in addition to other more specific codes from Table 1
CPT/HCPCS	50200	Excision procedures on the kidney (renal biopsy)	Procedure indicating possible renal impairment, may consider implementing this code in addition to other more specific codes from Table 1
Possible Exclusionary Criteria			
SNOMED	67406007	Disseminated intravascular coagulation (disorder)	May consider as an exclusionary factor for TMA as DIC must be ruled out prior to TMA diagnosis

Table 3: Exclusionary codes indicating an atypical-HUS diagnosis

These codes may indicate atypical-HUS diagnosis and may be considered as exclusionary criteria for the suspect patient list to decrease continued flagging of patients who have already been triaged and assessed.

Code Type	Code	Code Description	Suggestions for Implementation
Atypical-HUS Diagnosis Codes (exclusionary)			
ICD-10	D59.39	Other hemolytic uremic syndrome · Atypical (nongenetic) hemolytic uremic syndrome · Secondary hemolytic uremic syndrome	Indicates atypical-HUS diagnosis, may consider removing from suspect patient list to decrease continued flagging
ICD-10	D59.32	Hereditary hemolytic uremic syndrome · Atypical hemolytic uremic syndrome with an identified genetic cause	Indicates atypical-HUS diagnosis, may consider removing from suspect patient list to decrease continued flagging

This list of codes is not comprehensive and there may be other inclusionary and/or exclusionary codes that could be considered for BPAs.

The above codes and suggested use cases for codes are illustrative. Any code implementation should be aligned with Clinical Leadership at your institution.

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