With A Little Help From My Friends: Supportive Care Medications in Lymphoma

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Presenter Disclosure

- **Faculty:** Carla Pensack

- **Relationships with commercial interests:**
  - **Grants/Research Support:** none
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  - **Consulting Fees:** none
  - **Other:** none

Mitigating Potential Bias

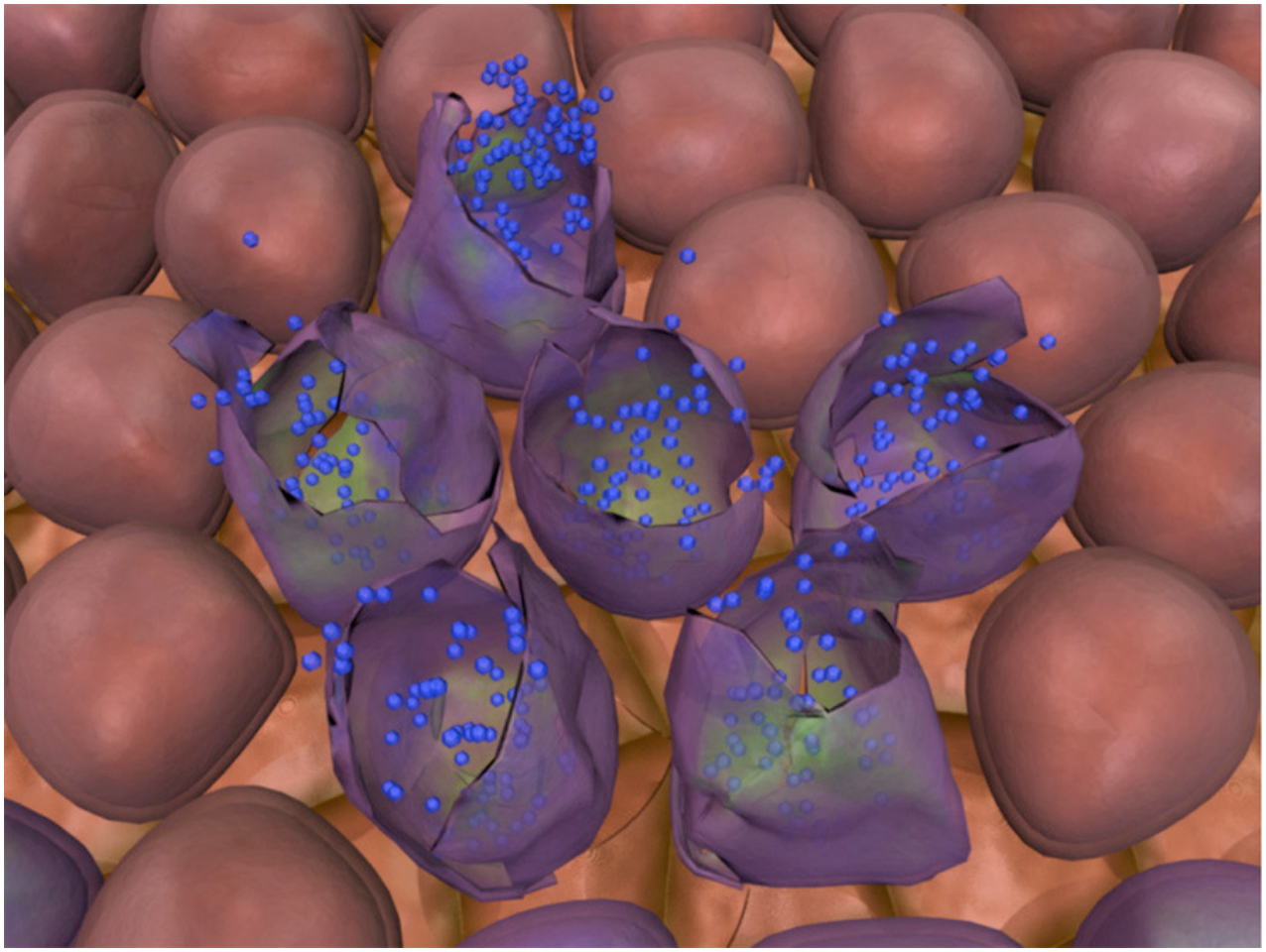
- This presentation is focused solely on supportive care medications and not on directing choice of chemotherapy agents.

Learning Objectives

By the end of this presentation, you should be able to:

- Describe tumor lysis syndrome, list some of its risk factors, and know which medications are used for prophylaxis.
- Understand the importance of *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis and know which antibiotics are used for PJP prophylaxis.
- Understand the rationale behind Herpes Zoster (HZ) prophylaxis and know which antivirals are used for HZ prophylaxis.

