
CLINICAL UPDATES IN ACUTE KIDNEY INJURY:
Outcomes for Patients Treated with High-Dose Methotrexate
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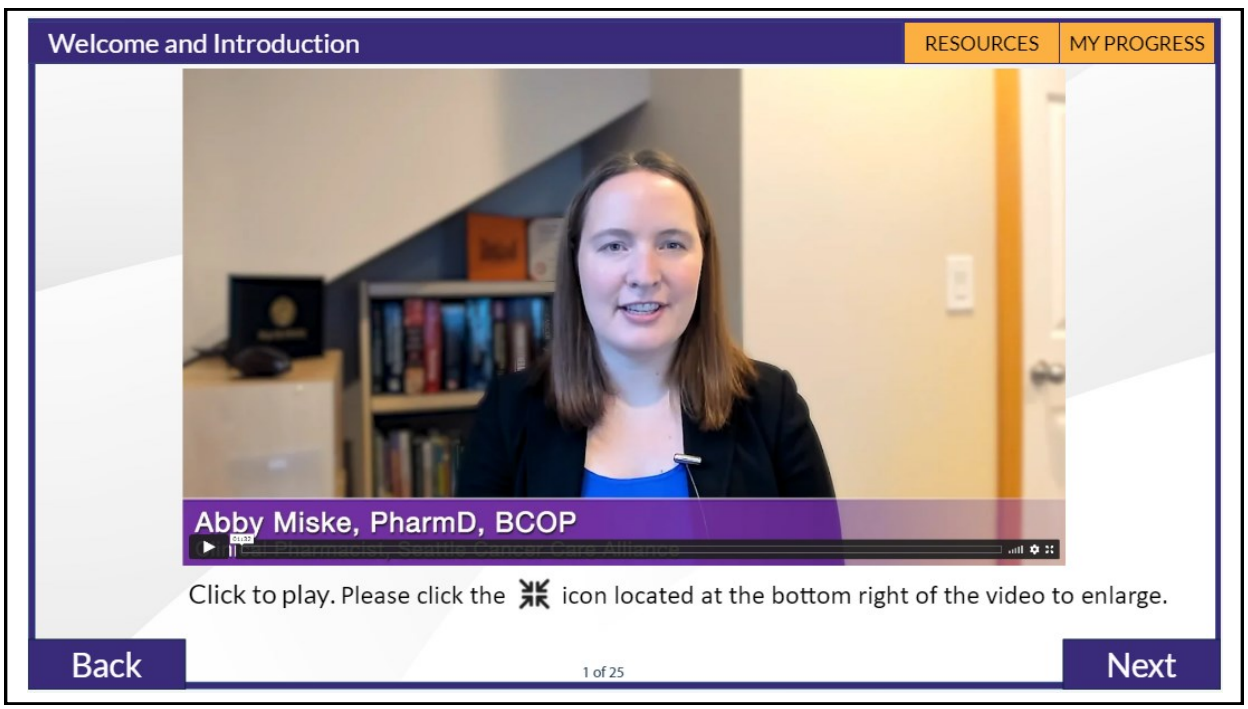
Welcome and Introduction
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MY PROGRESS
Abby Miske, PharmD, BCOP
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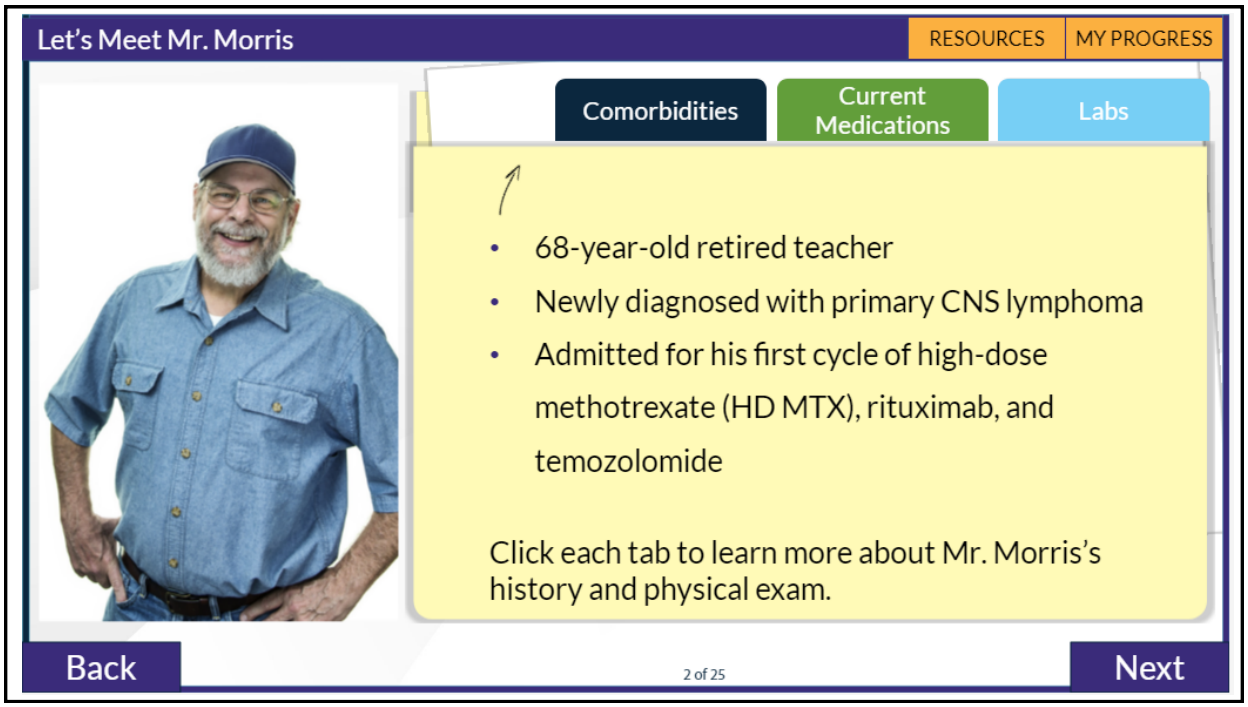
Let's Meet Mr. Morris
RESOURCES
MY PROGRESS
Comorbidities
Current Medications
Labs
68-year-old retired teacher
