UPDATE IN ITP AND TTP

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UNC-Chapel Hill
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Disclosures

- Consultancy: Takeda, Accordant, Emerging Therapeutics
- Research Support: Takeda

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Case 1

- A 33 y.o. woman presents with a new petechial rash and heavier than usual menstrual bleeding. She has otherwise been well, with no medical problems aside from seasonal allergies. Medications include nasal steroids, cetirazine and an oral contraceptive, all of which are long term medications. She has not recently been ill. Physical examination shows normal vital signs, No organomegaly, scattered bruises and petechiae over her lower extremities. Oral blood blisters
- Labs: CBC: platelets 8, Hgb 12.8, MCV 88, WBC 8.3
- CMP normal, TSH normal, smear—no schistocytes, no clumping

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ITP

- Immune-mediated platelet destruction
- Primary vs Secondary
  - Secondary causes include
    - Drugs—quinine, beta lactam antibiotics, sulfa
    - Other autoimmune conditions
    - Lymphoproliferative diseases (NHL, HD, CLL)
    - Immunocompromise (HIV, CVID)
    - Viral Illnesses (HepC, HIV)
    - Pregnancy
- No diagnostic test
- First line therapy—corticosteroids +/- IVIg
- Second line therapy—Rituximab, TPO-R agonists, splenectomy

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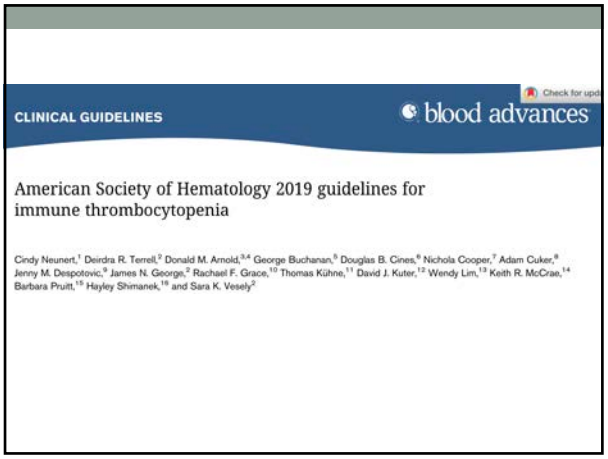

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Guideline takeaways

- In adults with newly diagnosed ITP and a platelet count of < 20K who are asymptomatic or have minor mucocutaneous bleeding, the ASH guideline panel *suggests* admission to the hospital rather than management as an outpatient
- Remark:
  - Patients who are refractory to treatment, those with social concerns, uncertainty about the diagnosis, significant comorbidities with risk of bleeding, and more significant mucosal bleeding may benefit from admission to the hospital. Patients not admitted to the hospital should receive education and expedited follow-up with a hematologist.
  - At UNC, call the coagulation attending on call to expedite an appointment

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Takeaway #2

- Management of adults with ITP who are corticosteroid-dependent or do not have a response to corticosteroids
  - In adults with ITP lasting >3 months who are corticosteroid-dependent or have no response to corticosteroids, the ASH guideline panel suggests either **splenectomy or a TPO-RA**
  - In adults with ITP lasting >3 months who are corticosteroid-dependent or have no response to corticosteroids, the ASH guideline panel suggests **rituximab rather than splenectomy**
  - In adults with ITP lasting >3 months who are corticosteroid-dependent or have no response to corticosteroids, the ASH guideline panel suggests a **TPO-RA rather than rituximab**

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Case 2

- A 24 yo man with a h/o ITP since childhood has been maintained on eltrombopag, 75 mg qd for the past 7 years. His platelet count varies between 10 and 60. He is variably adherent to the eltrombopag diet, since his favorite foods are milk, cheese, and ice cream.
- He has previously failed rituximab, vincristine, and splenectomy

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bjh research paper

Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia

Wojciech Jurczak, Krzysztof Chojnowski, Jiří Mayer, Katarzyna Krawczyk ... See all authors

First published: 07 September 2018 | https://doi.org/10.1111/bjh.15573 | Citations: 22

