Lgp Rain Laane
Eesti Haigekassa juhatuse esimees

1) **Palun kirjeldage, millistest tegevustest diagnostilise immuniseerimise teenus koosneb. Palume välja tuua tegevuste kestus.**
   Teenus sisaldab arsti või õe vastuvõttu (sh patsiendi hetkeseisundi hindamine enne vaktsineerimist, vaktsineerimise alane nõustamine, jälgimine 30 minutit pärast vaktsineerimist) ja vaktsineerimise teostamist

2) **Olete välja toonud, et 2018. aastal teostati ITK-s ligikaudu 60 patsiendile diagnostilist vaktsineerimist. Millised olid nende 60 patsiendi tulemused? Millist ravi rakendati positiivse diagnostika tulemusega patsientidele? Milline oleks alternatiivne tegevus nende patsientide ravis, kui diagnostilist immuniseerimist ei teostataks?**
   Diagnostilise vaktsineerimise läbinud patsientidest 18%-l kinnitus immuunpuudulikkuse diagnoos, mistõttu rakendati vastavalt immuunpuudulikkuse vormist ja raskusastmest lähtuvat ravi (sh immuunglobuliini asendusravi). Nende patsientide diagnostiliseks käsitluseks alternatiivi ei ole.

3) **Kas on erisusi kahe kasutatava vaktsiini vahel? Mille alusel otsustatakse diagnoosimiseks kasutatav vaktsiini valik? Kas on võimalik välja tuua proportsionaalne jagunemine, kui sageli kasutatakse ühte, kui sageli teist?**
   Hetkel loetakse pneumokoki polüsahhariidse vaktsiiniga vaktsineerimist spetsiifiliste antikeahade defitsiidi diagnoosikriteeriumiks (Bonilla 2015, Perez 2017, Sorensen 2019). Salmonella Typhi Vi vaktsiini eeliseks pneumokoki polüsahhariidse vaktsiini ees võiks olla selle kasutatavus immunoglobulin-asendusravil olevatel patsientidel (saadaolevad immunoglobuliini preparaadid ei sisalda S typhi antikehi) ning see, et konjugeeritud vaktsiinid ei ole erinevalt pneumokokist laialdlaselt kasutatavad, samuti on S typhi antikehade baastase lääneriikides madal. (Parker 2018)
   Hetkel piirab S typhi vastaste anikehade kasutamist immuunvastuse hindamisel Eesti tingimustes vastava antikehi määrava testi puudumine rutiinses kliinilises kasutuses.

4) **Esitatud tõendus vaktsineerimise kohta on piiratud. Millised on näidustused ja vastunäidustused, efektiivsuse ja ohutuse näitajad? Uuringute tulemused, konsensusdokumentide vastavate osade detailsemad kirjeldused? Palume konkreetseid tulemusi, soovitusi.**
   Vaktsineerimisele tekkiva immuunvastuse hindamine kuulub üldise variaabli immuunpuudulikkuse diagnoosimise juurde. On neli primaarset immuundefitsiiti, mille diagnoos põhineb suures osas puudulikul vastusel immuniseerimisele. Mitmeid primaarseid immuundefitsiite seostatakse puuduliku vastusega polüsahhariidsetele antigeenidele. Pneumokoki vastaste antikehade määramine enne ja pärast vaktsineerimist ja tekkinud immuunvastusega serotüüpide arvu hindamine on aktsepteeritud humoraalse immuunsuse hindamise meetod. (Orange 2012)
   Spetsiifiliste antikehade defitsiiti saab diagnoosida, kui vastus immuniseerimisele polüsahhariidse pneumokoki vaktsiiniga on puudulik, kuid valgulistele ja/või konjugeeritud vaktsiiniga normipärane ja immunoglobuliinide ning nende alaklasside tase on normipärane (Orange 2012, Sorensen 2019, Perez 2017)

   Diagnostilise vaktsineerimise näidustus erineb profülaktilise imuuniseerimise näidustusest.
   Vaktsineerimisele tekkiva immuunvastuse hindamine kuulub humoraalse immuunsüsteemi hindamise meetodite hulka (Orange 2012, Bonilla 2015).

On näidatud, et normipäraselt tekib vastusena pneumokoki polüsahhariidse vaktsiiniga vaktsineerimisele vähemalt kahekordne IgG tõus, pneumokoki polüsahhariidi vastase antikeha normi alumiseks piiriks pärast vaktsineerimist on 77 mg/l ning täiskasvanute hulgas ei mõjuta vanus immuunvastuse kujunemist (Parker 2019),
Salmonella Typhi Vi polüsahhariidse vaktsiiniga vaktsineerimise järel on näidatud 2-3 x IgG tõusu tervetel. On näidatud, et antikehade tõus 10x eristab üldise variaabli immuundefitsiidi patsiente tervetest kontrollidest 90,9% sensitiivsuse ja 62,5% spetsiifilisusega. (Parker 2018)

Vastunäidustused pneumokoki polüsahhariidse vaktsiiniga vaksineerimiseks (Pneumovax23) on raske allergiline reaktsioon vaktsiini või selle koostisosa vastu anamneesis ning äge haigestumine (viimasel juhul tuleb vaktsineerimine edasi lükata). S typhi vastase vaktsineerimise vastunäidustuseks (Typhim Vi) on ülitundlikkus Typhim Vi mõne komponendi suhtes või eluohtlike kõrvalnähtude teke pärast antud vaktsiini eelmist manustamist või pärast samu komponente sisaldanud vaktsiini eelmist manustamist. Vaktsineerimine tuleb edasi lükata palaviku või ägeda haigestumise korral.

