Vaccination guideline for patients under 18 years of age treated with eculizumab or ravulizumab

Title	Vaccination guideline for patients under 18 years of age treated with eculizumab or ravulizumab
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Reviewed by	NRCTC MDT
Target audience	Clinicians and healthcare professionals caring for children and young people with aHUS
Level of evidence	4 expert committee reports or opinions and / or clinical experiences of respected authorities
This guideline/SOP has NOT been registered with the Trust yet. Clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date	
Versions	
V1.0	25/03/2022

Background:

Eculizumab and ravulizumab treatment increases children's susceptibility to meningococcal infection approximately 600-2000 times. This includes disease due to uncommon serogroups (Y and W) as well as more common serogroups (including B or C). Meningococcal infections can be very serious, causing meningitis and sepsis, which can lead to severe brain damage, amputations and, in some cases, death.

Summary of recommendations:

To reduce the risk of meningococcal disease, the following steps should be followed in all children receiving eculizumab or ravulizumab:

1. Ensure that patient is vaccinated against serogroups ACWY and B either by confirming vaccination status as per regular schedule, or vaccinate the patient if no vaccine against meningococcus has previously been given or if vaccination status cannot be obtained.
2. Initiate long-term antibiotic prophylaxis – for the duration of eculizumab / ravulizumab therapy, (recommend a minimum of 2 half lives - 4 weeks post-discontinuation of eculizumab (half life approximately 14.5 - 15.8 days) and 4 months following discontinuation of ravulizumab (mean half life 51.8 days)
3. Children, young people and their families should be given information on the early symptoms of meningococcal disease and be made aware of the need for immediate medical review if infection is suspected. They should be made aware that infection can occur despite vaccination AND antibiotic prophylaxis.

In addition, specific guidance is given regarding the risk of other infections such as pneumococcus and Haemophilus influenza type B

Recommendations in more detail:

1. Vaccination against meningococcus

- It is mandated by the manufacturer of eculizumab and ravulizumab (Alexion), in the Summary of Product Characteristics (SmPC), that all individuals who are to receive eculizumab or ravulizumab therapy should be vaccinated against meningococcus at least two weeks prior to commencement of therapy
- If this is not possible, vaccination should be delivered as soon as practicable and the patient must receive at least 2 weeks continuous antibiotic prophylaxis

We recommend that children receiving eculizumab or ravulizumab should be vaccinated with <u>both</u>:

- **Meningococcal B vaccine (Bexsero®) and**
- **Conjugate meningococcal ACWY vaccine**

Meningococcal B vaccine (Bexsero®)

Bexsero® is a licensed meningococcal vaccine based on outer membrane vesicle and surface proteins. The vaccine has been included in the *routine* UK NHS vaccination programme at 8 weeks, 16 weeks and 12 months of age since May 2015 and the schedule can be viewed here NHS vaccinations and when to have them - NHS (www.nhs.uk). It is important to see evidence that Bexsero® has been given in eligible children (e.g. hand-held record or via the GP).

For children and young people who are to receive eculizumab or ravulizumab therapy but have not received a full course of Bexsero® vaccination, guidance regarding the number and timing of doses and requirement for boosters can be found within the Bexsero® SmPC Bexsero Meningococcal Group B vaccine for injection in pre-filled syringe - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Bexsero® boosters

The SmPC gives clear guidance for boosters of Bexsero® in children under the age of 2 years. However above this age, there is no clear evidence regarding boosters for any patient group, including those on eculizumab / ravulizumab. This is compounded by the fact that antibody titres for serogroup B cannot be measured in patients on eculizumab / ravulizumab, as the drugs interfere with the assay. Serogroup B is one of the more common strains in the UK and the Bexsero SmPC does highlight waning antibody titres over time following vaccination. Therefore, until further evidence becomes available to support decisions on boosters in this high-risk population, our recommendation is that it would be prudent to offer **5 yearly** Bexsero® boosters to this patient cohort.