Volume 183, Issue 3
November 2018
Pages 479-490

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Avatrombopag

- AEs
  - headache, contusion, upper respiratory tract infection, arthralgia, epistaxis, fatigue, gingival bleeding and petechiae, with exposure-adjusted incidence rates that were all comparable with, or lower than, placebo
- FDA approval for chronic ITP June 2019

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Dose	Dose Level
40 mg Once Daily	6
40 mg Three Times a Week *AND* 20 mg on the Four Remaining Days of Each Week	5
20 mg Once Daily*	4
20 mg Three Times a Week	3
20 mg Twice a Week *OR* 40 mg Once Weekly	2
20 mg Once Weekly	1

Platelet Count ($x10^9$/L)	Dose Adjustment or Action
Less than 50 after at least 2 weeks of DOPTELET	• Increase *One Dose Level* per Table 3. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
Between 200 and 400	• Decrease *One Dose Level* per Table 3. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
Greater than 400	• Stop DOPTELET. • Increase platelet monitoring to twice weekly. • When platelet count is less than 150 $x10^9$/L, decrease *One Dose Level* per Table 3 and reinitiate therapy.
Less than 50 after 4 weeks of DOPTELET 40 mg once daily	• Discontinue DOPTELET.
Greater than 400 after 2 weeks of DOPTELET 20 mg weekly	• Discontinue DOPTELET.

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Case 3

- A 32 y.o. woman without past medical history presents with fever and worsening confusion and abdominal pain of 2 days duration. She has noticed darkening urine and some new bruises.
- Physical examination shows a confused woman with some involuntary abdominal guarding. She is febrile and tachycardic. Mild jaundice and a few scattered bruises.
- Laboratory data: Hgb 8.2, WBC 9.4, platelets 22. BUN 41, Cre 1.5, LDH 2200 T Bili 2.1.
- Peripheral smear shows schistocytes.

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Is it TTP? The PLASMIC Score

- Bendapundi, PK, et al. 2017 Lancet Haematol 4:e157
  - Clinical prediction tool for severe ADAMTS13 deficiency
  - derived in a multicenter consortium
  - validated externally using a dataset assembled at a separate institution.
  - This scoring system includes historical and laboratory variables that would be obtainable rapidly in a wide range of clinical settings

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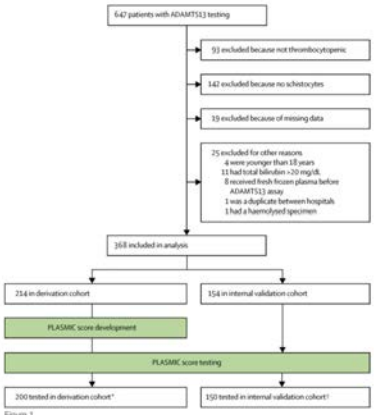

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The Plasmic score

	Points
Platelet count <30 × 10 ^{9} per L	1
Hemolysis variable (Reticulocyte count >2·5%, or haptoglobin undetectable, or indirect bilirubin >2·0 mg/dL)	1
No active cancer	1
No history of solid-organ or stem-cell transplant	1
MCV <90 fL	1
INR <1·5	1
Creatinine <2·0 mg/dL	1

a PLASMIC score of 0–4 denotes low risk (recorded in 0–4% of patients with severe ADAMTS13 deficiency), a score of 5 denotes intermediate risk (5–24%), and a score of 6 or 7 denotes high risk (62–82%)

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PLASMIC score validation

- Li, A et al 2017 J Thromb Haemost 15:1
  - 112 patients who met the appropriate MAHA criteria out of 239 consecutive patients. 108 (96%) had complete data for all seven components of the PLASMIC score assessment.
  - Validation cohort was drawn from a different geographic location and a different reference laboratory.
    - Other differences: allowance for prior FFP infusion, higher median ADAMTS-13 activity, lower proportion of severe deficiency, lower median LDH and higher median INR.
    - 27 patients received FFP prior to ADAMTS-13 testing.
    - 20 patients had severe ADAMTS-13 deficiency (including two patients with activities at 11% and 12%; both received FFP prior to testing).
    - Twenty-one patients had a clinical diagnosis of TTP (all had severe ADAMTS-13 deficiency, except one patient who had ADAMTS-13 activity of 21% but met clinical definition of TTP and responded to PEX).

