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Handling of allergen immunotherapy in the COVID-19 pandemic: An ARIA-EAACI statement

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Introduction

The current COVID-19 pandemic influences many areas of social life, medical treatments and the way allergy is performed. Allergen-specific immunotherapy (AIT) is one of the most important treatment options for IgE-mediated allergies and is based on immunological effects on the diseased patient. This manuscript outlines the EAACI recommendations regarding AIT during the COVID-19 pandemic and aims at supporting allergists and all physicians performing AIT in their current daily practice with clear recommendations how to perform treatment during the pandemic and in SARS-CoV-2 infected patients.

Coronavirus disease 2019 (COVID-19)

The World Health Organization (WHO), on March 11, 2020, declared a pandemic of an infectious disease recently referred to as "coronavirus disease 2019" (COVID-19). Currently, COVID-19 is fast spreading across the globe. COVID-19 is caused by a novel strain of human coronaviruses, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), named by the International Committee on Taxonomy of Viruses (ICTV). SARS-CoV-2 was first detected in a cluster of patients with pneumonia in December 2019 in Wuhan, China(1, 2). SARS-CoV-2 is a Betacoronavirus of the subgenus Sarbecovirus and the subfamily Orthocoronavirinae. It can be isolated from human samples obtained from respiratory secretions, nasal and pharyngeal smears and isolated on cell cultures(1, 2). SARS-CoV-2 is the 7th member of the coronavirus family able to infect humans. It differs from the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), and viruses responsible for the common cold (229E, OC43, NL63, and HKU1)(3). Coronaviruses are zoonotic, i.e. they can be transmitted between animals and humans.

COVID-19 presents with many different clinical manifestations, ranging from asymptomatic cases to mild and severe disease, with or without pneumonia(4).

Common signs of COVID-19 are respiratory problems, fever, cough, shortness of breath and difficulties in breathing. Other signs of viral airway infection may include nasal symptoms and sore throat. In more severe cases, infection with COVID-19 can cause pneumonia, severe acute respiratory syndrome, kidney failure, and even death(4-8). In published scientific literature on COVID-19, higher age, chronic respiratory diseases,

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diabetes mellitus, coronary artery disease and immunodeficiency of different origins are listed as risk factors for severe illnesses, hospitalization and death(4-6, 8).

As COVID-19 is caused by a newly identified viral strain, there are no therapeutics proved to be effective in clinical trials or vaccines, so far, and there is presumed to be no pre-existing immunity in the population(9). In most instances, coronaviruses are believed to be transmitted through large respiratory droplets from person to person, through inhalation or deposition on mucosal surfaces. Other routes implicated in the transmission of coronaviruses include contact with contaminated fomites and inhalation of aerosols produced during aerosol-generating procedures, such as sneezing or coughing. The SARS-CoV-2 virus has been detected in respiratory, faecal and blood specimens(10). The highest risk of healthcare-associated transmission occurs in the absence of standard precautions, when primary infection prevention and control measures for respiratory infections are not in place, and when handling patients whose COVID-19 diagnoses is yet to be confirmed. Since airborne transmission is possible, we recommend a cautious approach because of possible transmission through aerosols (11, 12).

More disease background information is available online from the European Centre for Disease Prevention and Control (ECDC)(13), WHO(14)) and the ECDC's Rapid Risk Assessment(9).

Allergen-specific immunotherapy (AIT)

AIT is the onlydisease-modifying therapy that confers a long-term clinical benefit for allergic airway diseases such as in allergic bronchial asthma or allergicrhinoconjunctivitisand other allergic conditions(15). Since its(16)emergence over hundred years ago (1911), AIT is an established and internationally recognized procedure for the causal treatment of immediate-type allergic reactions (type I allergy) and associated diseases.

AIT induces an immune tolerance responses against the allergen in sensitized patients(17).

Systematic reviews and meta-analyses have confirmed that AIT is effective in reducing symptomstogether with rescue medication in patients with allergic asthma (18)and allergic rhinoconjunctivitis(19).