Väljavõtted konsensusdokumentidest:

Bonilla et al 2015:
Summary statement 85. The diagnosis of CVID should be considered in male or female subjects older than 4 years who have low IgG and IgA levels and impaired antibody response but do not have genetic lesions or other causes of primary or secondary antibody deficiency. /..... / A universally accepted consensus definition of CVID does not exist. It has been proposed that a definitive diagnosis of CVID should include a serum IgG level of less than 450 to 500 mg/dL and a serum IgA or IgM level of less than the fifth percentile. Some authorities require that IgA levels must be low in addition to IgG levels. All agree that patients must have decreased ability to make specific antibodies and the exclusion of other primary (eg, XLA and X-linked lymphoproliferative disease [XLP]) and secondary (eg, medications; protein loss through the gastrointestinal tract, lymphatics, or kidney; B- cell lymphomas, and bone marrow failure) causes of hypogammaglobulinemia. Documenting impaired production of specific antibodies (in response to protein or polysaccharide antigens) is essential for diagnosis. /……./
Summary statement 105. The diagnosis of SAD should be given to patients older than 2 years with recurrent respiratory tract infections, normal immunoglobulin and IgG subclass levels, and impaired response to pneumococcal capsular polysaccharide. /..... / The diagnosis of SAD requires the demonstration of poor IgG response to polysaccharide antigens in the context of normal serum immunoglobulin concentrations. When a concomitant IgG subclass deficiency is present, the abnormality should be classified as a subclass deficiency because abnormal antibody responses to polysaccharides are frequently part of IgG subclass deficiency. The diagnosis of SAD is based on the level of antibodies present after receiving the 23-valent polysaccharide vaccine. /……./ Recently, a classification of severe, moderate, and mild forms of SAD has been proposed. This classification takes into account the patient's age to assess how the number of normal responses to individual serotypes defines the level of immunologic severity of SAD. This classification also accepts a form of SAD in which there is an initial serologic and clinical response to the 23-valent polysaccharide vaccine followed by the loss of protective antibodies within 6 months. This form of SAD is generally referred to as ''memory SAD.''

Bonilla et al 2016:
Consensus definition of CVID

1. Most patients will have at least 1 of the characteristic clinical manifestations (infection, autoimmunity, lymphoproliferation). However, a diagnosis of CVID may be conferred on asymptomatic individuals who fulfill criteria 2 to 5, especially in familial cases.
2. Hypogammaglobulinemia should be defined according to the age-adjusted reference range for the laboratory in which the measurement is performed. The IgG level must be repeatedly low in at least 2 measurements more than 3 weeks apart in all patients. Repeated measurement may be omitted if the level is very low (<100–300 mg/dL depending on age), other characteristic features are present, and it is considered in the best interest of the patient to initiate therapy with IgG as quickly as possible.
3. IgA or IgM level must also be low. (Note that some experts prefer a more narrow definition requiring low IgA level in all patients.)
4. It is strongly recommended that all patients with an IgG level of more than 100 mg/dL should be studied for responses to T-dependent (TD) and T-independent (TI) antigens, whenever possible. In all patients undergoing such testing, there must be a demonstrable impairment of response to at least 1 type of antigen (TD or TI). At the discretion of the practitioner, specific antibody measurement may be dispensed with if all other criteria are satisfied and if the delay incurred by prevaccination and postvaccination antibody measurement is thought to be deleterious to the patient's health.
5. Other causes of hypogammaglobulinemia must be excluded (Table I).
6. Genetic studies to investigate monogenic forms of CVID or for disease-modifying polymorphisms are not generally required for diagnosis and management in most of the patients, especially those who present with infections only without immune dysregulation, autoimmunity, malignancy, or other complications. In these latter groups of patients, however, single gene defects may be amenable to specific therapies (eg, stem cell therapy) and molecular genetic diagnosis should be considered when possible.

/……../

Specific antibody production may be variable in some patients with CVID. Antigen-specific IgG levels or vaccine responses in patients suspected to have CVID may be within normal limits at initial presentation, but may decrease over time, ultimately becoming consistent with the diagnosis. In a small study of childhood CVID, a large proportion of children (73%) retained normal isohemagglutinin titers and specific antibody responses to protein antigens were protective at the time of diagnosis in 44% to 62%. In contrast, absent responses to pneumococcal polysaccharide antigens was noted in 71% of children, whereas such response was impaired in 21% of children. In a study of 21 adults with CVID and receiving IgG replacement, about half responded to at least 1 of 5 different protein/peptide or conjugate vaccines. Four of 21 responded to more than 1 protein vaccine, and 3 of 17 made some measurable antibody to pneumococcal polysaccharide. /……../

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EIAS juhatuse nimel,

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