Approach to the Child With Too Many Infections

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Disclosures

- No disclosures

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Objectives

- Be better equipped to recognize children who need special attention for recurrent infections
- Determine which specialist should evaluate a child with recurrent infections
- Recognize groups of patients at risk for frequent or severe infections

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Primary Immunodeficiency Diseases (PIDD)

- Over 1 million Americans
- Over 10 million worldwide
- Incidence as high as 1:500
- Over 150 primary immunodeficiency diseases

Truth or Misconception?

- PI is a disease of childhood
- PI patients will appear ill
- A child with PI with have failure to thrive
- The most common infections in PI are invasive:
  - Pneumonia, osteomyelitis, bacteremia, meningitis

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When to suspect

- Infections of unusual
  - Frequency
  - Severity
  - Organism
  - Anatomical location
  - Host response
- Family history

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CASE

“My daughter needs allergy testing”

“My daughter needs allergy testing”

- 3 year old girl
- “always coughing and full of snot”

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“My daughter needs allergy testing”

- Cough
  - “Wet-sounding”
  - Often starts with a cold
  - Lasts for weeks
  - No wheeze, No SOB
  - No response to albuterol
  - Resolves with antibiotics
  - Multiple recurrences

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“My daughter needs allergy testing”

- Rhinitis
  - Often yellow/green
  - No itchy watery eyes
  - Allergy meds “do nothing”
  - Resolves with antibiotics

“My daughter needs allergy testing”

- No food allergy, no eczema
- Infections:
  - History of chronic otitis media
    - Improved with PET placement
  - No history of pneumonia, no invasive infections
  - No hospitalizations

- Normal growth and development

- No significant environmental or travel exposures

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“My daughter needs allergy testing”

- Family Hx:
  - Dad was “sick a lot” as a child
    - Mostly respiratory infections

“My daughter needs allergy testing”

- IgG: Slightly low
- Pneumococcal titers low

- Environmental allergy testing normal

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Practical Points

- "Always sick"
  - Could be early presentation of PI
  - Could be window of opportunity
    - Early diagnosis
- "Frequent / prolonged respiratory infections"
  - May masquerade as "allergy"

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CASE

“My baby can’t breathe through his nose”

“My baby can’t breathe through his nose”

- 2 month old male
  - Severe nasal congestion
  - Dyspnea during feeds
  - Difficulty finishing bottles
  - FTT
- Rhinitis medicamentosa?
  - Has used intranasal oxymetazoline for weeks