This applies to both, subcutaneous immunotherapy (SCIT)(20, 21)and sublingual

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immunotherapy (SLIT), liquid drops or tablets placed under the tongue(22).
Thereducedriskof developing asthma in patientswith allergic rhinitis is another advantage of AIT, that is still under debate but was demonstrated to be at least effective in the short term(23, 24). AIT is also effective in patients withIgE-mediated food allergy(23-26)and insect venom allergy(27).Moreover, analyses bythe European Academy of Allergy and Clinical Immunology (EAACI) demonstrated the cost-effectiveness of this disease-modifying therapy option(28-30).

AIT and viral infections

Eventhough it is well established that allergic airway diseases are associated with an increased risk of infections, little is known about the potential influence of viral infections on AIT(31).
In a prospective and comparative clinical study, Ahmetaji et al.found no significant difference in the efficacy or in the improvement of symptoms of allergic asthma patients under subcutaneous allergen-specific immunotherapy with or without symptomatic influenza,nor in the standard chemical and haematology parameters and different cytokines during a one-year follow up(32). These preliminary data suggest that SCITininfluenzainfected patientswas safe and well-tolerated.

Iemoli et al. evaluated the safety and clinical effectiveness of sublingual grass tablet immunotherapy in a group of HIV-positive patients with allergic rhinitis under antiretroviral HIV therapy.HIV infection has been regarded to be a relative contraindication for AIT. Highly active antiretroviral treatment has improved the immune function and life expectancy in HIV-infected patients whose respiratory allergic incidence is similar to that of the general population(33). Clinical efficacy data showed a significant improvement in SLIT-treated patients compared to controls but not any considerable alteration of peripheral T CD4 lymphocyte cell counts and HIV viral load in both groups. These data showthat SLIT therapy in viro-immunological controlled HIV positive patients was efficacious, safe and well-tolerated.

Cytomegalovirus (CMV) was shown to enhance the allergenic potential of otherwise poorly allergenic environmental protein antigens ina mouse model of airway co-exposure

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to CMV and ovalbumin (OVA)(34). In contrast, immune reactions to Virus-like-particles (Vlp) may enforce the immune responses in AIT and may even be used as AIT adjuvants for inhalational and food (peanut) allergen in the near future(35, 36).

With the limited experimental data available so far, it seems that patients with allergic rhinitis did not develop additional distinct symptoms and more severe courses than other patients(4). Allergic children showed a mild course, similar to other children(4).

Immune mechanisms in AIT and COVID-19 – differences and similarities

AIT aims to induce allergen-specific immune tolerance in allergy patients by using multiple mechanisms including T cells, B cells, innately lymphoid cells (ILC) and effector cells, such as eosinophils, mast cells and basophils. One of the main changes is the development of a T and B regulatory cell response and their suppressive cytokines such as IL-10andTGF-β and surface molecules such as CTLA-4 and PD1, all of which form a suppressive milieu(29, 37).This immune regulatory response is taking place in targeted antigen/allergen-specific T and B cells but does not affect the whole immune system and does not cause any systemic immune deficiency. T cell responses in severe COVID-19 are represented with lymphopenia that is mainly affecting memory T lymphocytes. Both CD4 and CD8 T cells decrease, however this change is more pronounced in CD8+ T cells. Cytotoxic T lymphocytes and NK cells in patients infected with SARS-CoV-2 are essential for an appropriate anti-viral response(38). A recent study suggests that patients show functional exhaustion of cytotoxic T lymphocytes associated with SARS-CoV-2 infection. The total number of NK and CD8+ T cells was markedly decreased in patients with SARS-CoV-2 infection (38). This may cause a disruption of antiviral immunity and may play a role in the pathogenesis and severity ofCOVID-19.