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	PLASMIC score risk prediction		
	Low risk, score 0–4 (*n* = 49)	Intermediate, score 5 (*n* = 34)	High risk, score 6–7 (*n* = 25)
ADAMTS-13 testing			
Severe ADAMTS-13 deficiency[†]	0 (0%)	2 (6%)	18 (72%)
ADAMTS-13 < 10%	0 (0%)	2 (6%)	16 (64%)
Positive ADAMTS-13 inhibitor[‡]	2 (4%)	2 (6%)	14 (56%)
Treatment received			
Plasma exchange (PEX)	15 (31%)	19 (56%)	22 (88%)
FFP prior to testing	10 (20%)	13 (38%)	4 (16%)

Li, A et al 2017 J Thromb Haemost 15:1

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Clinical diagnosis	Low risk, score 0–4 (*n* = 49)	Intermediate, score 5 (*n* = 34)	High risk, score 6–7 (*n* = 25)
Autoimmune TTP	0	2	19
HUS or aHUS	3	2	2
Rheumatologic	1	1	2
Malignant hypertension	3	5	0
Drug associated	1	1	0
Transplant associated	17	2	0
Sepsis +/− DIC	11	10	1
Cancer +/− DIC	3	3	0
Obstetric +/− DIC	2	3	0
Other DIC	3	2	1
TMA-mimic	5	3	0

Li, A et al 2017 J Thromb Haemost 15:1

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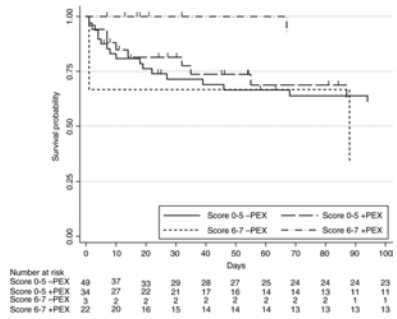

Overall survival by PLASMIC score risk and plasma exchange (PEX). In the high risk for TTP group (PLASMIC score 6–7), treatment with PEX was associated with a significantly longer survival (log rank *P*-value < 0.01). In the low-intermediate risk for TTP group (PLASMIC score 0–5), treatment with PEX was not associated with a difference in survival (log rank *P*-value 0.50) and both treated and untreated groups had worse prognosis.

Li, A et al 2017 J Thromb Haemost 15:1

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Case 3

- TTP is diagnosed based on a Plasmic score of 7 and Plasma Exchange (PLEX) is started.
- ADAMTS-13 level is <5%
- The patient's platelet count initially responds, then plateaus, and then becomes refractory to PLEX.

What is the next best step in management?

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Original Article

Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura

Flora Peyvandi, M.D., Ph.D., Marie Scully, M.D., Johanna A. Kremer Hovinga, M.D., Spero Cataland, M.D., Paul Knöbl, M.D., Haifeng Wu, M.D., Andrea Artoni, M.D., John-Paul Westwood, M.D., Magnus Mansouri Taleghani, M.D., Bernd Jilma, M.D., Filip Callewaert, Ph.D., Hans Ulrichts, Ph.D., Christian Duby, M.D., Dominique Tersago, M.D., for the TITAN Investigators

N Engl J Med
Volume 374(6):511-522
February 11, 2016

The NEW ENGLAND JOURNAL of MEDICINE

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- Thrombotic thrombocytopenic purpura is often caused by an autoantibody to ADAMTS13, resulting in ultralarge von Willebrand factor, which induces platelet aggregation.
- Caplacizumab blocks platelet aggregation and speeds recovery when combined with plasma exchange.