Newly diagnosed with primary CNS lymphoma
Admitted for his first cycle of high-dose methotrexate (HD MTX), rituximab, and temozolomide
Click each tab to learn more about Mr. Morris's history and physical exam.
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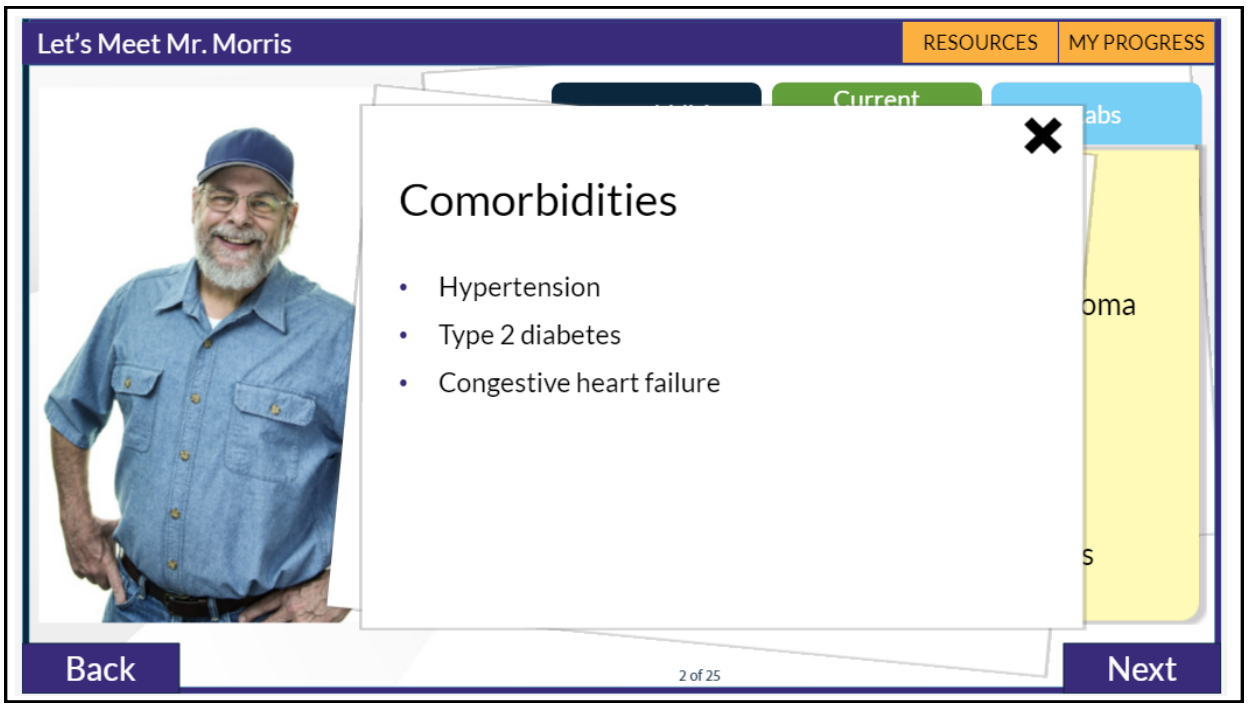
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Comorbidities
Hypertension
Type 2 diabetes
Congestive heart failure
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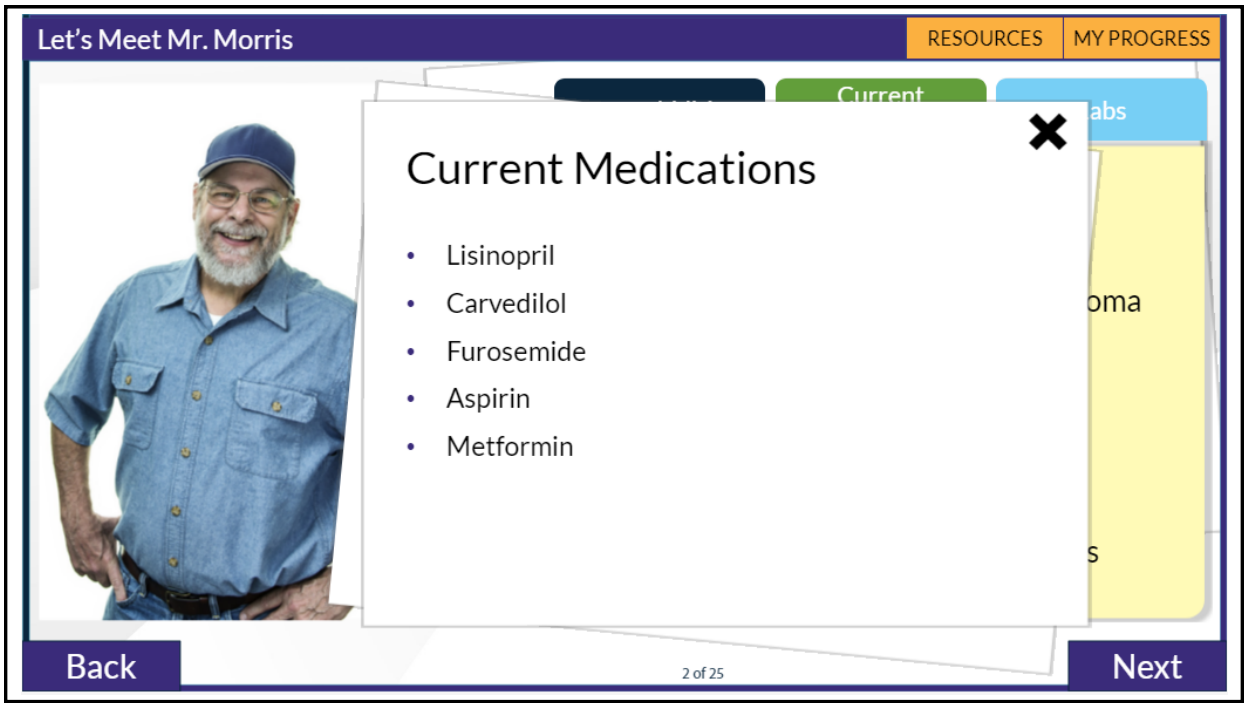
Let's Meet Mr. Morris
