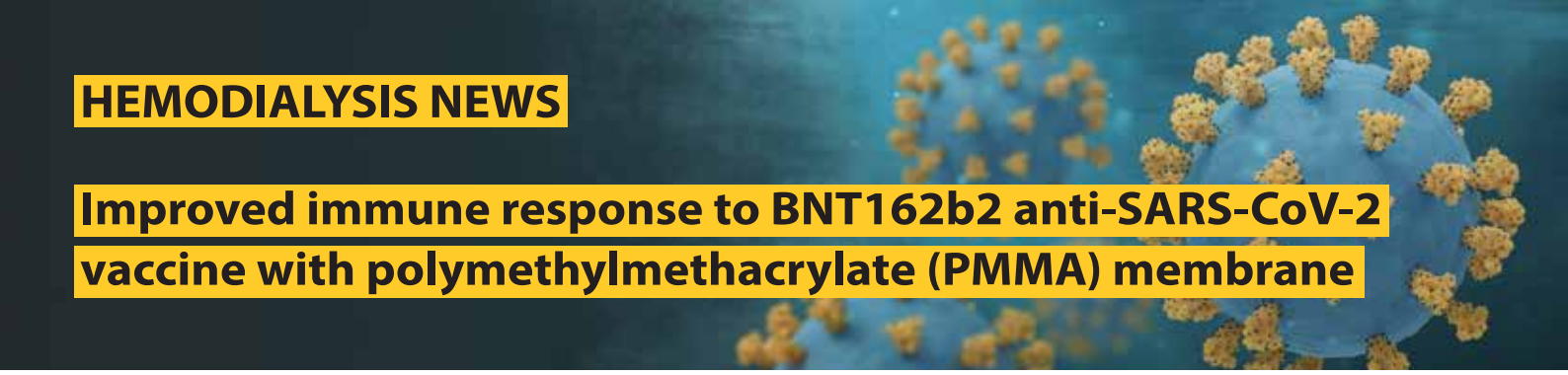


HEMODIALYSIS NEWS

Improved immune response to BNT162b2 anti-SARS-CoV-2 vaccine with polymethylmethacrylate (PMMA) membrane

New data on chronic hemodialysis patients show improved response to BNT162b2 anti-SARS-CoV-2 vaccine when treated with polymethylmethacrylate dialysis membrane compared to polysulfone.

At the recent 62nd annual meeting of the Italian Society of Nephrology (SIN), Prof. Castellano presented groundbreaking results on how chronic kidney disease (CKD) patients undergoing hemodialysis (HD) treatment with polymethylmethacrylate (PMMA) membrane show improved response to BNT162b2 anti-SARS-CoV-2 vaccine compared to patients hemodialyzed with a polysulfone (PS) membrane.

There is a strong rationale for ensuring an optimal immune-protective vaccine coverage in CKD patients. CKD patients are immuno-compromised due to their pathology and this is worsening with hemodialysis treatment. Patients undergoing hemodialysis are fragile patients with an increased risk of acquiring infections and developing severe COVID-19 with a fatal outcome [1, 2]. Previous studies have shown that HD patients due to their altered immune profile tend to have a reduced response to vaccinations, and this has also been demonstrated for the anti-SARS-CoV-2 vaccine [3].

In the following we introduce the immunological aspects of humoral and cell-mediated vaccine response before summarizing the data presented by Prof. Castellano. Finally, we elaborate on the characteristics of the PMMA dialysis membrane that may contribute to an improved response to anti-SARS-CoV-2 vaccination.

The immunology of humoral and cell-mediated response to vaccination

Protective and lasting immune responses to viral infections or vaccines arise from the combined actions of lymphocytes. Specifically, B cells are responsible for humoral antibody immunity and T cells are responsible for cellular immunity and helping B cell responses.

In the infographic we have illustrated how mRNA vaccines, such as Pfizer's BNT162b2, elicit immunity to SARS-CoV-2 virus [4, 5].

The mRNA encoding the SARS-CoV-2 Spike (S) protein encapsulated in lipid nanoparticles enter dendritic cells (DCs) at the injection site or within lymph nodes, which results in the production of high levels of S protein.

In addition, innate sensors are triggered by the intrinsic adjuvant activity of the vaccines, resulting in production of type I IFN, IFN-γ, pro-inflammatory cytokines and chemokines.