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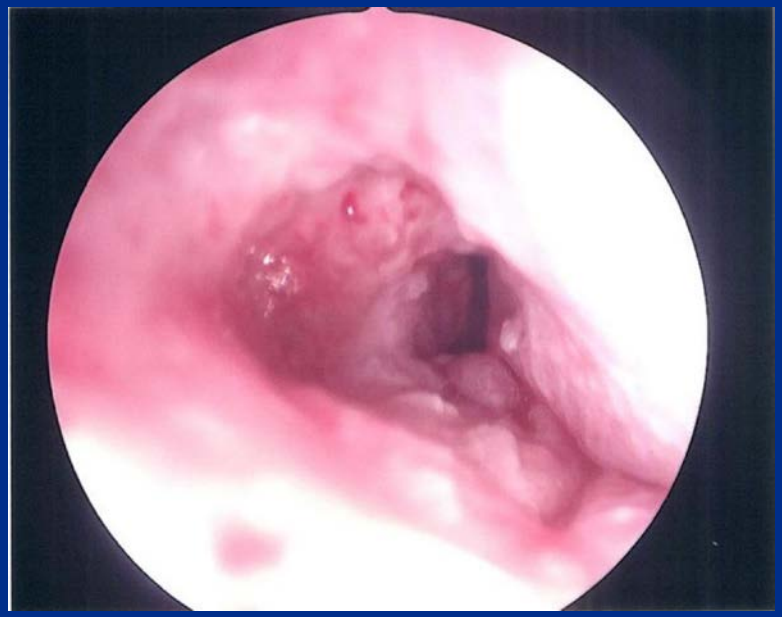
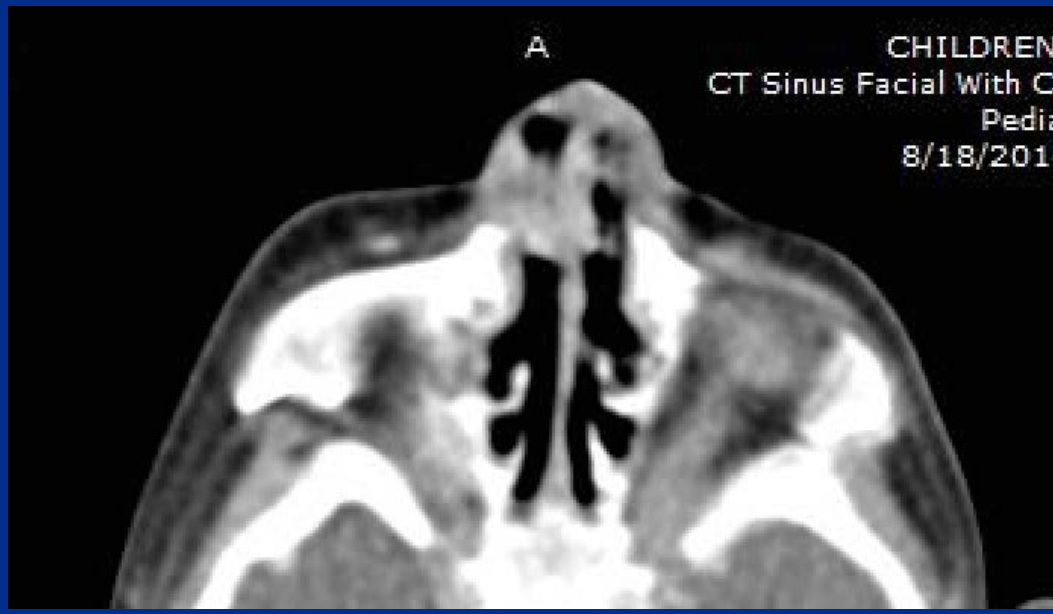
“My baby can’t breathe through his nose”





“My baby can’t breathe through his nose”

- Biopsy
  - Chronic inflammation
  - Granuloma formation
- Culture
  - Serratia marcescens

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“My baby can’t breathe through his nose”

- Chronic Granulomatous Disease

Chronic Granulomatous Disease

- Classic Presentation
  - 1 year old male
  - Staphylococcal liver abscess
- Most common organisms: Catalase +
  - S.aureus, Aspergillus, Burkholderia cepacia, Serratia marcencens, Nocardia
- Treatment of deep-seated abscesses
  - Surgical resection?
    - Delayed wound healing
    - Prolonged antibiotics and systemic steroids

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Chronic Granulomatous Disease

- Inheritance
  - X-linked
  - 1/3 are autosomal recessive!!
- Diagnostic testing
  - Dihydrorhodamine assay by flow cytometry
- Impaired NADPH oxidase system. Defective neutrophil respiratory burst
  - Recurrent abscesses and chronic granulomas
- Treatment
  - Consider BM transplant
  - Prophylactic bactrim, itraconazole, INF-©