AIT significantly decreases allergen-specific Th2 cells in circulation and reduces the general type2 response by decreasing Th2 cells and type 2 ILCs(39-41). COVID-19 does not significantly increase in severity in allergicpatients, with conditions such as rhinitis, urticaria and atopic dermatitis(4, 42).Ithas not been demonstrated if there is aswitch between TH1 and TH2 cellsin COVID-19, but there is developing data that disease severity is linked to a systemic Th1 response and inflammasome activation together with a cytokine storm. Similar to SARS and MERS,a cytokine storm is a common feature of

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severe COVID-19 cases and a major reason for acute respiratory distress syndrome (ARDS) and multi organ failure. Several levels of evidence suggest that the rapid COVID-19 mortality might be due to a virus-activated “cytokine storm syndrome”(43).In a study of 41 hospitalized patientswith high-levels of proinflammatory cytokines including IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα were obsered in severe COVID-19 cases(44).

AIT changes the cellular composition and inflammatory mediators in the affected organs, such as for examplesthe nose in allergic rhinitis(17). Eosinophils and their inflammatory mediators decrease in allergic rhinitis in the nose during AIT. In COVID-19, systemic eosinopenia was observed in 52.9% of the patients. Decreased blood eosinophil counts correlate positively with lymphocyte counts in severe ($r=0.486$, $p<0.001$) and non-severe ($r=0.469$, $p<0.001$) patients after hospital admission(4).The reasons and mechanisms of systemic eosinopenia remain to be investigated.

In AIT, reduced eosinophil counts and regulation of specific TH2 response is only seen after several years of continues therapy. This supports, that AIT is not going to interfere viral infections. AIT has a clear desensitization effect on effector cells. This effect is antigen specific and is acting early during the course of AIT. Mast cells are not considered to be relevant in viral infection response.

Allergen-specific antibody levels change in the course of AIT with decreased specific IgE in the long run and a relatively rapid increase in specific IgG1 and IgG4(29, 45). In COVID-19 like many viral infections SARS-CoV-2-specific IgM increases in the acute phase followed by specific IgG(46-48).

Overall, theCOVID-19 immunological mechanisms seem to be similar to SARS and MERS and also to severe influenza infections. An appropriate anti-viral immune response should develop with cytotoxic T cells and IgM and IgG antibodies, whereas a very strong uncontrolled immune response as in a cytokine storm, becomes detrimental (Table 1).

Table 1. Immunological characteristics of AIT and COVID-19.

Immunologic changes	AIT	COVID-19
T cell responses	Suppression of TH2 cells, induction of Treg and TH1 cells	Lymphopenia in severe cases

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CD8+ T cells	There is nomajor change	Severe lymphopenia is observed in CD8+ T cells
TH1-TH2 responses	AIT decreases allergen-specific Th2 responses in circulation and in the affected organs such as in the nose	Severe disease shows a systemic severe inflammatory response with a cytokine storm
Eosinophils	Decrease in their numbers and mediators in the nose	Systemic decrease in their numbers in more than half of the patients.
Specific antibody levels	Allergen-specific IgE decreases in the late course, with an early increase in specific IgG4	In the acute phase virus-specific IgM increases followed by virus specific IgG during convalescence.

Preventingin Allergy facilities and control measures in AIT

We recommend using the infection prevention and control measures in any patient undergoing AIT according to ECDC and WHO. This implies that the recommended infection prevention and control measures of individual regions or countries should be followed, including those in this document and the procedures for reporting and transfer of persons under investigation and of probable/confirmed COVID-19 cases.

Those feeling ill with typical respiratory symptoms should be encouraged to contact healthcare services by telephone or E-Health/telemedicine/online to seek medical advice (13, 49)(triage). This will reduce the number of people with symptoms of COVID-19 that have contact with the Allergy centerhealthcare personnel(13, 49).

Allergy services and primary care staff, including physicians, nursing and administrative staff with patient contact, should be aware of the following: a) the current COVID-19 epidemiologic situation in their country and globally, b) known risk factors for infections; c) clinical symptoms and signs of COVID-19; d) recommended infection prevention and control measures in their region or country, including those in this document; e) procedures for reporting and transfer of persons under investigation and of probable/confirmed cases.