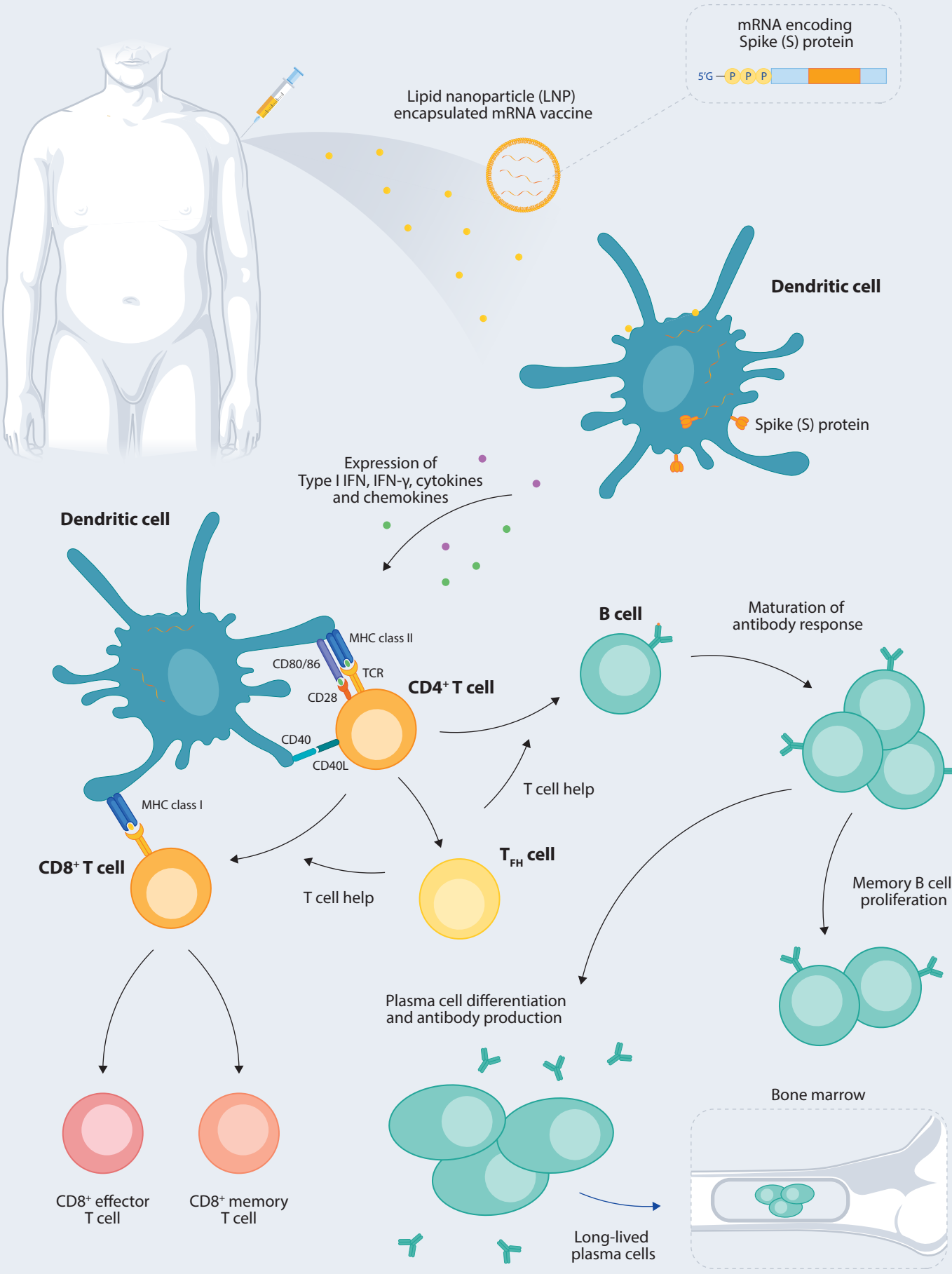
The resultant activated DCs present antigen and co-stimulatory molecules to S protein-specific naive T cells, resulting in their activation and differentiation into effector cells to form cytotoxic T lymphocytes or helper T cells.

T follicular helper (TFH) cells help S protein-specific B cells to differentiate into antibody-secreting plasma cells and promote the production of high affinity anti-S protein antibodies.

Following vaccination, S protein-specific memory T cells and B cells develop and circulate along with high affinity SARS-CoV-2 antibodies, which together help prevent subsequent infection with SARS-CoV-2 [5].

The immune system of an individual who has been vaccinated against a specific pathogen is able to more rapidly and more robustly mount a protective immune response when exposed to that specific pathogen in the future.