Tumor Lysis Syndrome



www.whyfiles.org

Case #1

- 55-year-old male with newly diagnosed stage IVB diffuse large B-cell lymphoma (DLBCL).
- Tumor masses < 10 cm diameter.
- Elevated LDH = 1000 (4 x ULN), normal uric acid, sCr, and Clcr.
- Proposed therapy: R-CHOP x 6 cycles

1) Does this patient require tumor lysis prevention?

2) What supportive medication should he receive for prophylaxis?

What is tumor lysis syndrome?

- A group of metabolic abnormalities caused by rapid tumor cell death as a result of anticancer therapies.
- Is due to the rapid release of intracellular metabolites (potassium, phosphorus, nucleic acids, and proteins).
- Is considered to be a life-threatening oncological emergency.

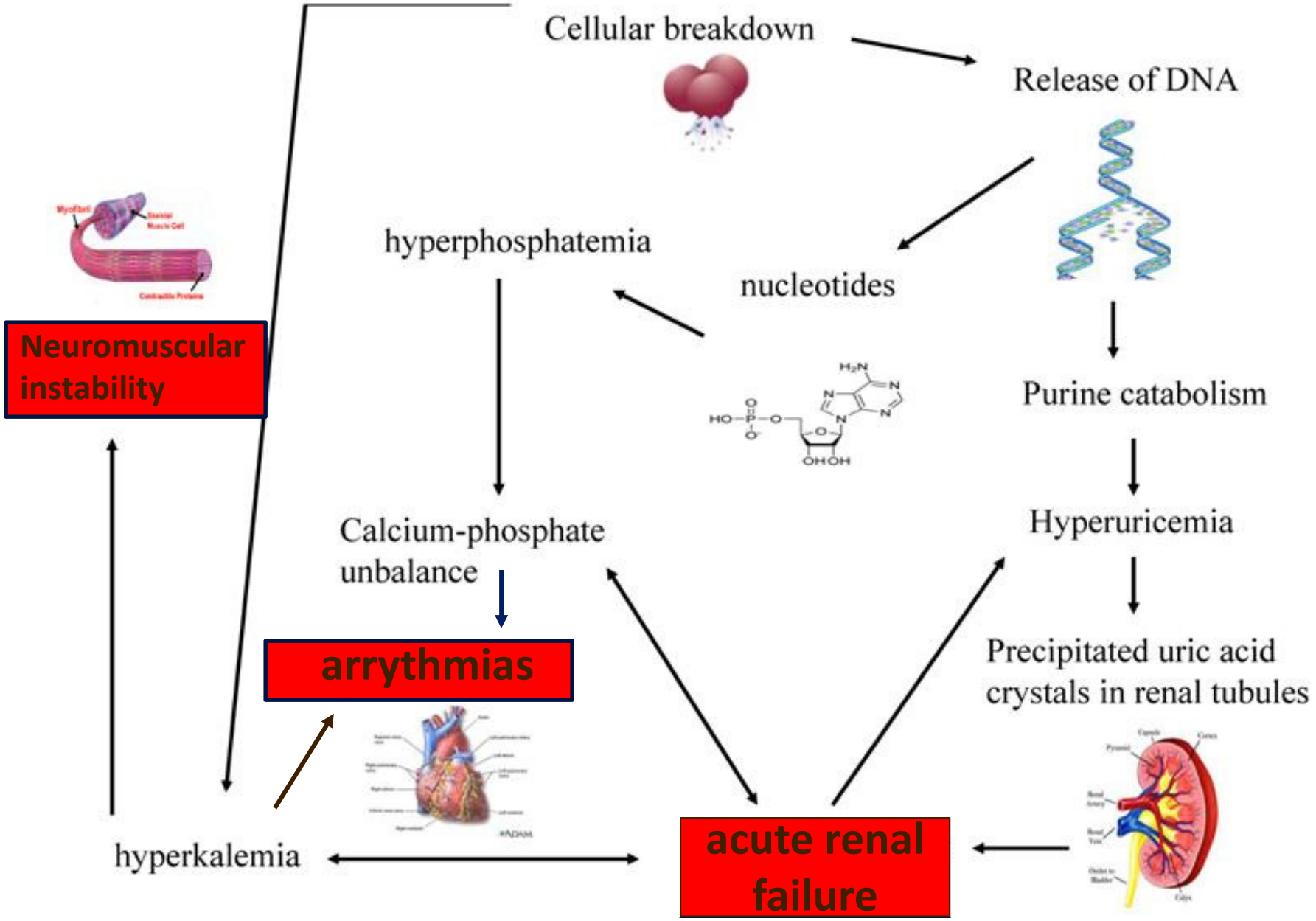
- Cairo, M.S., Coiffier, B. et al. Recommendations for the evaluation of risk and prophylaxis of tumor lysis syndrome. Br J Haematol. 2010 May.