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Current
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Current Medications
Lisinopril
Carvedilol
Furosemide
Aspirin
Metformin
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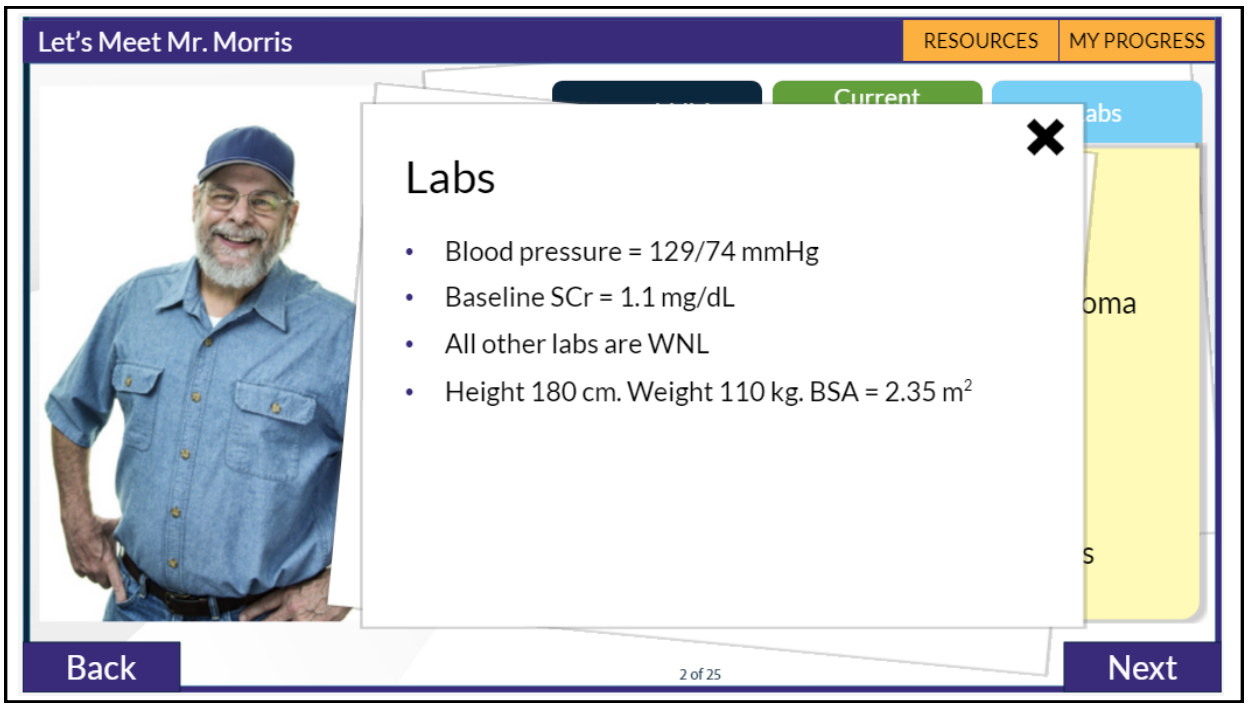
Let's Meet Mr. Morris
RESOURCES
MY PROGRESS
Current
abs
Labs
Blood pressure = 129/74 mmHg
Baseline SCr = 1.1 mg/dL
All other labs are WNL
Height 180 cm. Weight 110 kg. BSA = 2.35 m2
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Risk Factors

