Vaccination recommendations for infants exposed to maternal immunosuppression

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Background:

- An increasing number of infants are being exposed to maternal immunosuppression in utero, including biologic disease modifying anti-rheumatic drugs (bDMARDS).
- Due to concerns surrounding persistence of drug levels and resulting immunosuppression (and risk of vaccine associated disease), current case reports suggest avoidance of live-attenuated vaccines in an infant for 12 months following bDMARDS exposure. This has significant implications to rotavirus vaccination.
- To date, current information on long term effects of in utero exposure to biologics on infant immune responses, infectious complications and implications to vaccination have focused on anti-TNFα agents (infliximab, adalimumab) and to a lesser degree, rituximab. Less is known for other biologics and ongoing studies are required.
- The below recommendations are based on available case series data and expert opinion.
- Where possible, the below discussions should be facilitated in the third trimester with the mother to allow for timely vaccination in the infant.
- In Australia, the current oral rotavirus vaccine on the National Immunisation Program (NIP) is Rotarix, with the first dose recommended to be administered before an infant turns 15 weeks of age.

Vaccine and investigation recommendations:

Vaccine recommendations: The following vaccine recommendations are for otherwise healthy newborns (ie. no history of invasive or opportunistic infections) with a history of perinatal exposure to maternal biologics use.

Live-attenuated vaccines

- Receive the rotavirus vaccinations as per the recommended schedule.
- Bacille Calmette-Guerin (BCG) vaccine should be withheld for the first 12 months of life.
- No contraindication to measles, mumps, rubella (MMR) vaccine given routinely at 12 months and measles, mumps, rubella and varicella (MMRV) vaccine given routinely at 18 months of age.
- We suggest referral to specialist immunisation clinic for:
    - First nations infants (<12 months) or infants (<12 months) living or spending prolonged periods in tuberculosis-endemic areas for consideration of BCG vaccination. Emerging evidence has suggested that BCG can be facilitated in low-risk infants from 6 months of age.

- Infants travelling overseas (<12 months) where measles, varicella or yellow fever is endemic.

Inactivated vaccines

There is no risk of vaccine-associated disease associated with inactivated vaccines [e.g. Infanrix Hexa, Pneumococcal conjugate vaccine (PCV)]

- We recommend that a medical at-risk dose of PCV (i.e. Additional dose of 13vPCV at 6 months of age) should be considered in neonates exposed to more than one immunosuppressive agent in pregnancy (i.e. anti-TNFα agent + azathioprine or 6-meraptopurine).
- No additional booster doses of inactivated vaccines are required.

<u>Investigation recommendations (drug levels, immune work-up, vaccine responses):</u>

- For otherwise healthy infants, immune work-up, vaccine response serology and drug levels are not routinely required.
- We do not recommend the routine use of drug levels in the assessment of timing of live attenuated vaccines.
- Immune work-up, vaccine responses and drug levels +/- immunology referral should be considered on a case-by-case basis in the following higher risk settings:
    - Exposure to multiple concurrent maternal immunosuppression agents up to/and including the third trimester.
    - History of invasive or opportunistic infection

Risk assessment in an infant exposed to in-utero biologics:

- The risk of immunosuppression to an infant exposed to in-utero biologics is related to the timing of administration of maternal biologics and use of any other concurrent immunosuppressive therapy.
    - The greatest risk in the infant is in the first six months following exposure to in utero biological therapies (out to a maximum of 12-months, depending on the biologic therapy)
    - Increased risk in the infant is associated with 1) administration close to delivery and 2) multiple concurrent immunosuppressive agents.
- Counselling should be individualised for each infant, and the following factors should be considered:
    - Characteristics of the drug exposure (ie. drug and last use)
    - Concomitant maternal immunosuppressive therapy (present or absent)
    - Local infectious epidemiology
    - Live-attenuated vaccine(s) being considered
- In mothers who have received more than one immunosuppressive agent during pregnancy, we would suggest discussion +/- referral to specialist immunisation clinic ideally at 6 weeks of age.

Rationale for vaccine & investigation recommendations:

- Antenatal counselling on commencement of maternal biologic is recommended.
- Despite potential impacts to cellular and humoral immunity in infants exposed to bDMARDS in utero, adequate vaccination responses have been demonstrated following administration of standard inactive vaccines (despite persistence of drug levels) without any major infectious complications reported.
- Several case series have reported safe administration of rotavirus vaccine in this cohort of infants. Given the high rate of natural infection in those unvaccinated, it is likely that the benefits of rotavirus vaccine outweigh the potential risk of vaccine related gastroenteritis.
- The Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry suggests a higher rate of respiratory infections in neonates exposed to combination therapy (anti-TNFα agent with azathioprine or 6-mercaptopurine). Given this, we recommend that neonates exposed to more than one immunosuppressive agent receive medical at-risk dose of Prevenar 13 in the first year of life (at 6 months of age).
- Disseminated BCG infection is associated with high mortality rate and there is currently insufficient safety data to support routine administration of BCG vaccine in the first 12 months of life, following a fatal case of disseminated BCG infection in an infant exposed to peripartum infliximab.
- While serum drug levels in the infant may be useful as part of a clinician's assessment regarding safety for live-attenuated vaccine, it is unclear whether this correlates to immune dysfunction in an infant. Testing of serum drug levels of the various biologics is also not readily available in many countries.

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