Tumor Lysis Syndrome (TLS)

- **Characterized by metabolic imbalances:**
  - Hyperkalemia
  - Hyperphosphatemia
  - Hypocalcemia
  - Hyperuricemia

- **Can result in:**
  - Acute renal failure
  - Cardiac arrhythmias
  - Neuromuscular symptoms (muscle cramps/tetany)
  - Seizures

Cairo, M.S., Coiffier, B. et al. Recommendations for the evaluation of risk and prophylaxis of tumor lysis syndrome. Br J Haematol. 2010 May.



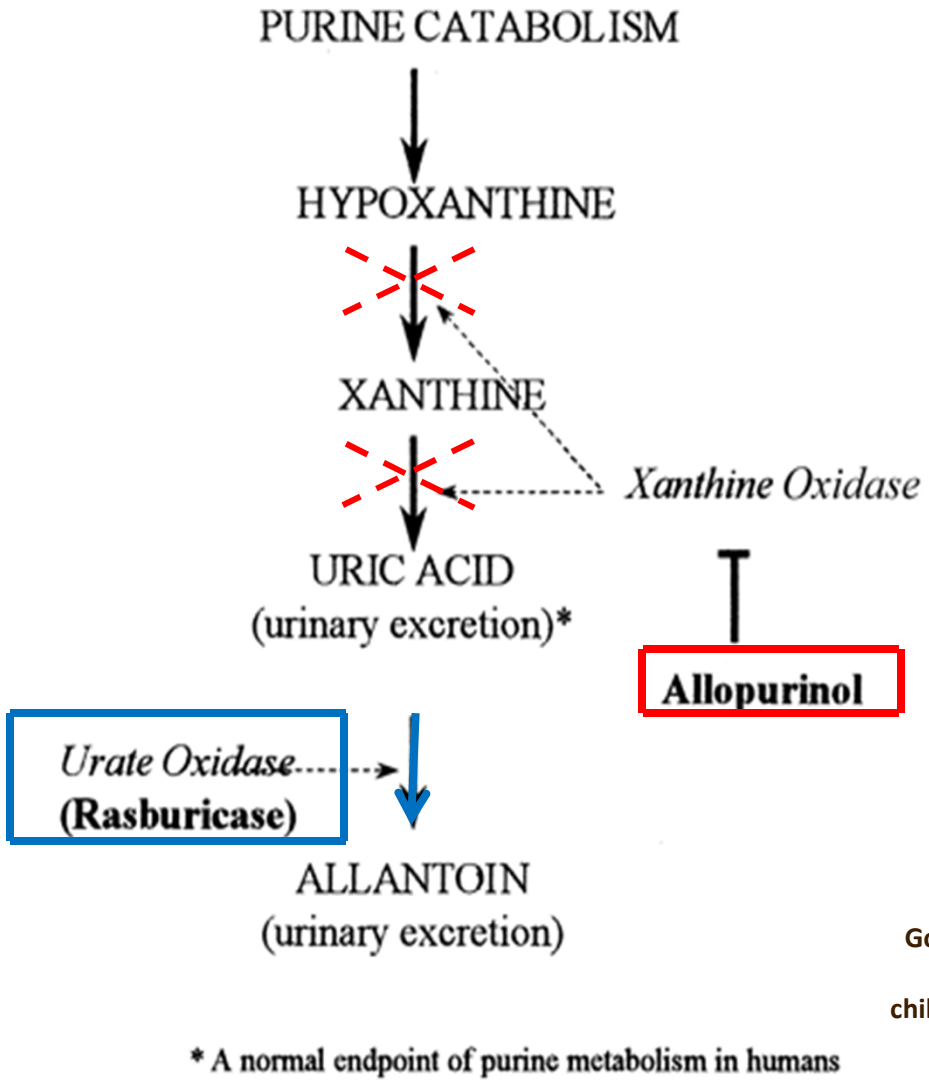
www.medsci.org

Risk factors for developing TLS

- **Tumor type**
  - Burkitt's, lymphoblastic = higher risk
- **Tumor burden/extent of disease**
  - Bulky disease (diameter ≥ 10cm), advanced stage, elevated LDH ≥ 2 x ULN, high chemosensitivity
- **Baseline uric acid**
  - Elevated uric acid > ULN
- **Renal function**
  - Renal dysfunction/renal involvement
  - dehydration, volume depletion

Cairo, M.S., Coiffier, B. et al. Recommendations for the evaluation of risk and prophylaxis of tumor lysis syndrome. Br J Haematol. 2010 May.