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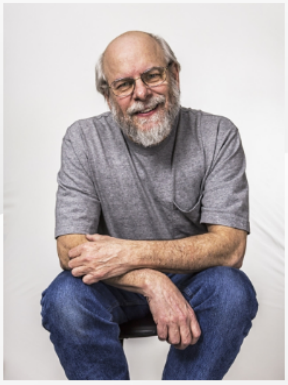

What risk factors does Mr. Morris have for developing AKI secondary to HD MTX? Choose all that apply:

- Age
- Heavily pretreated
- Drug interaction – furosemide
- Dehydration
- Drug interaction – aspirin
- Low albumin
- Drug interaction – lisinopril
- Multiple comorbidities
- Elevated LDH
- Borderline baseline SCr

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Risk Factors Explained

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Back to Mr. Morris

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- Rituximab was administered without incident.
- Temozolomide is planned to start with the next cycle because insurance authorization is still pending.
- Methotrexate 8 g/m^2 was administered over 4 hours.
- Leucovorin, urine alkalinization and hydration were administered per institutional protocol.

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Monitoring

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What parameters are important to monitor following administration of HD MTX? Choose all that apply:

- Daily weight
- Is/Os
- White blood count
- Glucose
- Urine pH
- Methotrexate level
- Blood pressure
- LDH
- SCr/CrCl

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Next Steps

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	Methotrexate	Serum Creatinine
Baseline	-	1.1 mg/dL
24 hours	40 µmol/L	1.7 mg/dL

- Maintain aggressive hydration and urine alkalinization
- Evaluate for third-space fluid/ascites
- Continue leucovorin
- Monitor urine output closely
- Review concurrent medications: discontinue furosemide, aspirin, and any other potential nephrotoxins
- Consider repeat MTX level at 36 hours

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Monitoring Methotrexate Levels

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- Mr. Morris's 36-hour methotrexate level comes back at 29 µmol/L, and his SCr is now 2.6 mg/dL.
- His 48-hour MTX level is 5.3 µmol/L. His SCr is 3.8 mg/dL. The team decides to administer glucarpidase.

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Ramsey LB, Balis FM, O'Brien MM, et al. Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance. *Oncologist*. 2018;23(1):52-61.

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Dosing Glucarpidase

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Time after MTX administration (hours)	MTX level (µmol/L)
24	40
36	29
48	5.3
56 (immediately after glucarpidase)	<0.01
72	0.08

What dose of glucarpidase is recommended for Mr. Morris?

Manufacturer recommended dose is 50 units/kg infused over 5 minutes, therefore the recommended dose for Mr. Morris is 5,500 units. The drug comes in 1,000-unit vials.

- 50 units/kg x 110 kg = 5,500 units

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Dosing Glucarpidase

RESOURCES | MY PROGRESS

Time after MTX administration (hours)	MTX level (µmol/L)
24	40
36	29
48	5.3
56 (immediately after glucarpidase)	<0.01
72	0.08

Mr. Morris's MTX level drops to <0.01 immediately following the glucarpidase administration, and his 72-hour MTX level is 0.08 µmol/L.

Would you recommend giving a second dose of glucarpidase?

Yes | No

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Dosing Glucarpidase

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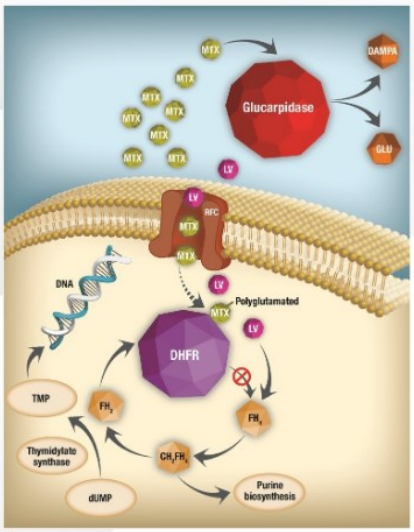

Your answer:
No, do not give a second dose of glucarpidase

Correct!

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Leucovorin Administration with Glucarpidase

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After the glucarpidase, you will continue treating Mr. Morris with leucovorin.

When should the next dose of leucovorin be administered in relation to the glucarpidase?

1. 12 hours later
2. Immediately after glucarpidase infusion
3. 2-3 hours after glucarpidase infusion
4. 2-3 hours after glucarpidase infusion IF methotrexate level increases above 5 µmol/L

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Resolution of Case 1

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Your answer:
2-3 hours after glucarpidase infusion

Correct!

Mr. Morris recovered to his baseline renal function within 2 weeks and he went on to complete his HD MTX course of treatment without further renal complications.

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Let's Meet Hannah

RESOURCES | MY PROGRESS

Medical History | Medications | Labs

- 16-year-old high school student
- Being treated for osteosarcoma
- She is admitted for her 3rd dose of HD MTX

Click each tab to learn more about Hannah's history and physical exam.