Generation of an immune response to a vaccine



Study: The role of the dialysis membrane in ensuring a better response to vaccination

During the recent 62nd annual meeting of SIN, Prof. Castellano presented groundbreaking results on how CKD patients undergoing HD treatment with PMMA membrane show improved response to BNT162b2 anti-SARS-CoV-2 vaccine compared to patients dialyzed with a PS membrane.
The study included 16 patients who had been undergoing hemodialysis for at least 12 months. Of these, 8 patients were treated with PMMA membrane and 8 patients with PS membrane.

All patients were vaccinated with two doses of BNT162b2 anti-SARS-CoV-2 vaccine and from all patients data were collected at the following time points: T0, prior to the first vaccine dose; T1, 15 days after the first dose; and T2, 15 days after the second dose. The following data were collected: standard blood chemistry data, lymphocyte count and type, anti-Spike IgG concentration (RDB-S1 and S2) and anti-Spike IgM concentration (S1-RBD).

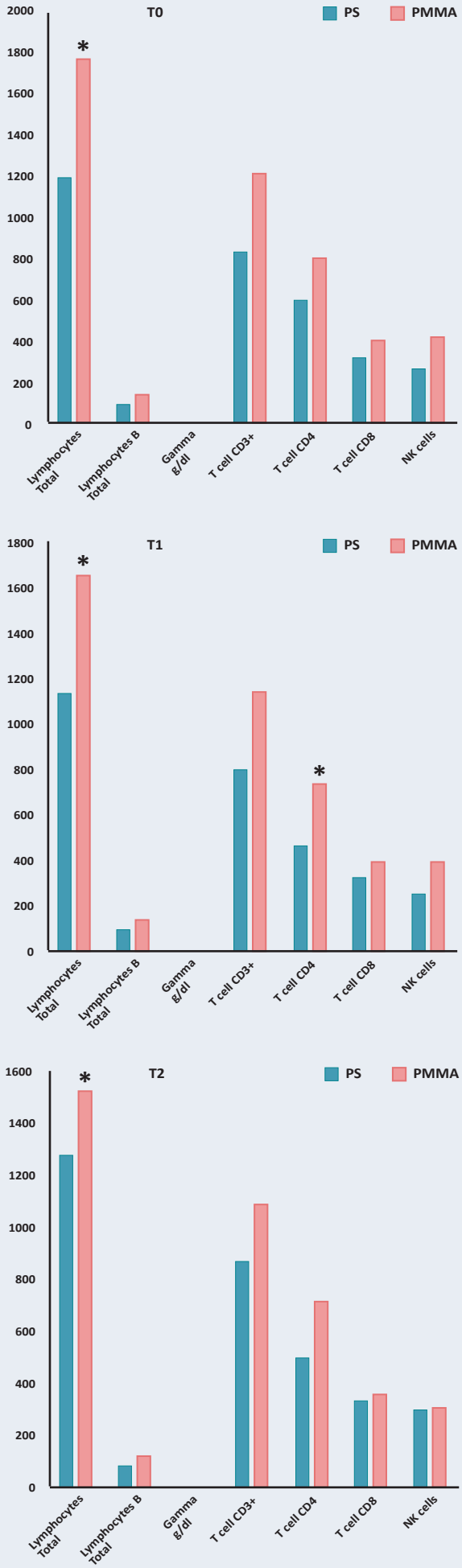
After the second vaccine dose patients who were dialyzed with PMMA membrane showed a significantly higher antibody response compared to patients dialyzed with PS membrane ($p < 0.05$).

As shown in the panel on the right, patients dialyzed with PMMA membrane presented a higher number of total lymphocytes both at T0 ($p < 0.02$) and T2 ($p < 0.05$).

Furthermore, the data also shows how PMMA can preserve and favorably modify T cell expression, although the sample size was not sufficient to show statistical significance, except for CD4 at T1 ($p < 0.05$).

The authors conclude that the complete vaccination protocol provided an adequate protection against SARS-CoV-2 virus, **but patients dialyzed with PMMA membrane showed a better response compared to patients dialyzed with polysulfone membrane.**

These results were also presented as an abstract published in the GIN journal.



Modulation of lymphocyte response at T0, T1 and T2 in patients treated with PS and PMMA, respectively.

Polymethylmethacrylate (PMMA): the dialysis membrane as immune-nephrological strategy

Polymethylmethacrylate (PMMA) is a synthetic polymer known for its outstanding hemo- and biocompatibility primarily due to the non-activation of the complement system during contact between the blood compartment and the artificial material.