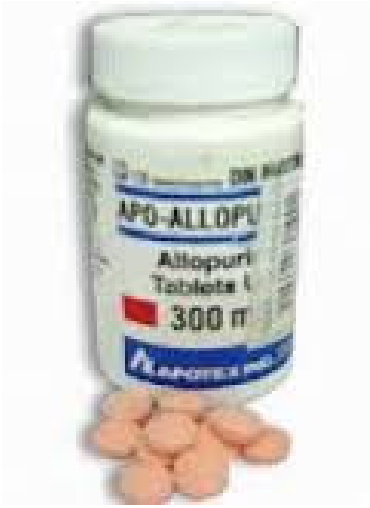
TLS prophylaxis: allopurinol and rasburicase



* A normal endpoint of purine metabolism in humans

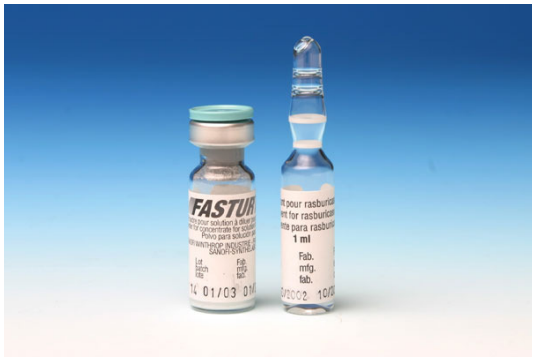
Goldman S et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood 2001.

Allopurinol



- Xanthine oxidase inhibitor.
  - blocks formation of uric acid
- Most common agent for TLS prophylaxis.
- Typically dosed at 300 mg po daily for duration of cycle 1 of chemo (21-28 days).
  - usually not required beyond cycle 1 (unless LDH remains elevated)
  - requires dose reduction in renal dysfunction (Clcr < 20 mL/min)
- S/E: rash/hypersensitivity rxns (increased risk with bendamustine).
- Not covered by Home Cancer Drug Program.

Rasburicase



- Recombinant form of urate oxidase.
  - Converts uric acid into allantoin (5x more soluble)
- Reserved for use in high-risk TLS.
- Contraindicated in glucose-6-phosphate dehydrogenase deficiency (G6PD).
- Dosing based on ABW (max 7.5 mg if > 40 kg) .
  - IV in 50 mL NS over 30 min as a single dose on day 1 (prior to first chemo agent)
  - Start allopurinol therapy within 48 hours after rasburicase administration in patients with bulky disease or persistently elevated LDH.

CCMB provincial oncology formulary criteria

Rasburicase is formulary for the following criteria:

- Non-Hodgkin's Lymphoma (NHL) with very aggressive histology (e.g. Burkitt's, Lymphoblastic Lymphoma) **AND,**
    - clinical tumor lysis syndrome, **OR**
    - stage III or Stage IV disease, **OR**
    - any stage disease with LDH > 2 times ULN and uric acid ≥ 476 micromol/L.

High risk (hydration + rasburicase)

- Stage III/IV Burkitt lymphoma, or early stage (I/II) Burkitt with LDH ≥ 2 x ULN.
- Stage III/IV lymphoblastic lymphoma or early stage (I/II) lymphoblastic lymphoma with LDH ≥ 2 x ULN.
- Adult T-cell lymphoma, DLBCL, peripheral T-cell, transformed, or mantle cell with LDH above ULN **and** bulky tumor mass.
- Intermediate risk with renal dysfunction/renal involvement or uric acid, potassium, or phosphate levels above ULN.

Tumor lysis syndrome: definition, pathogenesis, clinical manifestations, etiology, and risk factors. UpToDate. Accessed 3 July 2016.

Intermediate risk (hydration + allopurinol)

- Early stage Burkitt with LDH < 2x ULN.
- Early stage lymphoblastic lymphoma with LDH < 2x ULN.
- Adult T-cell lymphoma, DLBCL, peripheral T-cell, transformed, or mantle cell with LDH above ULN **without** bulky disease.

Tumor lysis syndrome: definition, pathogenesis, clinical manifestations, etiology, and risk factors. UpToDate. Accessed 3 July 2016.