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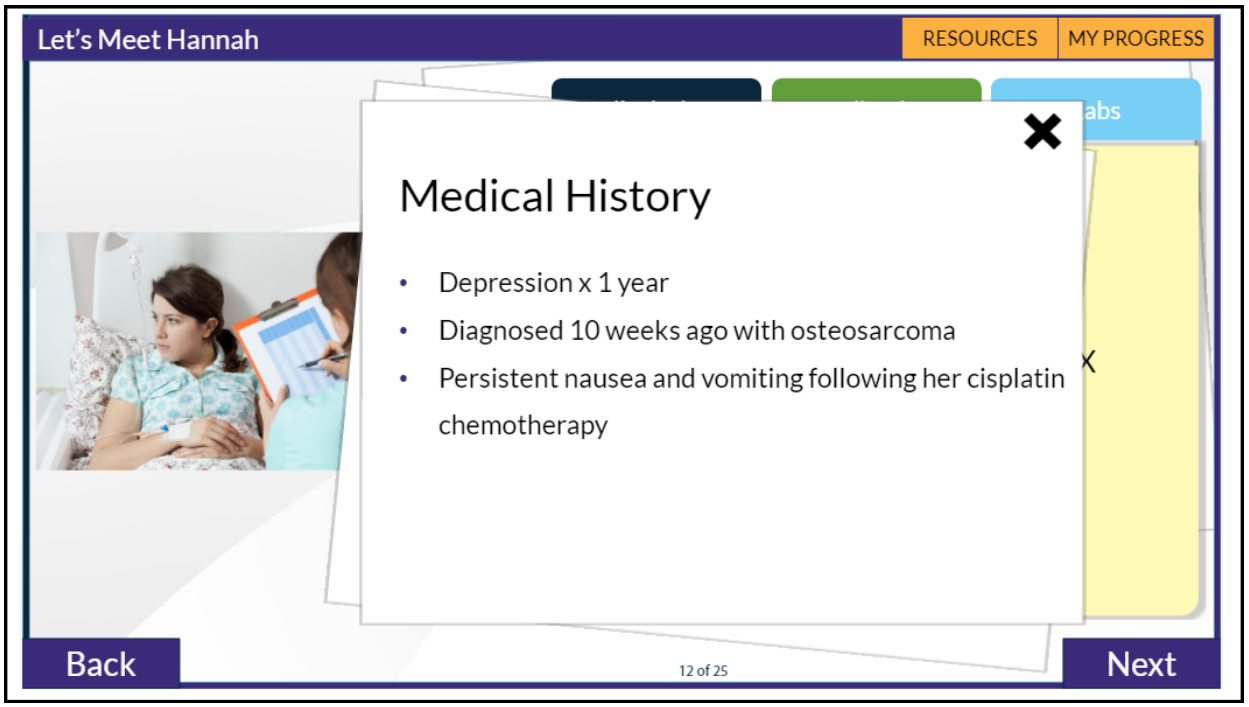
Let's Meet Hannah
RESOURCES
MY PROGRESS
Medical History
• Depression x 1 year
• Diagnosed 10 weeks ago with osteosarcoma
• Persistent nausea and vomiting following her cisplatin chemotherapy
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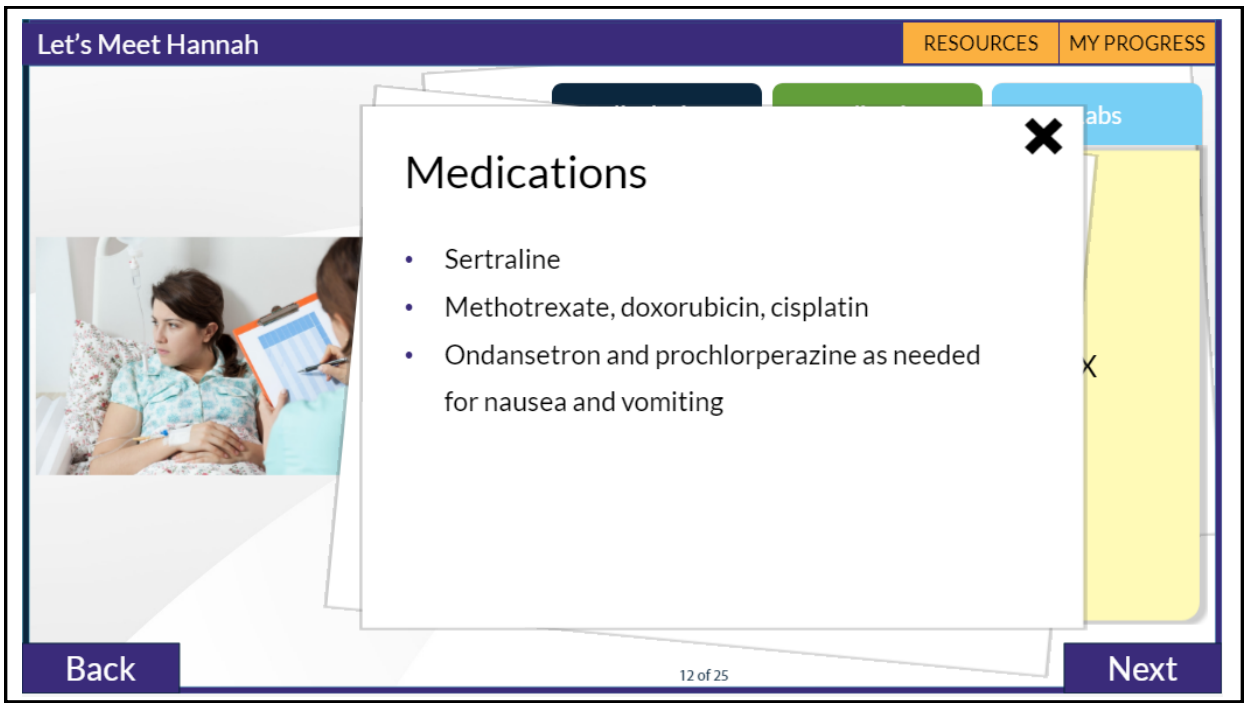
Let's Meet Hannah
RESOURCES
MY PROGRESS
Medications
• Sertraline
• Methotrexate, doxorubicin, cisplatin
• Ondansetron and prochlorperazine as needed for nausea and vomiting
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Let's Meet Hannah