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Practical Points

- Unusual organism
- Unusual anatomical location
- Unusual host response

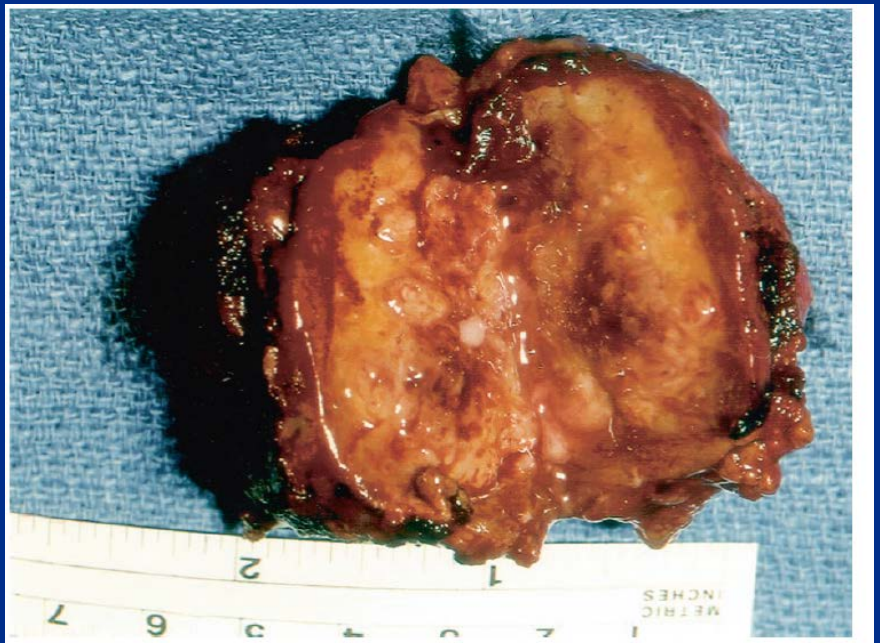

Figure 4. Typical appearance of a hepatic abscess in a patient with chronic granulomatous disease. Note the fibrous cuff surrounding the abscess and the thick, purulent center.

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CASE

"Swelling in his neck"

“Swelling in his neck”

- 6 year old male
- Presented to primary care
  - Bilateral cervical lymphadenopathy (R>L)
    - Progressive over 2 weeks
    - Unresponsive to 1 week of antibiotics
    - No fever
    - Some decreased energy
  - CBC, CMP normal, LDH slightly elevated

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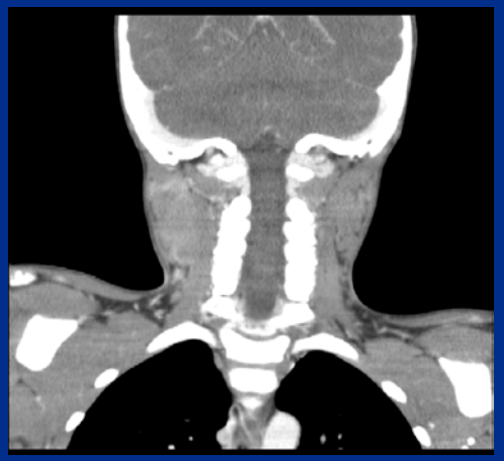
“Swelling in his neck”

- Diagnosed with EBV-associated lymphoma
- Hypogammaglobulinemia
- No history of prior infections
- Unremarkable family history



- Found to have:
  - X-linked Lymphoproliferative Disease

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X-Linked Lymphoproliferative Disease (XLP)

- Exquisite susceptibility to Epstein-Barr virus
- Phenotypes
  - Fulminant Infectious Mononucleosis
  - EBV Associated Lymphoma
  - Hypogammaglobulinemia (CVID-like)
  - Hemophagocytic Lymphohistiocytosis (HLH)
  - Aplastic Anemia
- Just over 100 families documented in literature
  - At least 3 families in LA
- Treatment
  - Maintain on IVIG while proceeding toward transplant

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Practical Points

- Suspect XLP in male child with
  - Severe EBV infection
  - EBV-related lymphoma with abnormal immunoglobulins
- “Thunderclap”
- Close attention to family history
  - Consider evaluate family even if asymptomatic
- Do not exclude based on negative family history
  - De-novo mutation

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DOWN SYNDROME

Down Syndrome

- The most common chromosome aneuploidy
- 1:700 live births in USA
- Variable phenotype

Parker SE et al. National Birth Defects Prevention Network.
Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004-2006. Birth Defects Res A Clin Mol Teratol. 2010 Dec;88(12):1008-16.

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A Systems View of Down Syndrome

- Neurologic
- Cardiovascular
- Gastrointestinal
- Endocrinologic
- Hematologic
- Orthopedic
- Dermatologic
- Immunologic

Anatomic and Functional Abnormalities

Requires Multidisciplinary Approach

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Susceptibility to infections

- Common infections
  - Otitis media
  - Sinusitis
  - Pneumonia, bronchitis, croup

– Anatomical, functional, and immunologic factors

DS: Complicated Infection Course

- Increased duration and severity
- Higher incidence of acute lung injury
- If mechanical ventilation is required
  - Higher incidence of acute respiratory distress syndrome (ARDS)
- Down Syndrome is a risk factor for death due to sepsis

Ram G, Chinen J. Infections and immunodeficiency in Down syndrome. Clinical & Experimental Immunology. 2011 Apr 1;164(1):9-16.