Appropriate personal protective equipment (PPE) should be available onsite for all personnel at the point-of-care to provide standard, contact and droplet protection.

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In each Allergy facility, a dedicated member of staff (e.g. head doctor/nurse) should lead the COVID-19 preparedness and implement relevant infrastructure and control measure policies.

Signs should beposted at all entrance doors listing the main symptoms compatible with COVID-19 (fever, cough and shortness of breath) and informing visitors with any of these symptoms not to enter theAllergy Unit. Everyone within the Allergy clinic and all those enteringthe practice should adopt appropriate hand hygiene measures, usingsoap and water, or an alcohol-based handrub.

Based on a case-by-case risk assessment, the use of PPE for AIT should be considered. With the current knowledge on the transmission of COVID-19, in which respiratory droplets seem to play a significant role (although airborne transmission cannot be ruled out at this stage), and taking into consideration the possible shortage of PPE in healthcare settings due to the increasing number of COVID-19 patients, the suggested set of PPE for droplet, contact and airborne transmission (gloves, goggles, gown and FFP2/FFP3 respirator) can be adapted for the clinical assessment of suspected COVID-19 cases.If available, provide a surgical mask for patients with respiratory symptoms (e.g. cough)(50).

Healthcare workers performing aerosol-generating procedures (AGP), such as swabbing(50), should wear the suggested PPE set for the prevention of droplet, contact and airborne transmission (gloves, goggles, gown and FFP2/FFP3 respirator)(51).

To maximize the use of PPE if there is an insufficient supply, staff should be assigned to carry out procedures, or a procedure, in designated areas(52).

Managing AIT during the COVID-19 pandemic

AIT is a treatment, that requires recurrentdoctor/nurse/patient contact over a more extended period, e.g. 3 years.

In SCIT, injections are administered with daily, weekly (up dosing phase) or monthly (continuation phase) intervals.

In SLIT, the initiation is given in allergy clinics or in a doctor´s office, while continuation is performed by patients themselves with regular control visits.

Each SCIT or SLIT product needs approval by the competent authority. It must contain information on how to use the AIT product for patients, allergologists and nurses. For

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most products authorized in Europe, instructions for use recommend that patients experiencing an acute respiratory tract infection should temporarily discontinue AIT treatment until the infection is resolved. We recommend taking similar action in COVID-19. Confirmed cases should discontinue AIT, both SCIT or SLIT, independent ofdisease severity until the symptoms have completely resolved and/or an adequate quarantine has been performed. The possibility of expanding injection intervals in the continuation phase may be beneficial. In patients, who recovered from COVID-19 or who are found to have a sufficient SARS-CoV-2 antibody response after (asymptomatic) disease(14), AIT can be started or continued as planned.

AIT can also be continued as usual in patients without clinical symptoms and signs of COVID-19 or other infections and without a history ofexposure ot SARS-CoV-2 or contact to COVID-19 confirmed individualswithin the past 14 days.

SLIT offers the possibility of taking it at home, thus avoiding the need to travel to or stay in an allergy clinic or doctor's office, which would be associated with a risk of infection.

Recommendations in noninfected individuals during COVID-19 pandemics or recovered patients after COVID-19 infection

Interrupting subcutaneous immunotherapy is not advised. Especially in potentially life-threatening allergies, such as venom allergy, SCIT should be regularly continued. The possibility of expanding injection intervals in the continuation phase should be checked and may be beneficial.
Interrupting sublingual immunotherapy is not advised. Supply the patient with sufficient medication for a minimum of a 14 days quarantine.
Sublingual immunotherapy can be taken at home. The intake of SLIT by the patient at home or any place is advantageous in avoiding contact to potentially infected persons.
Both subcutaneous and sublingual immunotherapy can be continued in the current COVID-19 pandemics, in any asymptomatic patients without suspicion for SARS-CoV-2 infection and/or contact to SARS-CoV-2 positive individuals, in any patient withnegative test result (RT-PCR) or in any patient after an adequate quarantine or with detection of serum IgG to SARS-CoV 2 without virus-specific IgM.
Preparedness of your Allergy clinic is imperative to cope with COVID-19. Follow WHO guidelines and advice staff accordingly.
These recommendations are conditional since there is a paucity of data and they should be revised

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regularly with incoming new information on COVID-19.