Patients undergoing maintenance hemodialysis have impaired immune responsiveness, which appears to deteriorate progressively with the duration of the dialysis treatment. Compared to un-dialyzed CKD patients, hemodialysis patients have an altered expression of genes involved in the immune response [6]. The hemo- and biocompatibility of the dialysis membrane is fundamental in this aspect. Blood-membrane contact affects both innate and adaptive immunity [7].

Maintaining a correct balance of immunological mediators and effectors is important for an optimal vaccine response.
Many of the proteins adsorbed by PMMA can be assigned to functions of immune system processes [8]. The adsorption capacity of the PMMA membrane, in addition to the mechanisms of diffusion and convection, allows the removal of medium to high molecular weight molecules not removable by filtration [9-12].

CD40/CD40L and sCD40

Contin et al. have evidenced a role for sCD40 in the alteration of humoral immune response in CKD patients and their impaired response to HBV vaccination [13]. CD40/CD40L interaction plays a key role in B cell response. CD40 is expressed by a wide range of immune cells including B cells and dendritic cells. The CD40 ligand (CD40L) is mainly expressed by activated CD4 T cells. CD40 triggering by CD40L is pivotal for B-cell growth, differentiation and isotypic switch. CD40 activation on the surface of dendritic cells induces expression of the co-stimulatory molecules CD80 and CD86 and cytokine production necessary for a proper T-cell activation. CD40/CD40L interaction is regulated by two major mechanisms that are the transient expression of CD40L on the surface of activated CD4+ T cells and the production of a soluble form of CD40 (sCD40) [13]. Soluble CD40 is not eliminated by classical dialysis procedure, but it is effectively removed by PMMA and this restores immune response to HBV vaccination [14].

The complement system

The complement system plays a role in both innate and adaptive immune response [15], but there are only few data available on the role of complement activation in the response to anti-SARS-CoV-2 vaccine.
A recent study sheds light on the unique properties of the PMMA membrane in significantly reducing tissue and systemic complement activation [16]. PMMA showed excellent removal capacity of soluble components involved in inflammation and in immune system and reduced local and systemic complement activation, recovering the balance between the pro- and anti-inflammatory mediators. PMMA also modulated gene expression of circulating leucocytes, thereby controlling complement system and innate immunity and preserving B and T cells response against infection, limiting immunological dysfunction and renal damage.

Protein bound uremic toxins (PBUT)

A link between PBUTs and CKD-associated immune dysfunction has recently emerged. Indoxyl sulfate and p-cresyl sulfate are currently the best characterized in terms of their effects on the immune system. The direct effects of PBUT on the immune system of p-cresyl sulfate seems to be associated to an immune deficiency status of CKD mainly related to the adaptative immune response, while indoxyl sulfate seems affect the activation of both innate and adaptative immune systems likely responsible for CKD-associated inflammation.

During the recent 62nd annual meeting of SIN, Dr. Marengo presented the results from a multicenter study on the role of CD40L in cardiovascular disease in HD patients. Interestingly, in this study they found that PMMA removes both p-cresyl sulfate and indoxyl sulfate resulting in a decreased release of sCD40L from platelets (manuscript in preparation – the presentation is available on-demand).

Natural killer cells

Also natural killer (NK) cells play an important role in innate immune responses to viral infections. Natural killer (NK) cells have recently emerged as key regulators of vaccine-elicited T and B cell responses [17]. In a study of 160 individuals who had received one dose of BNT162b2 anti-SARS-CoV-2 vaccine it was shown that in former COVID-19 patients and highly responsive individuals, a significant increase of antibody production was detected, simultaneous with an expansion of antigen-specific B cell response and the total number of NK-T cells [18]. The authors suggest that a favourable immune profile support the development of an effective response to BNT162b2 vaccination.

In CKD patients all immune effector cells appear to be affected. Monocytes have an activated phenotype, polymorphonuclear leukocytes have a decreased phagocytic capacity, the CD4/CD8 T cell ratio is decreased, functional defects in regulatory T cells have been demonstrated, and B cells as well as natural NK cells are decreased.

A subpopulation of NK cells is decreased in CKD patients. This decrease is associated with high circulating levels of the HLA-related molecule MICA. Peraldi et al. showed that dialysis with the PMMA membrane counteracts the decrease in NK cells [19]. The expression of MICA on the cell surface of monocytes, which is a marker of inflammation induced by cellular stress, was also lower in patients using PMMA membranes. The dialysis membrane can influence the modulation of both the phenotype of NK cells and MICA overexpression.