Low risk (hydration + monitoring)

- Hodgkin's, indolent NHL (e.g. follicular, marginal zone, MALT).
- Other adult NHL not meeting criteria for high or intermediate risk with normal LDH.

Tumor lysis syndrome: definition, pathogenesis, clinical manifestations, etiology, and risk factors. UpToDate. Accessed 3 July 2016.

Case #1

- 55-year-old male with newly diagnosed stage IVB diffuse large B-cell lymphoma (DLBCL).
- Tumor masses < 10 cm diameter
- Elevated LDH = 1000 (4 x ULN), normal uric acid, sCr, and Clcr.
- Proposed therapy: R-CHOP x 6 cycles

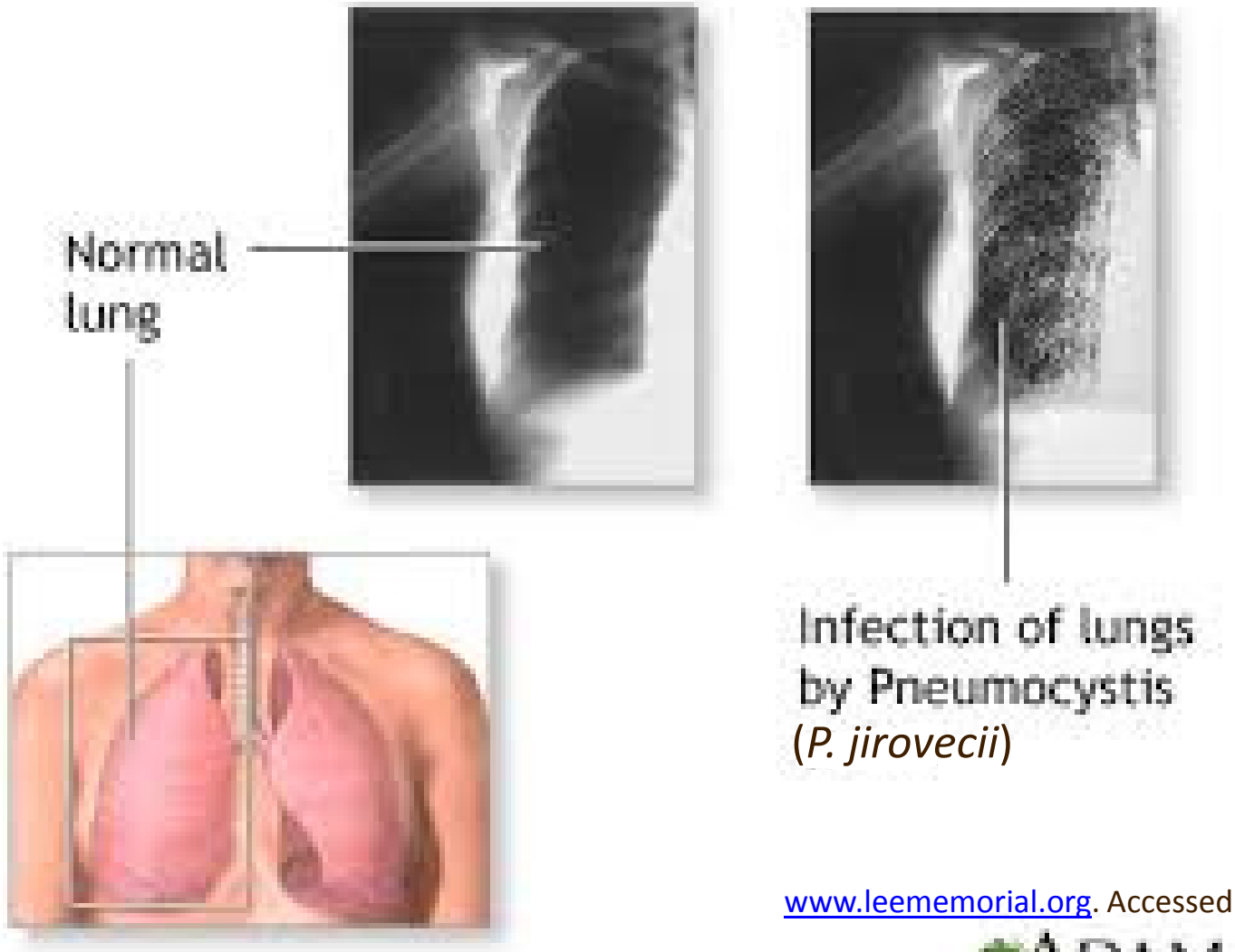
1) Does this patient require tumor lysis prevention?