Recommendations in COVID-19 diagnosed cases or suspected for SARS-CoV-2 infection

Interrupting subcutaneous immunotherapy is advised.
Interrupting sublingual immunotherapy is advised.
Both subcutaneous and sublingual immunotherapy should be discontinued in symptomatic patients with exposure or contact to SARS-CoV-2 positive individuals, or patients with positive test results (RT-PCR).

Conflict of Interest Statement

LK declares grants and/or personal fees from Allergopharma, MEDA/Mylan, LETIPharma, Sanofi, HAL Allergie, Allergy Therapeutics, ALK Abelló, Stallergenes, Quintiles, ASIT biotech, Lofarma, AstraZeneca, GSK, Inmunotek, and is a current member of the AeDA, DGHN, Deutsche Akademie fürAllergologie und KlinischeImmunologie, HNO-BV GPA, and EAACI. **MJ** reports personal fees from ALK-Abelló, Allergopharma, Stallergenes, Anergis, Allergy Therapeutics, Circassia, LETIPharma, Biomay, HAL Allergy, AstraZeneca, GSK, Novartis, Teva, Vectura, UCB, Takeda, Roche, Janssen, Medimmune, and Chiesi. **CA** reports grants from Allergopharma, Idorsia, Swiss National Science Foundation, Christine Kühne-Center for Allergy Research and Education, European Commission's Horizon's 2020 Framework Programme, Cure, Novartis Research Institutes, AstraZeneca, SciBase, and advisory role in Sanofi/Regeneron. **JB** reports personal fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Purina, Sanofi-Aventis, Takeda, Teva, Uriach, and others from KYomed INNOV. **CB** has received fees for delivering lectures. **IA** declares personal fees from Mundipharma, ROXALL, Sanofi, MSD, Faes Farma, Hikma, UCB, and AstraZeneca. **B-A** reports grants and/or personal fees from TEVA, AstraZeneca, Boehringer Ingelheim, GSK, Sanofi, and Mylan.**AC** reports grants and/or personal fees from GSK, AstraZeneca, Mylan Pharma, Boehringer Ingelheim, and Sanofi. **TH** reports personal fees from GSK, Mundipharma and Orion Pharma. **J-CI** received personal fees from Eurofarma Argentina, Faes Farma, and non-financial support from Laboratorio Casasco Argentina and Sanofi. **PK** has received personal fees from Adamed, Berlin Chemie Menarini, AstraZeneca, Boehringer Ingelheim, Chiesi, Lekam, Novartis, Orion, Polpharma, and Teva. **DL-L** reports personal fees

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References

Accepted Article

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1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. The New England journal of medicine. 2020;382(13):1199-207.

2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.

3. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nature microbiology. 2020;5(4):536-44.

4. Zhang J-J, Dong X, Cao Y-Y, Yuan Y-D, Yang Y-B, Yan Y-Q, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020.

5. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol. 2020;92(4):418-23.

6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.

7. Organization WH. www.who.int2020 [

8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.

9. Control ECfDPa. Rapid risk assessment: Novel coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK – sixth update https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-novel-coronavirus-disease-2019-covid-19-pandemic-increased#copy-to-clipboard2020 [

10. Organization WH. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19)2020 [

11. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020;382(10):929-36.

12. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. N Engl J Med. 2020;382(10):970-1.

13. Control ECfDPa. COVID-19 https://www.ecdc.europa.eu/en/covid-19-pandemic2020 [

Accepted Article

This article is protected by copyright. All rights reserved

14. Organization WH. Coronavirus disease (COVID-19) outbreak http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-192020 [

15. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. The Journal of allergy and clinical immunology. 1998;102(4 Pt 1):558-62.