RESOURCES | MY PROGRESS

Labs

- Blood pressure = 112/67 mmHg
- Her baseline SCr prior to starting chemotherapy was 0.54 mg/dL
- Prior to admission her SCr was 0.8 mg/dL, K 3.2 mEq/L and Mg 1.6 mg/dL
- All other labs are WNL
- Height 170 cm. Weight 68 kg. BSA = 1.79 m^2

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Hannah's Risk Factors

RESOURCES | MY PROGRESS

What risk factors does this patient have for developing AKI secondary to HD MTX? Choose all that apply:

- Age
- Borderline baseline SCr
- Drug interaction – sertraline
- Low albumin
- Prior chemotherapy
- Multiple comorbidities
- Dehydration
- Nausea/vomiting
- Elevated LDH

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Risk Factors Continued

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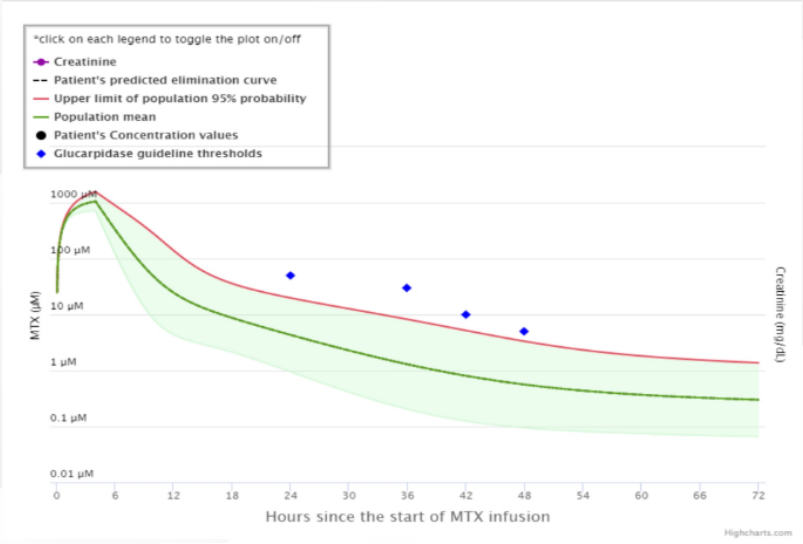

0.54 mg/dL - > 0.8 mg/dL 48% increase

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Supportive Care Measures

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Supportive Care Measures Prior to Giving HD MTX

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Which of these options is NOT a necessary supportive care measure prior to giving HD MTX? (Please continue answering until correct answer is selected).

- Maintain a urine flow of 2,500 mL/m^2 per day
- Discontinue or suspend medications that interfere with methotrexate clearance, including salicylates, sulfamethoxazole, and proton pump inhibitors
- Acidify the urine
- Administer sodium bicarbonate

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Supportive Care Measures Prior to Giving HD MTX

RESOURCES | MY PROGRESS

Which of these options is NOT a necessary supportive care measure prior to giving HD MTX? (Please continue answering until correct answer is selected).

- Maintain a urine flow of 2,500 mL/m^2 per day
- Discontinue or suspend medications that interfere with methotrexate clearance, including salicylates, sulfamethoxazole, and proton pump inhibitors
- Acidify the urine
- Administer sodium bicarbonate

Feedback:

Correct; the urine pH should be increased or alkalinized to ensure methotrexate excretion, not decreased or acidified

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Leucovorin Rescue

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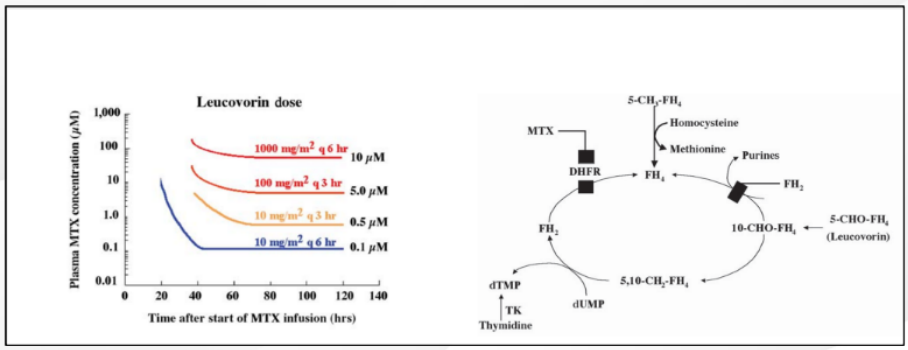

- Initial dose and frequency of leucovorin rescue depends on specific treatment regimen and should be adjusted based on measured MTX levels, as seen in the leucovorin dosing nomogram
- Serum MTX concentrations should be monitored with ongoing adjustments in hydration, alkalinization, and leucovorin rescue until the target of less than 0.05 – 0.1 μM is reached

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Back to Hannah

RESOURCES | MY PROGRESS

Stage	Creatinine concentration	Urine output
1	1.5-1.9 x baseline or ≥ 0.3 mg/dL	<0.5 mL/kg/h for 6-12 h
2	2.0-2.9 x baseline	<0.5 mL/kg/h for >12 h
3	≥3.0 x baseline or ≥4 mg/dL or dialysis	<0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h

Hannah will receive methotrexate at 12 g/m² (max 20 g) over 4 hours. Leucovorin, urine alkalinization and hydration will be administered per institutional protocol.

