SPOTTING MEASLES IN PEDIATRIC SOT RECIPIENTS

With low vaccination rates leading to the re-emergence of vaccine-preventable infections, measles exposure and infection pose a real risk to our solid organ transplantation recipients (SOT). These fast facts were developed for PID fellows to 'spot' measles and implement appropriate and timely interventions and management.

BACKGROUND

- Measles, first described in the 9th century, determined to be a respiratory tract infection in patients with fever who were noted to have a large buffy coat in blood in 1759[1]
- Became a reportable infection in 1912; pre-vaccination, estimated to cause ~3-4 million measles cases/yr in US
- 1st measles vaccine licensed in US in 1963, a two-dose vaccination schedule was recommended in 1989, and US endemic measles was declared eliminated in 2000.[2]
- In 2019, CDC reports the largest number of measles cases in US since 1994[3] ascribed to **low measles vaccination rates**, **outbreaks in close knit communities**, and **imported cases**, with 77% of cases occurring in children ≤ 19 yrs.[4] Worldwide, WHO estimates that 7 million measles cases occur/yr **with increasing global measles burden** since 2016.[4] From Jan-July 2019 WHO reported 364,808 cases, with the largest increases in Europe, Africa, and Western Pacific region.[5] In 2019, 1,276 cases reported in 31 US States[6]

EPIDEMIOLOGY

- RNA virus of the paramyxovirus family, one of the most contagious infectious diseases (R_0 9-18) with an attack rate ≥ 90% (9 out of 10 susceptible exposed people will develop disease)
- Transmission: largely respiratory
  - Direct contact with **infected droplets** over short distances
  - Small **aerosolized particles** that can remain in air or on surfaces for up to 2 hours after an infected person vacates that space
- **Any person who was in the same airspace with a contagious patient or for up to 2 hours after the infected person has left should be considered exposed**
- Period of infectivity (peak levels of viremia): From 4 days before rash onset through 4 days after rash appears
- Immunocompromised patients
  - Excrete virus for prolonged period
  - Contagious for duration of illness
- Incubation period: 10-14 days (range 7-23 days)[7,8]
- Temperate climates: Peaks in late winter and early spring
- Acceptable presumptive evidence of immunity pre-SOT[4,9]
  - Written documentation of adequate vaccination (two doses of measles-containing vaccine for school-age children and adults) OR
  - Laboratory evidence of immunity (rubeola IgG) or confirmation of prior disease

CLINICAL MANIFESTATIONS[10,11]

- **Case definition = (1) Fever ≥101°F, + (2) cough, coryza, or conjunctivitis, + (3) generalized MP rash lasting ≥ 3 days**
- Classic presentation Fever ≥101°F and 3Cs (first viremia) -> Koplik spots (1-3mm white elevations with erythematous base, lasting 12-72h) -> followed 2-4 days later by characteristic rash (second viremia) lasting at least 3 days
  - Rash is erythematous, maculopapular beginning ~14 days after exposure first on face and spreading cephalocaudally to involve trunk and extremities, and fades in the order it appeared
  - Immunocompromised hosts may have an atypical clinical presentation, with 30% NOT developing a rash[12]
- 'Atypical measles' may occur in persons receiving killed measles vaccine and exposed to wild-type measles, presenting with fever, pneumonia, pleural effusions, and edema. Rash is variable (may be MP or petechial, but can be urticarial, purpuric, vesicular) and appears first on wrist/ankles
- Modified measles occurs in persons with pre-existing, but incompletely protective measles antibody (vaccine or immunoglobulin), may be milder
- Complications[11] occur in ~ 20-30% of measles cases: diarrhea (8%), otitis media (7%), laryngotracheobronchitis

Severe complications: At highest risk for severe disease and complications are children <5 y and those with compromised immune systems. Heralded by persistence or recrudescence of fever beyond the 3rd/4th day of rash onset and include:

- Measles virus causes a suppression of B and T cell responses
  - Secondary bacterial and viral infections, including pneumonia (6%)
  - Perturbations in naïve and memory B cells, leading to immune amnesia[13,14]
- Respiratory: measles giant cell pneumonia or pneumonitis[12,15,16] leading to respiratory failure and ARDS
  - Accounts for >90% of measles-associated deaths, esp in children <5 yrs[11,16]
- Keratoconjunctivitis leading to blindness (rare post vaccination and vitamin A supplementation)
- CNS syndromes[17,18]
  - Acute encephalitis (0.1%), CSF with elevated protein and pleocytosis; 25% neuro complication, case fatality rate of 15%
    - Subacute measles encephalitis may occur in SOT, 2-4 wks afterwards with AMS and no fever[19]
  - ADEM occurring in 1/1,000 cases day to weeks after infection: fever, AMS, seizures
  - Measles inclusion body encephalitis (MIBE)[20] occurring in immunocompromised hosts[21,22] up to 1 yr after infection; present with afebrile focal seizures and altered mentation; CSF may be normal and not detect measles PCR or measles Ab, abnormal EEG (epilepsia partialis continua), Dx requires brain biopsy with measles IHC or RT-PCR
  - Subacute Sclerosing Pan Encephalitis (SSPE): progressive neurodegenerative disease developing 7-10 yrs after infection[23], most frequently in unvaccinated children infected during infancy[24]; occurs in every 7-11 measles cases/100,000, though may be more frequent than previously thought (1/1700 cases).[24,25]
- Other: hepatitis[26], myocarditis[27] and heart block [28], agranulocytosis[29]
- Death occurs in 2-3 out of every 1,000 reported cases