16. Durham SR, Leung DY. One hundred years of allergen immunotherapy: time to ring the changes. J Allergy Clin Immunol. 2011;127(1):3-7.

17. Jutel M, Van de Veen W, Agache I, Azkur KA, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy and novel ways for vaccine development. Allergol Int. 2013;62(4):425-33.

18. Dhami S, Kakourou A, Asamoah F, Agache I, Lau S, Jutel M, et al. Allergen immunotherapy for allergic asthma: A systematic review and meta-analysis. Allergy. 2017;72(12):1825-48.

19. Dhami S, Nurmatov U, Arasi S, Khan T, Asaria M, Zaman H, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: A systematic review and meta-analysis. Allergy. 2017;72(11):1597-631.

20. Klimek L, Brehler R, Hamelmann E, Kopp M, Ring J, Treudler R, et al. CME-Fortbildung. Entwicklung der subkutanen Allergen- Immuntherapie (Teil 1): von den Anfängen zu immunologisch orientierten Therapiekonzepten. Evolution of subcutaneous allergen immunotherapy (part 1): from first developments to mechanism-driven therapy concepts. Allergo J Int 2019;28:78-95 / CME-Fragebogen. Allergo-Journal. 2019;28(3):26 / 47.

21. Klimek L, Brehler R, Hamelmann E, Kopp M, Ring J, Treudler R, et al. CME Zertifizierte Fortbildung. Entwicklung der subkutanen Allergen-Immuntherapie (Teil 2): präventive Aspekte der SCIT und Innovationen. Allergo J Int 2019;28:107-19: Development of subcutaneous allergen immunotherapy (part 2): preventive aspects and innovations / CME-Fragebogen. Allergo-Journal. 2019;28(4):31 / 45.

22. Durham SR, Emminger W, Kapp A, de Monchy JGR, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. The Journal of allergy and clinical immunology. 2012;129(3):717-25.e5.

Accepted Article

This article is protected by copyright. All rights reserved

23. Nurmatov U, Dhami S, Arasi S, Roberts G, Pfaar O, Muraro A, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic overview of systematic reviews. Clinical and translational allergy. 2017;7:24.

24. Queisser A, Hagedorn S, Wang H, Schaefer T, Konantz M, Alavi S, et al. Ecotropic viral integration site 1, a novel oncogene in prostate cancer. Oncogene. 2017;36(11):1573-84.

25. Blumchen K, Trendelenburg V, Ahrens F, Gruebl A, Hamelmann E, Hansen G, et al. Efficacy, Safety, and Quality of Life in a Multicenter, Randomized, Placebo-Controlled Trial of Low-Dose Peanut Oral Immunotherapy in Children with Peanut Allergy. J Allergy Clin Immunol Pract. 2019;7(2):479-91 e10.

26. Chu DK, Wood RA, French S, Fiocchi A, Jordana M, Waserman S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet. 2019;393(10187):2222-32.

27. Dhami S, Zaman H, Varga EM, Sturm GJ, Muraro A, Akdis CA, et al. Allergen immunotherapy for insect venom allergy: a systematic review and meta-analysis. Allergy. 2017;72(3):342-65.

28. Asaria M, Dhami S, van Ree R, Gerth van Wijk R, Muraro A, Roberts G, et al. Health economic analysis of allergen immunotherapy for the management of allergic rhinitis, asthma, food allergy and venom allergy: A systematic overview. Allergy. 2017;73(2):269-83.

29. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International Consensus on Allergen Immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. The Journal of allergy and clinical immunology. 2016;137(2):358-68.

30. Meadows A, Kaambwa B, Novielli N, Huissoon A, Fry-Smith A, Meads C, et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. Health technology assessment (Winchester, England). 2013;17(27):vi, xi-xiv, 1-322.

31. Woehlk C, von Bülow A, Kriegbaum M, Backer V, Porsbjerg C. Allergic asthma is associated with increased risk of infections requiring antibiotics. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2018;120(2):169-76.e1.