Response to meningococcal B vaccination – antibody titre measurement

- Response to vaccination should be assessed – B antibody titres should **only** be checked in patients **not** receiving eculizumab / ravulizumab, who are awaiting kidney transplantation with pre-emptive eculizumab (B titres, along with CW and Y titres should be measured annually in this group)
- A serum sample should be sent to the Meningococcal Reference Unit (UK Health Security Agency) for meningococcal B serum bactericidal antibody
- Patients with a sub-optimal response (titre less than 4 for any serogroup subtypes: B fHbp; B Nada; B PorA should be re-vaccinated – advice about this can be obtained from the aHUS specialist nurses (ahus.nurses@nhs.net)
- No further vaccination should be given if a sub-optimal response (titre less than 4 of any components) is seen **after one additional booster**

Conjugate meningococcal ACWY vaccine (MenACWY)

There are two approved tetravalent meningococcal ACWY polysaccharide vaccines in the UK:

- Menveo® - licensed for children aged 2 years and older
- Nimenrix® - licensed for children aged 6 weeks and older

The MenACWY vaccination was introduced into the UK NHS vaccination programme in 2016 at age 14 years of age. When starting eculizumab / ravulizumab treatment, it is important to see evidence that this has been given in eligible children, noting this would only routinely include children aged over 14 years.

For children and young people who are to receive eculizumab or ravulizumab therapy, guidance regarding the type of vaccine and number and timing of doses is given in Table 1. More details can be found in the SmPCs for both products Nimenrix - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) and Menveo Group A,C,W135 and Y conjugate vaccine - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Table 1: MenACWY vaccination schedule for children and young people who are to receive eculizumab / ravulizumab therapy:

Age	**Initial MenACWY vaccination**	**Subsequent boosters for MenACWY**
Less than 6 weeks	Antibiotic prophylaxis only until 6 weeks of age, then at 6 weeks of age, give a two doses of Nimenrix® 4 weeks apart	
6 weeks to <12 months	Two doses of Nimenrix® 4 weeks apart	One dose conjugate MenACWY vaccine when aged over 10 years (this could be given at 14 years as part of the UK vaccination schedule). *Or as indicated following results of annual CWY meningococcal titre measurement*
12 months to 23 months	*If not yet administered, give the routine vaccines due at 1 year of age (Hib/MenC/ PCV13/MMR/MenB) plus:*	One dose conjugate MenACWY vaccine when aged over 10 years (this could be given at 14 years as part of the UK vaccination schedule)

	One dose of Nimenrix® at least 8 weeks after *Hib/MenC/ PCV13/MMR/MenB* vaccines	*Or as indicated following results of annual CWY meningococcal titre measurement*
24 months to less than 10 years	Give one dose of conjugate MenACWY	One dose conjugate MenACWY vaccine when aged over 10 years (this could be given at 14 years as part of the UK vaccination schedule) *Or as indicated following results of annual CWY meningococcal titre measurement*
10 years – <14 years	Give one dose of conjugate MenACWY	One dose conjugate MenACWY vaccine when aged over 10 years (this could be given at 14 years as part of the UK vaccination schedule) *Or as indicated following results of annual CWY meningococcal titre measurement*
14 years – 18 years	Give one dose of conjugate MenACWY**	If received a MenACWY via UK vaccination schedule already, measure meningococcal titres (CWY). Offer MenACWY booster if any of these serotypes less than 8.

** If not received a MenACWY already via the UK vaccination schedule

Response to meningococcal ACWY vaccination – antibody titre measurement and when to offer MenACWY boosters

- Response to vaccination should be assessed – CWY* antibody titres should be checked 4-6 weeks post-vaccination or booster, and should be performed in any vaccinated patient in whom they have not been previously assessed
- A serum sample should be sent to the Meningococcal Reference Unit (UK Health Security Agency) for meningococcal C, W and Y serum bactericidal antibody. The form needed can be found on our website: https://www.atypicalhus.co.uk/wp-content/uploads/2022/01/Manchester-Lab-Form-Patient-on-Treatment.pdf)
- Patients with a sub-optimal response (titre less than 8 for any serogroup C,W or Y) should be re-vaccinated – advice about this can be obtained from the aHUS specialist nurses (ahus.nurses@nhs.net) and titres should be checked 6 weeks later