TAKE HOME MESSAGES

- **There is a strong rationale for ensuring an optimal immune-protective anti-SARS-CoV-2 vaccine coverage in CKD patients.**
- **CKD-HD patients have an increased risk of acquiring infections and developing severe COVID-19 with a fatal outcome**
- **The data presented at SIN shows that the PMMA membrane enhance the response to anti-SARS-CoV-2 vaccination in a population of CKD-HD patients**
- **The use of PMMA membrane represents an immuno-nephrological strategy, optimizing the immune profile of the patient and ensuring the best possible vaccine response**

References

1. Gansevoort, R.T. and L.B. Hilbrands, CKD is a key risk factor for COVID-19 mortality. Nat Rev Nephrol, 2020. 16(12): p. 705-706.
2. Oetjens, M.T., et al., Electronic health record analysis identifies kidney disease as the leading risk factor for hospitalization in confirmed COVID-19 patients. PLoS One, 2020. 15(11): p. e0242182.
3. Grupper, A., et al., Humoral Response to the Pfizer BNT162b2 Vaccine in Patients Undergoing Maintenance Hemodialysis. Clin J Am Soc Nephrol, 2021. 16(7): p. 1037-1042.
4. Pollard, A.J. and E.M. Bijker, A guide to vaccinology: from basic principles to new developments. Nat Rev Immunol, 2021. 21(2): p. 83-100.
5. Teijaro, J.R. and D.L. Farber, COVID-19 vaccines: modes of immune activation and future challenges. Nat Rev Immunol, 2021. 21(4): p. 195-197.
6. Zaza, G., et al., A specific immune transcriptomic profile discriminates chronic kidney disease patients in predialysis from hemodialyzed patients. BMC Med Genomics, 2013. 6: p. 17.
7. Donati, D., et al., Effects of hemodialysis on activation of lymphocytes: analysis by an in vitro dialysis model. J Am Soc Nephrol, 1992. 2(10): p. 1490-7.
8. Hashida, T., et al., Proteome analysis of hemofilter adsorbates to identify novel substances of sepsis: a pilot study. J Artif Organs, 2017. 20(2): p. 132-137.
9. Memoli, B., et al., Hemodialysis related induction of interleukin-6 production by peripheral blood mononuclear cells. Kidney Int, 1992. 42(2): p. 320-6.
10. Abe, M., et al., Effect of dialyzer membrane materials on survival in chronic hemodialysis patients: Results from the annual survey of the Japanese Nationwide Dialysis Registry. PLoS One, 2017. 12(9): p. e0184424.
11. Galli, F., Protein damage and inflammation in uraemia and dialysis patients. Nephrol Dial Transplant, 2007. 22 Suppl 5: p. v20-36.
12. Memoli, B., et al., Hemodialysis-related lymphomononuclear release of interleukin-12 in patients with end-stage renal disease. J Am Soc Nephrol, 1999. 10(10): p. 2171-6.
13. Contin, C., et al., Potential role of soluble CD40 in the humoral immune response impairment of uraemic patients. Immunology, 2003. 110(1): p. 131-40.
14. Contin-Bordes, C., A. Lacraz, and V. Precigout, Potential role of the soluble form of CD40 in deficient immunological function of dialysis patients: new findings of its amelioration using polymethylmethacrylate (PMMA) membrane. NDT Plus, 2010. 3 [Suppl 1]: p. i20-i27.
15. Salehen, N. and C. Stover, The role of complement in the success of vaccination with conjugated vs. unconjugated polysaccharide antigen. Vaccine, 2008. 26(4): p. 451-9.
16. Stasi, A., et al., PMMA-Based Continuous Hemofiltration Modulated Complement Activation and Renal Dysfunction in LPS-Induced Acute Kidney Injury. Frontiers in Immunology, 2021. 12(994).
17. Cox, A., et al., Targeting natural killer cells to enhance vaccine responses. Trends Pharmacol Sci, 2021. 42(9): p. 789-801.
18. Colucci, M., et al., Associations between Allelic Variants of the Human IgH 3' Regulatory Region 1 and the Immune Response to BNT162b2 mRNA Vaccine. Vaccines (Basel), 2021. 9(10).
19. Peraldi, M.N., et al., Natural killer cell dysfunction in uremia: the role of oxidative stress and the effects of dialysis. Blood Purif, 2013. 35 Suppl 2: p. 14-9.