Yes

2) What supportive medication should he receive for prophylaxis?

Allopurinol 300 mg po OD x 21 days

Pneumocystis jirovecii pneumonia (PJP)



www.leememorial.org. Accessed 16 July 2016

ADAM

Case #2

- 50-year-old female newly diagnosed with Stage III gastric MALT lymphoma.
- Allergies/current meds: NKDA; taking weekly methotrexate for rheumatoid arthritis.
- Proposed therapy: BR x 6 cycles.

1) Does this patient require PJP prevention?

2) What supportive medication should she receive for prophylaxis?

P. jirovecii pneumonia (PJP)

- Previously known as *P. carinii* pneumonia (PCP).
- Officially classified as a fungal pneumonia, but does not respond to antifungal agents.
- Opportunistic infection in immunocompromised hosts.
  - decreased CD4+ T-cells
- Attacks alveoli ➡ hypoxia, SOB, fever, non-productive cough, weight loss; can be fatal.
  - chest x-ray: widespread pulmonary infiltrates

Bennett NJ et al. Pneumocystis jirovecci pneumonia. www.emedicine.medscape.com

Risk factors for PJP in lymphoma

- Very immunosuppressive chemotherapy.
  - d/t significant neutropenia (decreased CD4+ T-cell count)
  - fludarabine, cladribine, alemtuzumab, idelalisib, prolonged steroid use (> 1 month).
- Autoimmune disorder (eg. HIV, lupus), pre-existing immunodeficiency, concurrent immunosuppressants (eg. methotrexate).
- Stem cell transplant (allogeneic).
- Previous history of PJP.

Adapted from New York-Presbyterian Hospital medication use manual. http://www.cumc.columbia.edu/dept/id/documents/Anti-InfectiveProphylaxisinHeme-OncAdultPatients02-02-11.pdf. Accessed 15 July 2016.

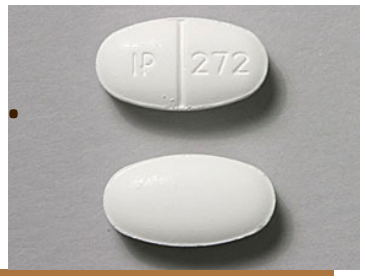
Prophylaxic antibiotics for PJP

- Sulfamethoxazole-trimethoprim
- Dapsone
- Pentamidine
- Atovaquone

- Prophylaxic agent should be started once chemo begins and typically continued until 2 months after chemo completed.
- Currently, CCMB does not have policies in place for use of prophylactic antimicrobials or antivirals in lymphoproliferative disorders.
  - decisions on when these are used are at the oncologist's discretion

Sulfamethoxazole-trimethoprim (Septra, co-trimoxazole, TMP/SMX)

- Preferred agent (efficacy, cost, ease of use).
- Dose: 1 DS tablet (800/160 mg) po BID on two days per week (eg. Sat and Sun).
- Dose adjustment in renal dysfunction (Clcr <30 mL/min).
- Avoid in sulfa allergy, G6PD deficiency.
- Can cause bone marrow suppression (rare).
- Not covered by Home Cancer Drug Program.



New York-Presbyterian Hospital medication use manual. http://www.cumc.columbia.edu/dept/id/documents/ Anti-InfectiveProphylaxisinHeme-OncAdultPatients02-02-11.pdf. Accessed 15 July 2016.

Dapsone

- Sulfone antibiotic
- Inferior efficacy compared to Septra.
- Generally reserved for pts intolerant to sulfa or mild sulfonamide allergy (eg. rash).
  - Consider switching to dapsone if suspicion of Septra causing myelosuppression
- Avoid in anaphylactic sulfa allergy, G6PD deficiency .
- Dose: 100 mg po three times per week (eg. Mon/Wed/Fri), or 100 mg po daily.
- Not covered by Home Cancer Drug Program.

New York-Presbyterian Hospital medication use manual. http://www.cumc.columbia.edu/dept/id/documents/ Anti-InfectiveProphylaxisinHeme-OncAdultPatients02-02-11.pdf. Accessed 15 July 2016.

Pentamidine

- Antifungal; inhaled via nebulizer.
- Generally reserved for pts with anaphylactic sulfa allergy or intolerant to Septra and dapsone.
- Dose: 300 mg via nebulizer over 20-30 min q 4 weeks .
  - administered at cancer center in negative pressure room
- More expensive, poorer lung penetration, bronchospasm, staff exposure .

