Medical Conditions as Risk Factors for Invasive Meningococcal Disease

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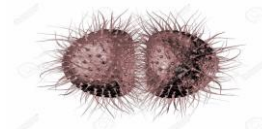
Invasive Meningococcal Disease (IMD)

- Caused by the bacterium *Neisseria meningitidis*
- 2017 Notification rate in Australia: 1.6 per 100,000 person[1]
- Vaccines available in Australia against: Serogroups B, C, and ACWY



1. Invasive meningococcal disease national surveillance report, 31 Dec 2017. Department of Health
Source of graph: https://www.123rf.com/photo_66213129_stock-illustration-bacteria-neisseria-gonorrhoeae-or-neisseria-meningitidis-gonococcus-and-meningococcus-3d-illustratio.html

Current recommendations for high-risk medical conditions

- Australian and international guidelines recommend additional doses of 4vMenCV and MenB for:
  - Defects or deficiency of complement components
  - Current or future treatment with eculizumab
  - Functional or anatomical asplenia
  - HIV infection, regardless of stage or CD4$^+$ count
  - Haematopoietic stem cell transplant (HSCT)

What's the epidemiological evidence?

Literature review to answer:

- Which groups are at increased risk for IMD?
  ⇨ Epidemiology
- If they are, what's the appropriate schedule?
  - Which vaccine ⇨ Epidemiology (serogroups)
  - Are additional doses needed ⇨ Vaccine

Methods

- Comprehensive literature search, from the inception of Medline and Embase up to 31 December 2017
- Inclusion criteria
  - Magnitude of risk
  - Performance of vaccine
- Quality assessment, modified from GRADE

Downgrading factors	Upgrading factors
Risk of bias	Clear dose effect
Indirectness	Large magnitude of effect
Inconsistency	
Imprecision	

GRADE Handbook: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html

Increased risk? – the "yes"

HIV infection
- Three large cohort studies in the UK and US[1, 2, 3]
- Consistently reporting risk ratio ~10 in adults

Complement deficiency
- One comprehensive review[4]
- 50% had at least one episode of IMD, and often had recurrent infections

Eculizumab treatment
- Clinical studies and post-marketing monitoring[5]
- 330 or 830 IMD cases per 100,000 person-years

1.Harris CM et. al. *Open Forum Infect Dis* 2016;3:ofw226.
2. Miller L et al. *Annals of Internal Medicine* 2014;160:30-7.
3. Simmons RD et al. *BMC Med* 2015;13:297.
4. Figueroa JE, Densen P. *Clin Microbiol Rev* 1991;4:359-95.
5. Alexion Pharmaceuticals. Drug Safety and Risk Management Advisory Committee, Briefing Document for Soliris.2014.

Increased risk? – the "maybe"

Asplenia

- Inconsistent:
  - Incidence of severe bacterial infection post-splenectomy: ranged from <1 – 8/100 person-year[1]
  - Proportion caused by *N. meningitidis*: ranged from 0 - 3.6%[1]
- Indirect: unable to determine incidence rate specific to IMD
- Higher risk in subgroups: people with underlying haematological conditions, and the first 2 years post-splenectomy[1]

HSCT

- Indirect: unable to determine incidence rate specific to IMD[2]

1. Hellenbrand W et al. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2015;58:1314-43.
2. van Veen KE et al. *Bone Marrow Transplant* 2016;51:1490-5.

Increased risk? – the "maybe"

Pre-term birth or low birth weight

- Inconsistent: relative risk of IMD ranging from nil[1, 3] to 3.7[2]
- Maternal smoking is a potential confounder[1,3]

Cerebrospinal fluid leak

- One data linkage study: OR 8.8 (1.2 – 62.4) [4]

Autoimmune disease

- One data linkage study: OR ~2 [4, 5]

Solid organ transplant

- One data linkage study: OR 20.0 (5.0 – 80.0) [5]

1. Sorensen HT et al. *Int J Epidemiol* 2004;33:816-20.
2. Tully J et al. *BMJ* 2006;332:445-50.
3. Goldacre MJ, Wotton CJ, Maisonneuve JJ. *Epidemiol Infect* 2014;142:371-8.
4. Lundbo LF et al. *Open Forum Infectious Diseases* 2016;3:957-.
5. Lundbo LF et al. *Open Forum Infectious Diseases* 2017;4:S7-S.

Is repeated vaccination required? – the "yes"

Risk factor	Multiple vs. one dose	Serogroups/vaccine
HIV infection	Improved immune response against serogroup C; Less waning of immunity [1, 2, 3]	Increased risk of B, ACWY
Complement deficiency	Multiple episodes of breakthrough disease after one dose* [4]	Increased risk of B, ACWY
Eculizumab treatment	Higher seroprotection rate [5]	Increased risk of B, ACWY

*No studies investigating effect of booster vaccine doses

1. Lujan-Zilbermann J et al. *J Pediatr* 2012;161:676-81 e2.
2. Siberry GK et al. *Pediatr Infect Dis J* 2012;31:47-52.
3. Siberry GK et al. *Pediatr Infect Dis J* 2010;29:391-6.
4. Fijen CA et al. *Clin Exp Immunol* 1998;114:362-9.
5. Alashkar F et al. *Ann Hematol* 2017;96:589-96.

Is repeated vaccination required?– the "maybe"

- Similar immune response as healthy controls in:
  - Asplenia, except in some subgroups [1]
  - HSCT [2]
  - Autoimmune disease (juvenile idiopathic arthritis) [3]
- Inconsistent results for people after solid organ transplant [4, 5]

1. Balmer P et al. *Infection and Immunity* 2004;72:332-7.
2. Patel SR et al. *Clin Infect Dis* 2007;44:625-34.
3. Stoof SP et al. *Ann Rheum Dis* 2014;73:736-34.
4. Zlamy M et al. *Vaccine* 2011;29:6163-6.
5. Wyplosz B et al. *Transpl Infect Dis* 2015;17:322-7.

Conclusion

- Variation in quality of evidence
  - Risk factors needing additional vaccination:
    HIV infection, complement deficiency, eculizumab treatment
  - New evidence may change the current recommendations:
    Asplenia, HSCT, and other immunocompromised conditions
- Large population studies, such as using linked data, would be valuable in understanding risk factors

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