Guidelines for the prevention of meningococcal disease in adult patients receiving eculizumab or ravulizumab, or pre-approved to receive eculizumab at point of renal transplantation

Title	Vaccination guideline for patients over 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 adults with aHUS who are on eculizumab or ravulizumab, or have been pre-approved to receive eculizumab at the point of renal transplantation (and have been activated on the transplant list).
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	25/032022

Background:

Eculizumab and ravulizumab treatment increases 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 adults receiving eculizumab / ravulizumab, or those activated on the transplant list who have been pre-approved to receive eculizumab at the point of renal transplantation:

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. Patients 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.

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 adults receiving eculizumab or ravulizumab should be vaccinated with both:

- **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 since 2015, so currently adults will not have routinely received this vaccine.

For adults 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 C,W 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 (formerly PHE) 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 aged 2 years and older
- Nimenrix® - licensed for 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 adults, noting this would only routinely apply to adults born in 2002 onwards.

For adults who are to receive eculizumab or ravulizumab therapy, or are pre-approved to receive eculizumab at the point of renal transplantation, 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 adults who are to receive eculizumab / ravulizumab therapy, or have been pre-approved to receive eculizumab at the point of renal transplantation:

Age	**Initial MenACWY vaccination**	**Subsequent boosters for MenACWY**
18 years and above	Give one dose of conjugate MenACWY** *Both Menveo® and Nimenrix® licensed for adults*	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, noting this would only routinely apply to those born from 2002 onwards.

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 (formerly PHE) 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 evidence 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 or those pre-approved to receive eculizumab at the point of renal transplant 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 adults receiving eculizumab/ravulizumab 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 – we recommend continuation for 4 weeks after discontinuation of eculizumab, and for 4 months after discontinuation of 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**
18 years +	250mg twice daily

Erythromycin* (if allergic to penicillin)

Age	**Dose of Erythromycin**
18 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 adult patients 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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Streptococcus pneumonia (pneumococcus)

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 letter for further information – "UK Standard Response Letter".

Other vaccines

We would recommend that patients with atypical HUS on complement inhibition therapy receive all routine vaccines offered via the UK vaccination programme. We recognise however that there might be contraindications for some patients e.g. patients post kidney transplant also on concomitant immunosuppressive therapy are generally not permitted to receive live vaccines. see separate document entitled "UK Standard Response".

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Review date: 25th March 2027