Perth Haematology: PCP prophylaxis. http://www.perthhaematology.com.au/pcp.htm. Accessed 15 July 2016.

Atovaquone

- Antiprotozoal agent with activity against *P. jirovecii*.
- 4th line; typically reserved for pts unable to receive Septra, dapsone, and pentamidine.
- Comes as liquid suspension only (Mepron®) 750mg/5mL.
- Dose: 1500 mg daily (5 mL BID or 10 mL OD).
- Very expensive, compliance issues.
- Not covered by Home Cancer Drug Program.

Mepron® product monograph. www.hc-sc.gc.ca. Accessed 28 Aug 2016.

Case #2

- 50-year-old female newly diagnosed with Stage III gastric MALT lymphoma.
- Allergies/current meds: NKDA; taking weekly methotrexate for rheumatoid arthritis.
- Proposed therapy: BR x 6 cycles

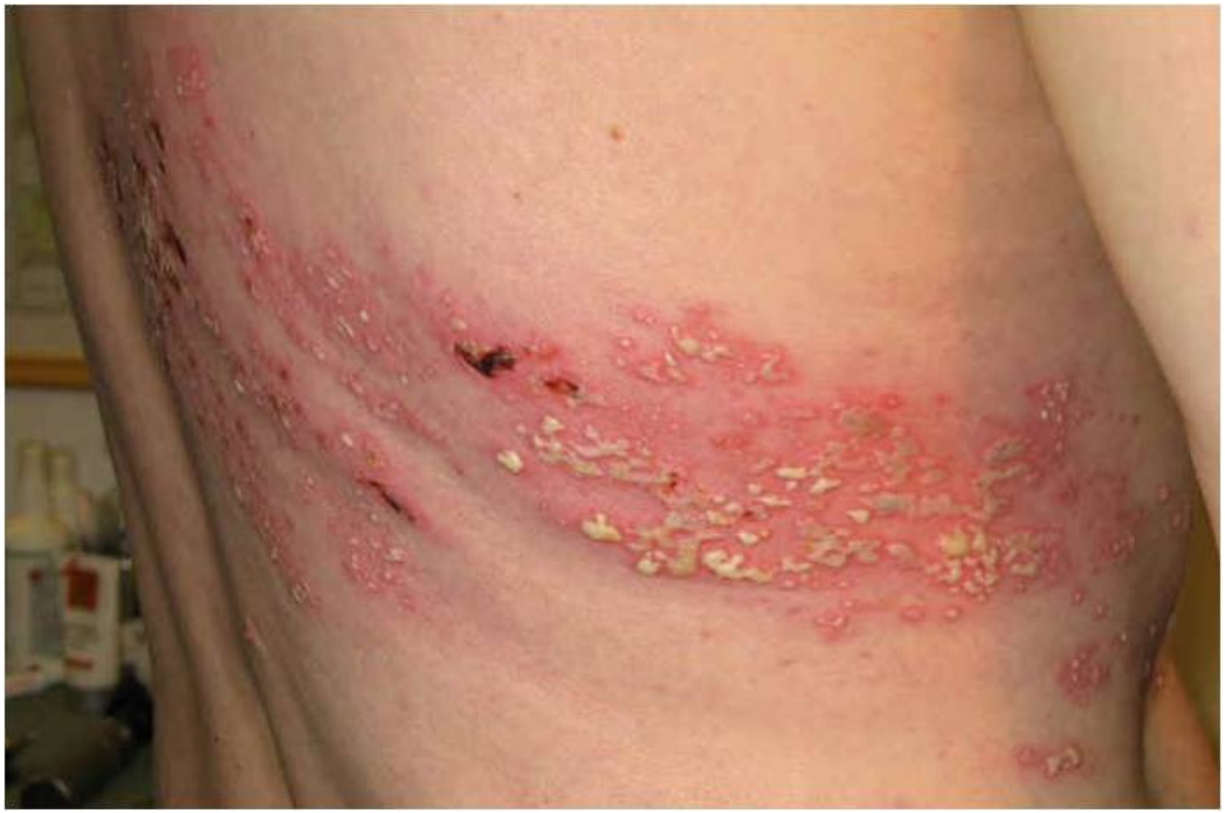
1) Does this patient require PJP prevention?

Yes

2) What supportive medication should she receive for prophylaxis?

Septra DS 1 tab BID twice weekly (Sat & Sun)

Herpes Zoster (HZ)



www.cailsilorin.com. Accessed 16 July 2016

Case #3

- 75-year-old female newly diagnosed with Stage IVB follicular lymphoma.
- No hx shingles; has not rec'd shingles vaccine.
- Proposed therapy: BR x 6 cycles.