- If a sub-optimal response (titre less than 8 of any components) is seen after this second vaccination, anecdotal experience suggests it may be of benefit to try a further vaccination with the alternative brand of MenACWY vaccine, but after this, no further vaccination should be given
- Patients on eculizumab / ravulizumab should have **annual** meningococcal titres measured

* Titres to the A serogroup are no longer measured routinely due to the low incidence of this serogroup in the UK. Measurement of A titres may be appropriate if individual are planning travel to an area of higher incidence – contact the aHUS specialist nurses in the first instance if this is considered necessary (ahus.nurses@nhs.net)

2. Antibiotic prophylaxis against meningococcus

Meningococcal disease can occur in people on eculizumab and ravulizumab despite vaccination. Therefore, we recommend that all children receiving eculizumab should take antibiotic prophylaxis against meningococcal disease (see Table 2).

Antibiotic prophylaxis should start immediately and continue through the duration of treatment with eculizumab or ravulizumab and for a minimum of 4 weeks after discontinuation (eculizumab) and for a minimum of 4 months for ravulizumab.

Table 2: dose of antibiotic prophylaxis for children on eculizumab/ravulizumab (based on dosing for prevention of pneumococcal disease in asplenia – closest indication to prevention of meningitis in children commencing C5 inhibition therapy)

Penicillin V

Age	**Dose of Penicillin V**
1 month – 11 months	62.5mg twice daily
1 - 4 years	125mg twice daily
5 – 17 years	250mg twice daily

Erythromycin* (if allergic to penicillin)

Age	**Dose of Erythromycin**
1 month – 23 months	125mg twice daily
2 - 7 years	250mg twice daily
8 – 17 years	500mg twice daily

*If intolerant/allergic to erythromycin as well, discuss with a microbiologist to find a suitable alternative

3. Information on the early features of meningococcal disease

All children and carers of children receiving eculizumab or ravulizumab should be told about the features of meningococcal disease and how to access medical care immediately if they develop these features.

Information regarding symptoms can be found as follows:

- https://www.nhs.uk/conditions/meningitis/symptoms/
- www.meningitis.org/symptoms
- "Meningitis symptoms mobile app" available from Meningitis Now at https://www.meningitisnow.org/meningitis-explained/signs-and-symptoms/download-our-mobile-app/

At risk cards

- Meningitis and septicaemia symptoms "at risk" cards should be given to patients – the manufacturer usually sends these to the prescribing clinician for handing to patients
- In addition, the National Renal Complement Therapeutic Centre (NRCTC) sends these directly to patients commenced on eculizumab or ravulizumab . If more cards are required please email: ahus.nurses@nhs.net

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Reducing the risk of other infections in children on eculizumab / ravulizumab therapy

The drug manufacturer mandates that patients less than 18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections, and strictly need to adhere to the national vaccination recommendations for each age group.

Haemophilus influenzae
In the UK, all children currently under 18 years of age will have been offered *Haemophilus influenzae* type b (Hib) vaccination as part of the routine NHS vaccination schedule. It is important to see evidence that this has been given and to vaccinate if not given previously. For more information see NHS vaccinations and when to have them - NHS (www.nhs.uk)

For children not previously vaccinated or incompletely vaccinated against Hib, please refer to the following link for advice: Vaccination of individuals with uncertain or incomplete immunisation status (publishing.service.gov.uk)

Streptococcus pneumoniae (pneumococcus)
Pneumococcal conjugate vaccine has been included in the NHS vaccination schedule since 2006. **Therefore children born before 2006 are unlikely to have received this vaccination.** It is important to check if this has been given and to vaccinate if not given previously. For more information see NHS vaccinations and when to have them - NHS (www.nhs.uk)

The Green book (Chapter 25) indicates that certain clinical risk groups should have a dose of the PPV23 vaccine in addition to the routine infant PCV13 vaccination course. Although complement disorders are listed as a clinical risk group, patients on specific C5 inhibition therapy are not included in this group.

Live vaccines

There are no contra-indications to any kind of vaccine for patients on eculizumab or ravulizumab. Whilst specific data on the safety of live vaccines for patients on these treatments is not available, we recommend all indicated vaccinations take place, since the benefit outweighs the theoretical risk of live vaccines based upon information available from the manufacturer (see separate document entitled "UK Standard Response").

References:

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