She continues to struggle with nausea and vomiting after receiving HD MTX.

Her 24-hour MTX level is 52 μmol/L. SCr is 1.4 mg/dL, and her urine output has decreased.

0.8 mg/dL → 1.4 mg/dL = 75% increase over less than 48 hours, fits AKIN criteria for stage 1 acute kidney injury

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Next Step in Treatment

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What should be the next step in Hannah's treatment?

- Initiate dialysis
- Administer glucarpidase
- Administer another dose of leucovorin immediately followed by glucarpidase
- Continue supportive care measures and wait for next MTX level to be drawn

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Next Step in Treatment

RESOURCES | MY PROGRESS

Feedback: Correct! Hannah's MTX level of 6 µmol/L at 48 hours is above the recommended 48-hour MTX level of 5 µmol/L.

- Guidelines published in 2018 recommend glucarpidase for a MTX level >5 at 48 hours in the setting of worsening renal function. Hannah's MTX level of 6 at 48 hours, combined with a 250% increase in serum creatinine over 48 hours, indicates that administration of glucarpidase is necessary to quickly reduce her methotrexate levels to decrease the risk of further kidney injury.
- The team asks you if there is data showing a benefit for the use of glucarpidase over other interventions like dialysis. You inform them of a 2019 study of Medicare patients with methotrexate toxicity that indicated that patients who received glucarpidase had a shorter length of stay, lower inpatient mortality and lower 90-day mortality than patients who received other interventions like dialysis instead of glucarpidase.

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Timing of Glucarpidase

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The team decides to give glucarpidase. You obtain authorization to order drug and are able to expedite an emergency drug delivery to arrive later that same day.

Time is of the essence

- Ideally, glucarpidase should be administered 48 to 60 hours from the initiation of MTX infusion
- Early and rapid reduction of MTX concentration can lower the risk of irreversible organ damage
- According to the Ramsey, et al. Consensus Guideline, life-threatening toxicities—including irreversible kidney and other organ damage that can happen if methotrexate levels remain elevated— may not be preventable beyond 48-60 hours

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Monitoring and Supportive Care Post-Glucarpidase Administration

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Hannah receives a dose of glucarpidase.

Ongoing monitoring and supportive care after glucarpidase administration include:

- Leucovorin should continue to be given at the pre-glucarpidase dose for a minimum of 48 hours and until MTX levels have normalized to < 0.1. Leucovorin should be administered 2 hours after glucarpidase
- MTX levels may appear falsely elevated for approximately 48 hours after glucarpidase administration if an immunoassay-based lab test is used
- Hydration and urine alkalinization should continue per standard protocol
- MTX levels should continue to be monitored daily due to potential for rebound levels following redistribution
- Renal function, urine output and daily weights should continue to be monitored closely
- Nephrotoxins should be avoided as much as possible until MTX is cleared and renal function has recovered

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Resolution of Case 2

RESOURCES | MY PROGRESS

Hannah's SCr continued to increase over the following few days, peaking at 6.4 mg/dL before trending back down to baseline approximately 2 weeks post-HD MTX administration.

- Nausea improved
- Urine output remained stable throughout the admission

Can Hannah receive HD MTX again?

- Rechallenge upon resolution of renal dysfunction has been done successfully in pediatric patients
- The treatment team should consider risks/benefits to continuation of HD MTX and consider rechallenge if appropriate
- If the patient receives HD MTX in the future, she should be closely monitored for early signs of AKI, and glucarpidase should be accessible if needed

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Immunogenicity and Adverse Events

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Conclusion of Case 2

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Adverse events: Nausea/vomiting, hypotension, paresthesia, flushing, and headache (mostly grade ≤2), were recorded each in less than 3% of patients.

After recovering from this episode of AKI and optimizing her antiemetics, Hannah went on to receive HD MTX again without complication.

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Review of Important Points

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Important Points

- Recognize and minimize risk factors for renal toxicity in patients receiving HD MTX
- Administer appropriate supportive care for HD MTX including hydration, urine alkalinization, and leucovorin rescue
- Obtain baseline chest x-ray prior to administration of high-dose methotrexate in order to rule out pleural effusions.
- Be aware of medications that are contraindicated, such as selective serotonin reuptake inhibitors (SSRIs), vancomycin, salicylates, proton pump inhibitors (PPIs), and others.
- Monitor the patient closely following HD MTX administration, including daily weight, SCr, Is/Os, urine pH, and methotrexate level
- Administer glucarpidase promptly within 48-60 hours if there is evidence of delayed methotrexate clearance and renal toxicity
- Continue leucovorin and other supportive care measures following glucarpidase administration