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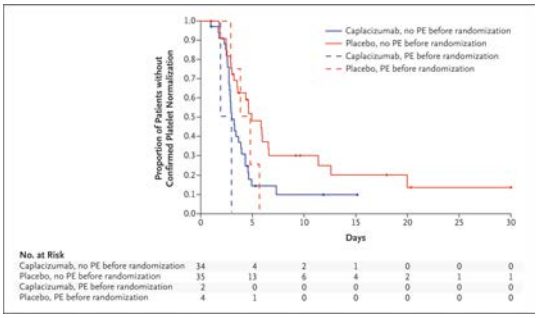
Time to Confirmed Normalization of Platelet Count in the Intention-to-Treat Population.



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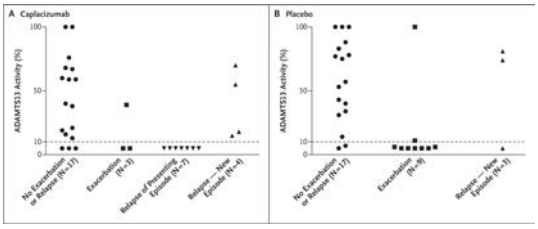
ADAMTS13 Activity According to Exacerbation and Relapse Status.



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- Caplacizumab induced a faster resolution of the acute TTP episode than did placebo.
- The platelet-protective effect of caplacizumab was maintained during the treatment period.
- Caplacizumab was associated with an increased tendency toward bleeding, as compared with placebo.

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Original Article

Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura

Marie Scully, M.D., Spero R. Cataland, M.D., Flora Peyvandi, M.D., Ph.D., Paul Coppo, M.D., Ph.D., Paul Knöbl, M.D., Johanna A. Kremer Hovinga, M.D., Ara Metjian, M.D., Javier de la Rubia, M.D., Katerina Pavenski, M.D., Filip Callewaert, Ph.D., Debjit Biswas, Ph.D., Hilde De Winter, M.D., Robert K. Zeldin, M.D., for the HERCULES Investigators

N Engl J Med
Volume 380(4):335-346
January 24, 2019

The NEW ENGLAND JOURNAL of MEDICINE

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- Among patients with thrombotic thrombocytopenic purpura, the addition of caplacizumab, an anti–von Willebrand factor humanized, bivalent variable-domain-only immunoglobulin fragment, to daily plasma exchange resulted in
  - faster platelet recovery,
  - fewer TTP-related deaths,
  - fewer recurrences and thromboembolic events.

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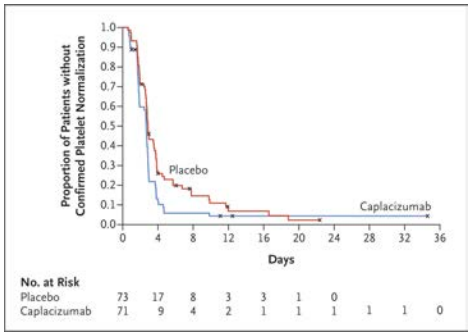
Time to Confirmed Normalization of the Platelet Count in the Intention-to-Treat Population.



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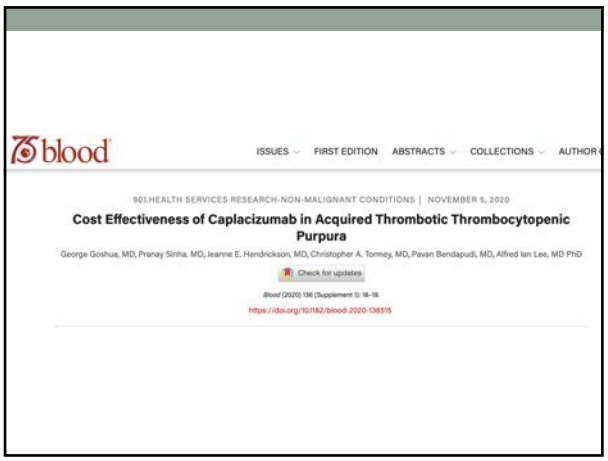