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Down Syndrome: Immunologic Abnormalities

- T cell abnormalities
- B cell abnormalities
- Neutrophil abnormalities
- NK cell abnormalities have been investigated but unclear significance

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Practical Points

- Many syndromes are associated with immune defects
- A potential pitfall is to blame infections on non-immunologic factors alone
- Do not hesitate to refer to immunology

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NEW CASE

Adult-onset primary immunodeficiency?

Adult-onset primary immunodeficiency?

- 38 year old Caucasian female
- “Sick a lot as a child, but didn’t go the doctor. My mom treated me with tea and triaminic.”
- Otherwise well until 30’s
- Chronic sinusitis started age 32
- Recent hospital admission for severe lobar pneumonia
  - Chest CT demonstrated bronchiectasis
- No otitis media or other infections

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Adult-onset primary immunodeficiency?

- CBC
  - normal
- IgG 310 L
- IgA <10 L
- IgM 94

- Zero out of 14 pneumococcal titers protective post vaccine

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Adult-onset primary immunodeficiency?

Common Variable Immune Deficiency

CVID

Common Variable Immune Deficiency

- Most prevalent form of severe antibody deficiency
- Affects children and adults
  - Average age at onset of symptoms 25 y/o
- Diagnosis (all of the following)
  - Low IgG
  - Low IgA and/or IgM
  - Poor response to immunizations

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CVID

- Clinical Manifestations
  - Infections 94%
  - Autoimmunity and cytopenia 29%
  - Chronic lung disease 29%
  - Inflammatory bowel disease 15%
  - Bronchiectasis 11%
  - Granulomatous disease 10%
  - Liver disease 9%
  - Lymphoma 8%
  - Other cancers 7%
  - Malabsorption 6%

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CVID: Sinopulmonary Infections

- 30% of patients have infections as their ONLY manifestation of CVID
  - Sinusitis (Very Common)
  - Pneumonia
  - Bronchitis
- 75% of patients will develop pneumonia prior to diagnosis
- Organisms
  - Pneumococcus
  - Haemophilus
  - Mycoplasma