1) Does this patient require HZ prophylaxis?

2) Which prophylactic agent should she receive?

Herpes Zoster (shingles)

- Acute, cutaneous viral infection caused by reactivation of varicella zoster virus.
- Painful rash with blisters along one or more dermatomes (thoracic most common).
- Post-herpetic neuralgia most common complication.
  - also ophthalmic/organ involvement, bacterial infection of lesions, nerve palsies
- Immunosuppressed pts at increased risk of HZ and its complications, more severe rash, longer duration of rash, more disseminated rash.

Shingles (Herpes Zoster). Centers for Disease Control and Prevention. http://www.cdc.gov/shingles/hcp/clinical-overview.html. Accessed 16 July 2016.

Risk factors for HZ in lymphoma

- Very immunosuppressive chemotherapy
  - significant & prolonged T-cell suppression
  - fludarabine, cladribine, alemtuzumab, bortezomib
  - bendamustine + other risk factor(s)
- Autoimmune disorder
- Age > 65 years
- Stem cell transplant (allogeneic)
- Previous history of shingles

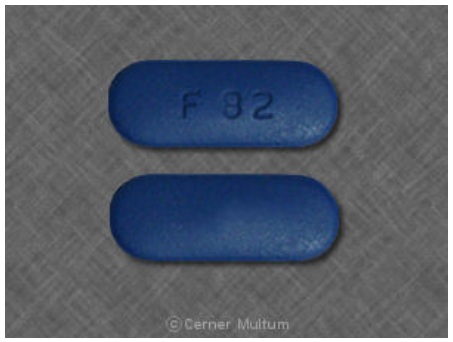
Sandherr M et al. Antiviral prophylaxis in patients with haematological malignancies and solid tumours: Guidelines of the Infectious Diseases Working Party of the German Society for Hematology and Oncology. *Ann Oncology* 17: 1051-1059, 2006.

Prophylactic antivirals for HZ

- Valacyclovir 500 mg po OD
- Acyclovir 400 mg BID

- Start prophylactic antiviral agent on Cycle 1 Day 1 of chemo and typically continued until 2 months after chemo completed.
- If already received shingles vaccine (Zostavax®), typically no prophylactic agent is necessary.
  - Patients should avoid shingles vaccine while on treatment (including while on maintenance rituximab) as it is a live vaccine.
- Instruct patients to monitor for early signs/symptoms of shingles and to seek treatment as soon as possible.

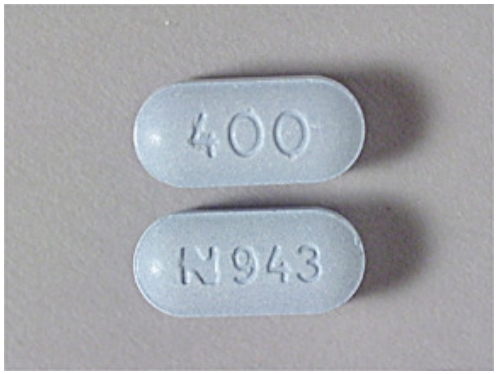
Valacyclovir



- Preferred agent (efficacy, cost, ease of use).
- Prodrug of acyclovir; inhibits viral replication.
- Dose: 500 mg po OD.
- Dose adjustment in renal dysfunction (Clcr <30 mL/min).
- Not covered under Home Cancer Drug Program.

Valacyclovir monograph. MicroMedex Solutions. www.micromedexsolutions.com. Accessed 17 Aug 2016.

Acyclovir



- 2nd line agent; typically reserved for pts intolerant to valacyclovir.
- Dose: 400 mg po BID.
- Dose adjustment in renal dysfunction (Clcr < 10 mL/min).
- Not covered under Home Cancer Drug Program.

Acyclovir monograph. MicroMedex Solutions. www.micromedexsolutions.com. Accessed 17 Aug 2016.

Case #3

- 75-year-old female newly diagnosed with Stage IVB follicular lymphoma.
- No hx shingles; has not rec'd shingles vaccine.
- Proposed therapy: BR x 6 cycles.

1) Does this patient require HZ prophylaxis?

Yes

2) Which prophylactic agent should she receive?

valacyclovir 500 mg po OD

Key points

- Tumor lysis syndrome, PJP, HZ associated with varying degrees of morbidity/mortality.
- Identifying those most at risk and providing adequate prophylaxis is important.
- Must provide education to patients in order to improve understanding and increase compliance.

Questions?

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