DIAGNOSIS[30]

- **Isolation of measles virus from urine, nasopharynx, blood, throat; *or* positive measles IgM, *or* 4-fold rise in measles IgG (by EIA or HI)** (at rash onset and 10-30 days later)**.** Serologic testing methods may not be reliable in immunocompromised hosts.
- **Contact your infection prevention/control team to coordinate testing with local (county, state) health departments**
- **Early recognition is important since the sensitivity of serologic (IgM) and molecular tests decline as disease course progresses**
- Serologic testing
  - May have reduced sensitivity in SOT
  - IgM may not be positive until 4 days *after* rash onset [repeat test if initial early test negative and high suspicion][31]
- Molecular testing (i.e. PCR)
  - Send as soon as diagnosis suspected
  - Detection window is short but prolonged viral shedding can be seen in SOT[18]
  - Can be more sensitive than serology[32] especially in SOT
  - Testing from multiple sites improves sensitivity: can send from NP, OP, urine; BAL fluid, CSF (when applicable)

TREATMENT

- No established role for antiviral therapies (ribavirin, interferon, immune globulin) in any form of measles in SOT
  - Decisions re: treatment should be on a case-by-case basis
- Consideration of reduction in immunosuppression, if clinically possible
- **Ribavirin** has demonstrated possible efficacy in healthy and immunocompromised patients based on case reports and series but its role in the SOT recipient is unknown

- Ribavirin
  - Early trials demonstrated some benefit in healthy children with measles; Possibly beneficial in adults with severe pneumonitis[33]
  - Early therapy in immunocompromised patients may improve outcomes[34]
  - Potential benefits should be weighed against possible severe side effects
- **Vitamin A** has been shown to improve outcomes in children and is recommended for SOT with measles[35]
  - Vitamin A
    - Vitamin A deficiency is associated with more severe disease and complications from measles infection
    - Supplementation during infection in developed countries improves morbidity and mortality in children under 5[35] and is recommended by WHO for all children with measles
    - In the U.S. and other developed countries, Vitamin A should be given to all children with acute measles[36,37], including hospitalized and immunocompromised hosts: HCT[38], including SOT
    - Dosage and administration: Given PO once daily for 2 days (IV formulation also available in US)
      - <6 months: 50,000 IU
      - 6-11 months: 100,000 IU
      - ≥12 months: 200,000 IU
      - Consider 3rd dose 4-6 weeks later in patients with signs/symptoms of Vitamin A deficiency

PREVENTION ≥ 98% of persons receiving 2 doses of MMR develop serologic evidence of immunity[38,39]

VACCINATION[9]

PRE-TRANSPLANT

- Review immunization records at any time a patient is being considered for SOT and first pre-SOT visit
  - Candidates should have received 2 doses of MMR vaccine (first dose after first birthday, second dose minimum of 28 days later) to be considered immune
- If unable to obtain immunization record or if in doubt, obtain measles/rubeola IgG
- If non-immune and transplant not expected within 4 weeks of vaccine administration:
  - Candidates ≥12 months of age: Ensure 2 doses of MMR, separated by a minimum of 4 weeks
  - Candidates 6-12 months of age: 1 dose of MMR
    - Passively acquired maternal antibody may interfere with child's ability to respond to vaccine
    - If transplant has not occurred by child's 1st birthday, MMR should be repeated
  - Blood products interfere with response to vaccine and a sufficient time interval should elapse between blood products and MMR administration, if clinically possible. Refer to: https://redbook.solutions.aap.org/chapter.aspx?sectionid=189639967&bookid=2205)
- Exclude organs from living or deceased donors
  - With proven or suspected measles
  - Who are suspected recent contacts of a measles case

POST-TRANSPLANT

- MMR vaccine is *generally* contraindicated after SOT
- Certain SOT recipients (liver, kidney SOT receiving low dose immunosuppression) may be candidates for MMR administration[40,41] after transplant and during an outbreak or if must travel to an endemic country

POST-EXPOSURE PROPHYLAXIS

- If a susceptible SOT recipient has been exposed to measles:

  - Provide immunoglobulin (IG) within 6 days of exposure
    - IGIM at a dose of 0.5 mL/kg IM (max dose 15 mL)
    - IGIV at a dose of 400 mg/kg IV (preferred for those >30 kg or those who are severely immunocompromised)
    - Not necessary for children receiving IVIG at regularly scheduled intervals at a dose of 400 mg/kg or more if last dose within 3 weeks of exposure
    - Do NOT provide MMR vaccine and IG simultaneously
- Avoid travel to areas of active measles outbreak or endemicity
- Vaccinate household and close contact of SOT recipient
  - Safe and *recommended* for siblings, non-immune adult family members, and anyone who has contact with the SOT recipient