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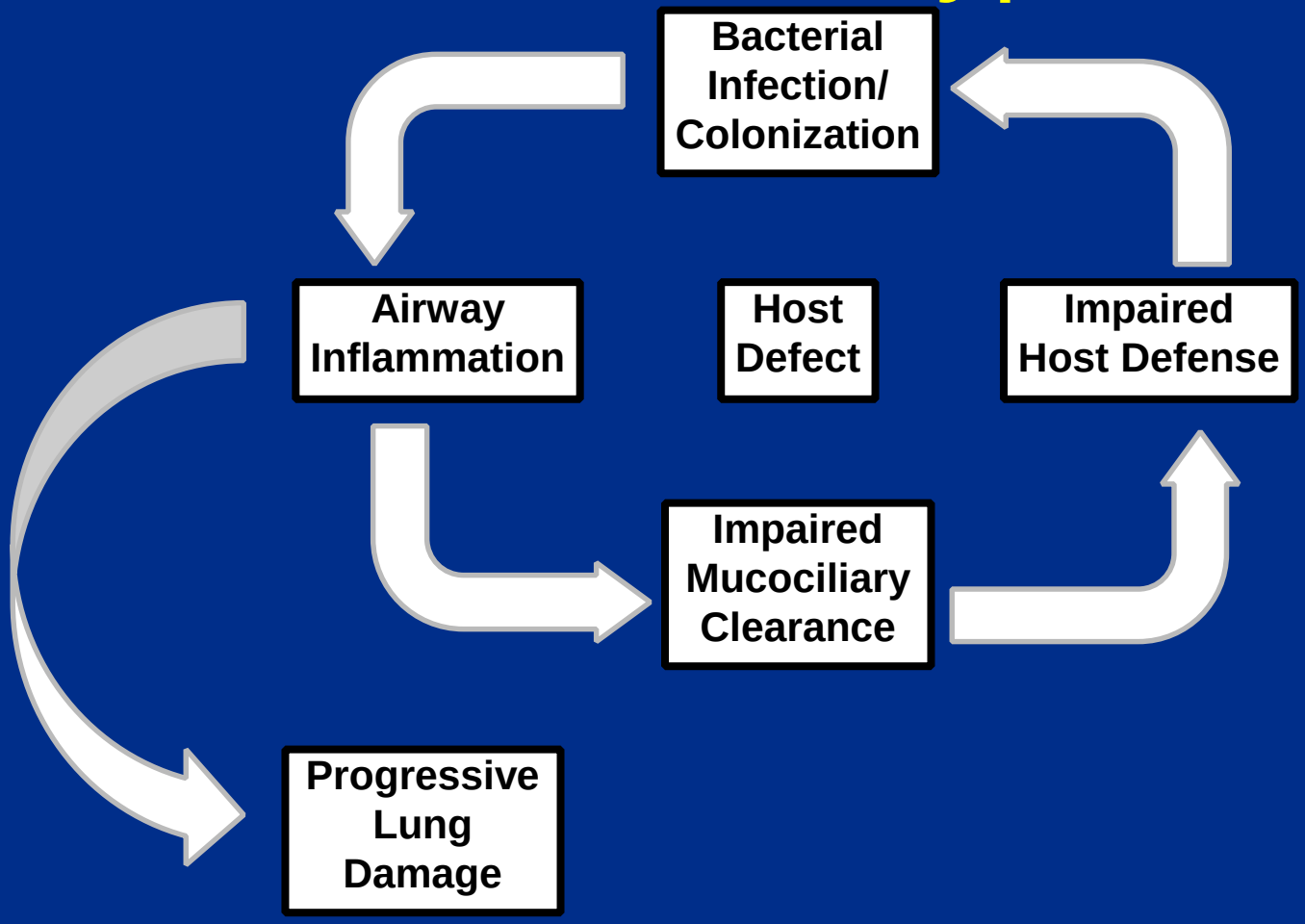
Vicious Circle Hypothesis



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Practical Points

- Patients with CVID
  - Commonly diagnosed in adult years
  - Commonly have bronchiectasis at diagnosis
- Important to diagnose as early as possible
  - Remember our first case?
  - “Always sick” or frequent respiratory infections could be a red flag
- CVID could present with autoimmunity

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CONCLUSION

Conclusion

- Maintain suspicion of PI
- Early treatment may prevent morbidity
- Do not expect to see invasive infections
- Infections of unusual
  - Frequency
  - Severity
  - Organism
  - Anatomical location
  - Host response

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Additional Take-Homes

- Refer to immunology center
  - Evaluation and treatment plan

- Refer to other specialists based on anatomical location of infections, other complications
  - ENT
  - Pulmonary
  - Others (derm, rheum, heme/onc, ID)

- **Do not forget HIV screening**
  - CDC recommends
    - At least once (age 13-64)
    - At least yearly if risk factors

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10 Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. **If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.**

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PI.

References

- Cunningham-Rundles, C. et al. Clinical manifestations, epidemiology, and diagnosis of CVID in adults. Uptodate.com. 2012.
- Immune Deficiency Foundation. PRIMARY IMMUNE DEFICIENCY DISEASES IN AMERICA: 2007.
- Info4PI.org. Jeffrey Modell Foundation.
- Bellanti, J., ed. Immunology IV: Clinical applications in health and disease. I Care Press. Bethesda, 2012.
- https://www.cdc.gov/hiv/testing/index.html

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Resources

- Jeffrey Modell Center for Primary Immunodeficiency
  - New Orleans: 504-896-9589
  - Website: Info4PI.org
  - My email: lwall@lsuhsc.edu

- Immune Deficiency Foundation
  - Website: primaryimmune.org

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Southern Regional Meeting
February 13-15, 2020
New Orleans. Louisiana

Academic Pediatric Association
Southern Section – American Federation for Medical Research
Southern Society for Clinical Investigation
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Southern Society for Pediatric Research

SOUTHERN SOCIETY FOR PEDIATRIC RESEARCH (SSPR)

February 13-15, 2020

Hotel Intercontinental, New Orleans

Abstract deadline October 11, 2019

Thank You!

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