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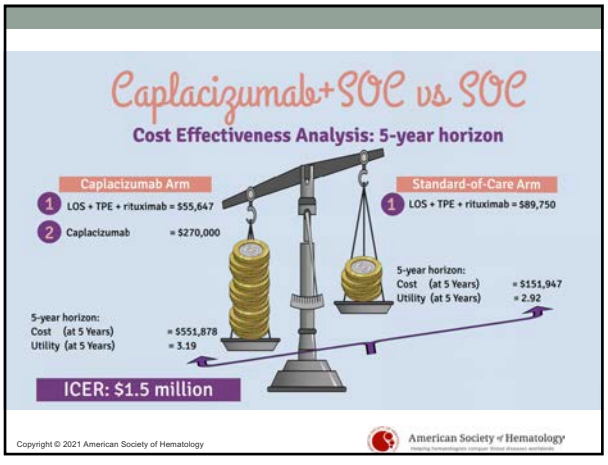

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Case 4

- A 66-year-old woman presented with 2 weeks of easy bruising and epistaxis. She had chronic obstructive pulmonary disease (COPD), mild cognitive impartment, and essential hypertension. Her platelet count was 7000 per microliter
- She was diagnosed with immune thrombocytopenic purpura (ITP).
- Her medications on admission were salmeterol, fluticasone, hydrochlorothiazide, lisinopril, and amlodipine.
- She lives alone. Her daughter lived 2 hours away but visits every weekend because her mother tends to confuse her medications. The patient is anxious about starting a new drug and the side effects that she might experience from it.
- She has had 3 hospitalizations for COPD exacerbation in the past 12 months; however, she had never been in the intensive care unit or been intubated.
- The medical team discussed a 4-day course of dexamethasone 40 mg once daily; however, the patient and her daughter argued against it given an episode of confusion the patient experienced while on dexamethasone during her last admission for COPD exacerbation. However, the patient stated that she has been on prednisone before and tolerated it well. The plan is now for IV immunoglobulin and prednisone taper over 4 to 8 weeks, starting at 1 mg/kg per day.

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Risk factors for infection

- Patient factors
  - Age
  - Co-morbidities, organ dysfunction, other immunodeficiencies
  - Concomitant medications
  - Socioeconomic factors
- Disease and Treatment factors
  - Regimen, agents, dose
  - Length of treatment
  - Time to initiation of therapy
  - Number of lines of therapy needed

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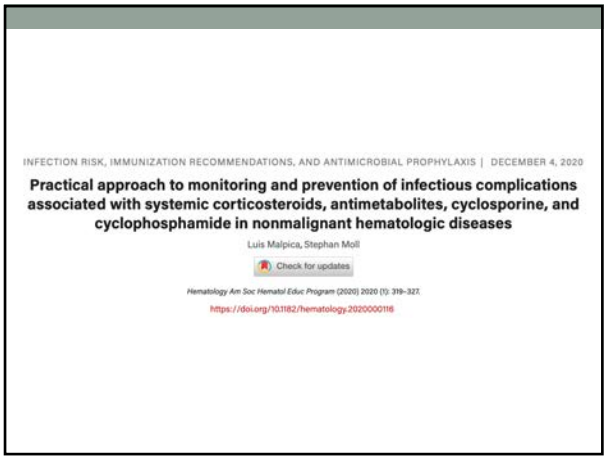

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Patient education and general recommendations

- Hand hygiene
- Management of febrile illness
- Early management of animal bites
- Avoidance of mosquito and tick-borne illnesses
- Travel
- HIV screening
- Immunizations
  - annual influenza vaccine and the herpes zoster vaccine for patients 50 years and older; the recombinant herpes zoster vaccine (SHINGRIX) is preferred over the live attenuated vaccine (Zostavax),
  - live or live attenuated vaccines - contraindicated in patients receiving immunosuppressive therapy (eg, corticosteroids ≥ 10 mg prednisone-equivalent dose [PEQ] daily or a cumulative dose > 700 mg PEQ in 3 months) and that vaccination should be deferred for ≥1 month after discontinuation of such therapy.