Accepted Article

This article is protected by copyright. All rights reserved

32. Ahmetaj L, Mehić B, Gojak R, NezİRİ A. The Effect of Viral Infections and Allergic Inflammation in Asthmatic Patients on Immunotherapy. Turkish Journal of Immunology. 2018.

33. Iemoli E, Borgonovo L, Fusi A, Magni C, Ricci ED, Rizzardini G, et al. Sublingual allergen immunotherapy in HIV-positive patients. Allergy. 2016;71(3):412-5.

34. Reuter S, Lemmermann NAW, Maxeiner J, Podlech J, Beckert H, Freitag K, et al. Coincident airway exposure to low-potency allergen and cytomegalovirus sensitizes for allergic airway disease by viral activation of migratory dendritic cells. PLoS Pathog. 2019;15(3):e1007595.

35. Klimek L, Kundig T, Kramer MF, Guethoff S, Jensen-Jarolim E, Schmidt-Weber CB, et al. Virus-like particles (VLP) in prophylaxis and immunotherapy of allergic diseases. Allergo J Int. 2018;27(8):245-55.

36. Storni F, Zeltins A, Balke I, Heath MD, Kramer MF, Skinner MA, et al. Vaccine against peanut allergy based on engineered virus-like particles displaying single major peanut allergens. J Allergy Clin Immunol. 2019.

37. Pfaar O, Agache I, de Blay F, Bonini S, Chaker AM, Durham SR, et al. Perspectives in allergen immunotherapy: 2019 and beyond. Allergy. 2019;74 Suppl 108:3-25.

38. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol. 2020.

39. Akdis CA, Akdis M, Blesken T, Wymann D, Alkan SS, Muller U, et al. Epitope-specific T cell tolerance to phospholipase A2 in bee venom immunotherapy and recovery by IL-2 and IL-15 in vitro. J Clin Invest. 1996;98(7):1676-83.

40. Jutel M, Akdis M, Budak F, Aebischer-Casaulta C, Wrzyszcz M, Blaser K, et al. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. Eur J Immunol. 2003;33(5):1205-14.

41. Kortekaas Krohn I, Shikhagaie MM, Golebski K, Bernink JH, Breynaert C, Creyns B, et al. Emerging roles of innate lymphoid cells in inflammatory diseases: Clinical implications. Allergy. 2018;73(4):837-50.

42. Dong X, Cao YY, Lu XX, Zhang JJ, Du H, Yan YQ, et al. Eleven Faces of Coronavirus Disease 2019. Allergy. 2020.

43. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive care medicine. 2020.

Accepted Article

This article is protected by copyright. All rights reserved

44. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pacific journal of allergy and immunology. 2020;38(1):1-9.

45. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. The Journal of allergy and clinical immunology. 2005;116(3):608-13.

46. Xiang J, Yan M, Li H, Liu T, Lin C, Huang S, et al. Evaluation of Enzyme-Linked Immunoassay and Colloidal Gold- Immunochromatographic Assay Kit for Detection of Novel Coronavirus (SARS-Cov-2) Causing an Outbreak of Pneumonia (COVID-19): Cold Spring Harbor Laboratory Press; 2020.

47. Zhang W, Du R-H, Li B, Zheng X-S, Yang X-L, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerging microbes & infections. 2020;9(1):386-9.

48. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin: biorxiv; 2020.

49. Organization WH. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-(ncov)-infection-is-suspected-202001252020 [

50. Organization WH. Infection prevention and control of epidemic-and pandemic prone acute respiratory infections in health care https://www.who.int/csr/bioriskreduction/infection_control/publication/en/2014 [

51. Control ECfDPa. Guidance for wearing and removing personal protective equipment in healthcare settings for the care of patients with suspected or confirmed COVID-19 https://www.ecdc.europa.eu/en/publications-data/guidance-wearing-and-removing-personal-protective-equipment-healthcare-settings2020 [

52. Organization WH. Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19) https://apps.who.int/iris/bitstream/handle/10665/331215/WHO-2019-nCov-IPCPPE_use-2020.1-eng.pdf2020 [

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