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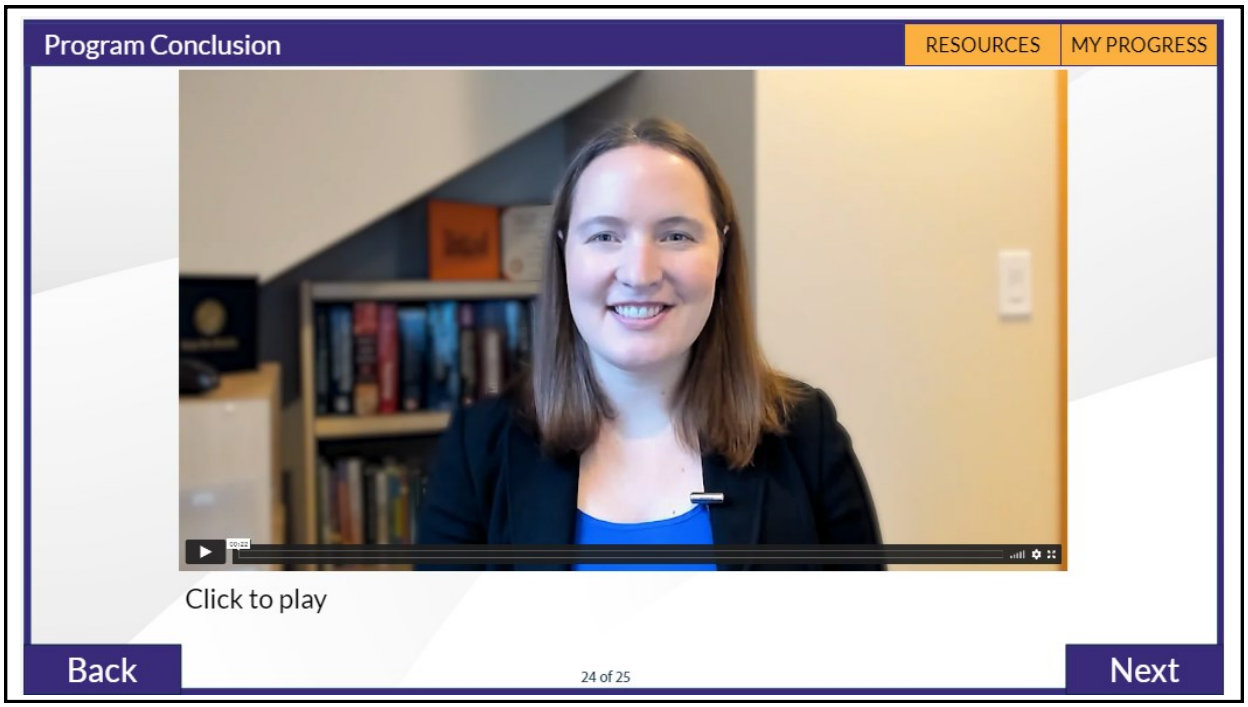
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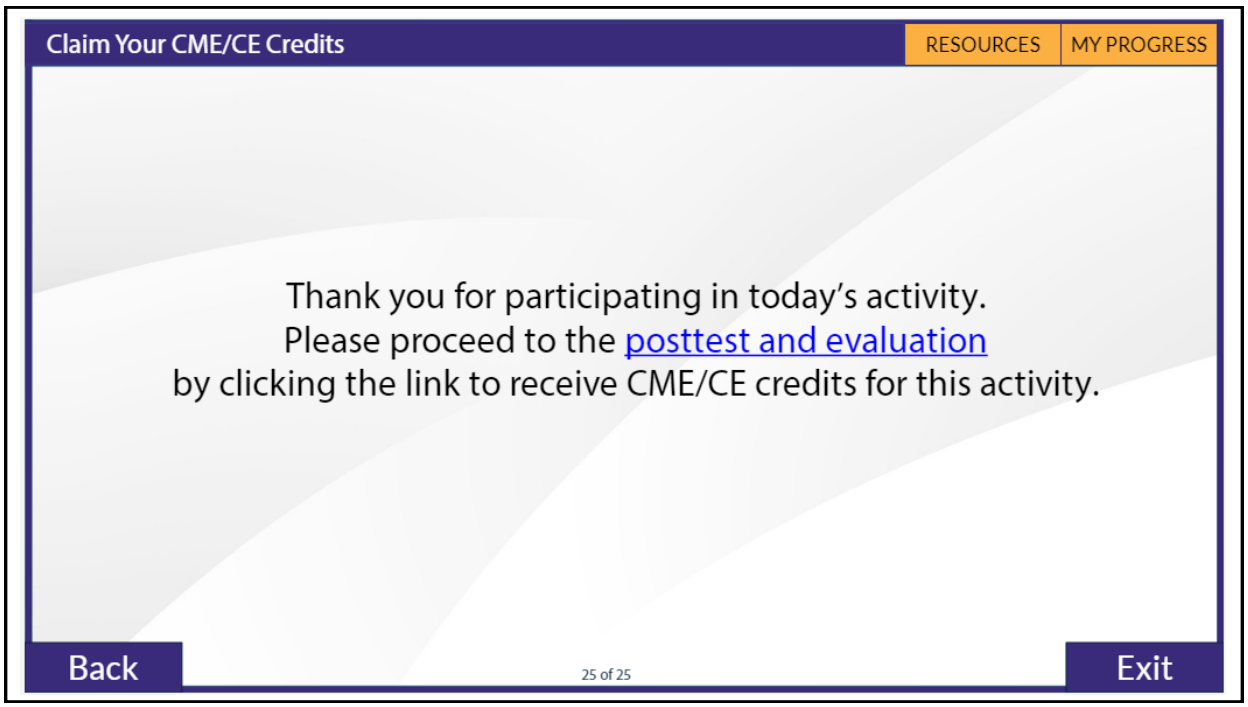
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