INFECTION CONTROL[38,39]

- Do not direct stable patients with suspected measles to your transplant clinic. Preplanning required to minimize transmission risk. Patients who require hospitalization should be masked, removed from common areas, and immediately placed in airborne isolation (ensure negative pressure ≥ -2.5 Pa).
- Staff should wear N95 masks
- Notify your local health department (Class A reportable disease)

This timely topic in peds TID was created by PIDS Transplant ID Education Subcommittee members: Victoria Statler (U Louisville), Thomas Fox (Emory) and Monica I. Ardura (Nationwide Children's & The Ohio State University); v. December 2019

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Spotting measles in peds SOT: it is not 'just' a rash

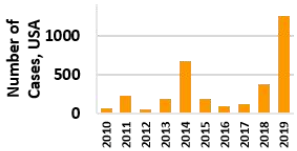
Measles (ssRNA)
Exposure

Incubation

14 days [6-21 days]

Asymptomatic
Mild respiratory symptoms

9 out of 10 unvaccinated people will contract measles after exposure



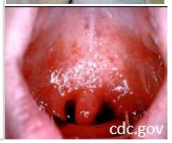
Prodrome

2-4 days

Fever >101, malaise, anorexia

3Cs:
Conjunctivitis
Cough
Coryza

Koplik spots



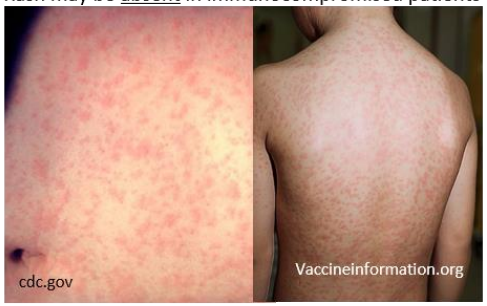
Exanthem

2-4 days

Lymphadenopathy, ongoing fever, worsening C's

Rash

maculopapular, head to toe, lasts ≥ 3 days
Rash may be absent in immunocompromised patients



Recovery

Complications
(per 1,000 infected)

- Hospitalized x50
- Pneumonia x10
- Permanent Disability
- Death
- Encephalitis

Occurring more frequently in children <5 years and immunocompromised

Virus enters via respiratory tract or conjunctivae, replicates locally, and primary viremia leads to dissemination

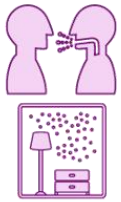
Airborne Isolation

Management

suspect | isolate | confirm diagnosis | report | prevent

Immunocompromised patients with measles should remain in airborne precautions for duration of illness (not just 4 days after rash onset)

Ascertain exposure & risk for disease



Lives in air and on surfaces for up to 2 hrs

Mask
- patient & ill family members
- yourself

Isolate suspected patient & family into **airborne isolation** room ASAP

Measles RNA detection by RT-PCR
- NP, throat swab, BAL
- Serum
- Urine

Serology (serum)
- measles IgM (EIA) + (if collected ≤3 days from rash onset, recheck in 7-10 days)
- 4-fold increase in acute and convalescent measles IgG (minimum 10 days apart)

Test ASAP after rash onset & increase diagnostic yield by testing serum, throat, and urine

Treatment
- Vitamin A (oral, once daily x 2 days)
  - <6 mos: 50,000 IU
  - 6-11 mo: 100,00 IU
  - ≥ 12 mo: 200,000 IU
- Treat bacterial superinfections
- Unknown role: ribavirin (IV, aerosol), IFN, IG

Coordinate diagnostic testing with lab and local health department

Prevention

Population immunity required to stop ongoing measles transmission

Vaccination

Moments for MMR vaccination:

PRE-SOT
Measles live-attenuated vaccine (MMR): 2-dose series at 12 months (as early as 6 months of age) and at 4 years, minimum 28 days apart

POST-SOT MMR *may* be an option in certain SOT recipients

ANY TIME for caregivers and household contacts and as PEP (see below)

Evidence of measles immunity:
1. pre-K: Documentation of 1 dose of MMR after 12 moa
2. K-12: As above + a 2nd MMR dose a minimum of 28 days after first
3. Laboratory evidence of immunity or disease

Post-exposure prophylaxis

For susceptible people exposed to measles
1. MMR vaccine within 72 hours (if no contraindication to vaccine)
2. Immune globulin within 6 days
   - IGIM if <30 kg [dose 0.5 mL/kg, max 15 mL]
   - IGIV if >30 kg or severely immunosuppressed or pregnant [dose 400 mg/kg]

https://www.cdc.gov/infectioncontrol/pdf/guidelines/Measles-Interim-IC-Recs-H.pdf
https://www.cdc.gov/measles/hcp/index.html#prophylaxis
Link to measles CDC infographic for patients
English:https://www.cdc.gov/measles/parent-infographic.html
Spanish:https://www.cdc.gov/measles/parent-infographic-sp.html