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PJP Prophylaxis

- Risk factors
  - A. Steroid dose ≥ 30 mg PEQ daily given for ≥4 wk
    B. Steroids ≥ 15 mg to <30 mg PEQ daily given for ≥8 wk uninterrupted or in intermittent doses
    C. Combination of medium-dose corticosteroids (ie, ≥15 mg to <30 mg PEQ daily) and CP (oral or IV pulses)
    D. Steroids ≥ 10 mg PEQ daily and ≥2 of the following: advanced age > 65 y, coexisting lung disease (eg, COPD, lung fibrosis), use of immunotherapeutics (eg, rituximab, anti-TNF).
- Treatment-- For all patients in (A) through (D), PJP prophylaxis is indicated.
  • TMP/SMX, 1 single-strength tablet (80 mg of TMP and 400 mg of SMX) daily, or TMP/SMX, 1 double-strength tablet 3 times weekly.
  • If TMP/SMX intolerance or contraindicated, alternative therapies are atovaquone, dapsone, or once-monthly nebulized pentamidine.
  • For patients in (D), PJP prophylaxis should be continued until the corticosteroid dose is ≤5 mg PEQ daily.

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Zoster

- Risks for infection
  - A. Advanced age > 60 y
    B. Corticosteroid dose > 7.5 mg to 10 mg PEQ
    C. History of recurrent shingles
- Immunization
  - • RZV (ie, SHINGRIX) preferred over ZVL (ie, Zostavax)
    • Indicated in all adults aged ≥ 50 y, including those who received ZVL in the past; had chickenpox or do not recall whether they had chickenpox; had shingles, but not an active flare at the time of vaccination; and have chronic comorbidities (eg, chronic renal failure, diabetes mellitus, autoimmune diseases, COPD)
    • In adults aged ≥ 50 y anticipating immunosuppression or currently on immunosuppressive therapy, important considerations are to vaccinate ideally ≥4 wk before treatment; okay in patients taking low-dose immunosuppressive therapy (eg, <20 mg/d prednisone or equivalent, or using inhaled or topical steroids, azathioprine, mycophenolate mofetil); and okay in patients who have recovered from an immunocompromising illness
    • Adults aged < 50 y: ACIP does not have a recommendation to administer either zoster vaccine to people younger than 50 y. However, based on the available evidence, clinicians may choose to administer a vaccine off-label, if, in their clinical judgment, they think that the vaccine is indicated (eg, history of shingles). The patient should be informed that the use is off-label and that efficacy and safety of the vaccine have not been tested in people younger than 50 y.
- Antimicrobial prophylaxis
  - No evidence outside of the transplant setting exists on the use of antiviral prophylaxis. However, it might be reasonable that patients with history of recurrent shingles or heavily treated with immunosuppressive agent should consider antiviral prophylaxis. Doses as low as 400 mg of acyclovir daily have shown to an effective strategy in immunocompromised patients.

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Strongyloides

- Risk factors for infection
  - A. Major risk factor is provenance/travel history: tourists, military, and immigrant populations coming from high prevalence areas, such as Africa (Ghana, Zambia, Gabon, Sudan), Asia (Thailand, Cambodia), Central America (Guatemala), and South America (Peru, Venezuela, Brazil).
    B. There are no clear data on the dosage or duration of corticosteroid therapy that triggers the risk for severe strongyloidiasis.
- Screening
  - Given the available data, any patient coming from a high-risk area and scheduled to start corticosteroids at a dose > 10-15 mg PEQ daily for ≥4 wk should be screened with stool sample for ova and parasites and serum IgG against SS.
- Treatment
  - Given the poor sensitivity and high cost of SS screening, empiric therapy with ivermectin represents a safe and cost-effective approach in patients at high-risk for severe strongyloidiasis (ie, people walking barefoot in endemic areas).

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Hep B reactivation

- Risk factors
  - A. High-dose corticosteroids (>20 mg PEQ daily) for >4 wk
    B. Chronic (≥8 wk) medium-dose corticosteroids (10-20 mg PEQ daily)
- Screening
  - (A) and (B) need screening with anti-HBc and HBsAg.
  - Results interpretation:
    - Patients in (A) or (B) with positive anti-HBc and positive HBsAg have a high risk for HBV reactivation (≥10% risk for reactivation).
    - Patients in (A) with positive anti-HBc, but negative HBsAg, have a moderate risk for HBV reactivation (1-10% risk of reactivation).
- Treatment
  - Patients with high risk for HBV reactivation require antiviral prophylaxis.
    - For patients with moderate risk for HBV reactivation, 2 options are available: preemptive therapy guided by serial HBV DNA monitoring, with antiviral therapy initiated as soon as HBV DNA becomes detectable, and routine prophylactic antiviral therapy.
    - Entecavir or tenofovir is the preferred agent because of the low risk of resistance.
    - Infectious disease input is encouraged.

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Infectious complications with AZA/MMF

- Infections
  - Virus: JC virus, cytomegalovirus, VZV
    Reported cases:
    - Bacteria: *Listeria*, *Mycobacterium* spp.
    - Viral: BK virus
    - Fungi: *Cryptococcus*, *Aspergillus*, PJP
    - Parasite: *Toxoplasma*
- Management
  - In patients managed with antimetabolites and presenting with new-onset neurological symptoms such as hemiparesis, apathy, confusion, cognitive deficiencies, ataxia, blurry vision or loss of vision, severe otalgia or hearing loss, need evaluation for a neurotropic infection (eg, PML, HZ reactivation, toxoplasmosis, *Cryptococcus*).
    - Brain imaging and neurology consultation are recommended in those with neurologic symptoms.
    Immunization:
    - HZ immunization is recommended

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Infectious complications with Cyclosporine

- Infections
  - Recognized association:
    - Virus: cytomegalovirus in transplanted patients

    Reported cases:
    - Bacteria: Gram-negative sepsis
    - Virus: Herpes simplex, VZV
- Management
  - No evidence outside of the transplant setting exists on the use of preventive strategies to minimize opportunistic infections.

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Infectious complications with cyclophosphamide

- Infections complications
  - Recognized association:
    - Infections associated with neutropenia (common bacterial infection)

    Reported cases:
    - Bacterial: TB
    - Fungal: PJP, *Aspergillus*
    - Parasitic: SS
- Management
  - Antimicrobial prophylaxis:
    - Antimicrobial prophylaxis against bacterial, fungal, or viral infection might be considered in certain cases of neutropenia and at the discretion of the managing physician.
    - In case of neutropenic fever, antibiotic therapy is indicated, as well as consideration for growth factors, especially in patients considered to be at increased risk for neutropenia complications (eg, elderly patients).
    - PJP prophylaxis in patients treated with combination CP and moderate-dose corticosteroids (ie, ≥15 mg to <30 mg PEQ daily). PJP prophylaxis can be discontinued once PEQ ≤ 5 mg daily.

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Clinical Tips for ITP

- Before starting IVIg, please draw hepatitis B serologies
  - The patient might end up needing Rituximab, and we need to know if they have hepB.
  - IVIg will have a conglomeration of Hep antibodies, and drawing hep serologies AFTER IVIg will give a “false positive” anti core antibody to HepB, making the patient need to take anti-viral agents suchas entecavir for a year

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Clinical Tips for ITP

- Before giving Rituxan, make sure patient gets vaccines
  - Rituxan blocks vaccine efficacy for 6 mo, so will make splenectomy (if needed) less safe
  - This may make a COVID vaccine less effective
- Vaccines needed
  - Pneumococcus
    - Pneumococcal conjugate vaccine or PCV13 (Prevnar®)-give first
    - Pneumococcal polysaccharide vaccine or PPSV23 8 weeks later
  - Meningococcus
    - Meningococcal conjugate or MenACWY vaccines (Menactra® and Menveo®)
    - Serogroup B meningococcal or MenB vaccines (Bexsero® and Trumenba®)
  - H. flu
    - HiB polyconjugate

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Clinical tips for ITP

- When using romiplostim (N-Plate), use the dosing algorithm (and not the full vial), since otherwise, you risk overdosing the patient and leading to too high platelet counts.

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QUESTIONS?

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