

Would hemodialysis patients benefit from a *Staphylococcus aureus* vaccine?



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Staphylococcus aureus bloodstream infection can have potentially catastrophic consequences for patients on hemodialysis. Consequently, an effective vaccine to prevent *S aureus* infection would have a significant influence on morbidity and mortality in this group. To date, however, efforts to develop a vaccine have been unsuccessful. Previous antibody-inducing vaccine candidates did not prevent or attenuate *S aureus* infection in clinical trials. Recent advances have helped to elucidate the role of specific T-cell subsets, notably T-helper cell 1 and T-helper cell 17, in the immune response to *S aureus*. These cells are essential for coordinating an effective phagocytic response via cytokine production, indirectly leading to destruction of the organism. It is now widely accepted that next-generation *S aureus* vaccines must also induce effective T-cell-mediated immunity. However, there remains a gap in our knowledge: how will an *S aureus* vaccine drive these responses in those patients most at risk? Given that patients on hemodialysis are an immunocompromised population, in particular with specific T-cell defects, including defects in T-helper cell subsets, this is likely to affect their ability to respond to an *S aureus* vaccine. We urgently need a better understanding of T-cell-mediated immunity in this cohort if an efficacious vaccine is ever to be realized for these patients.

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The need for a *Staphylococcus aureus* vaccine in patients on hemodialysis

Staphylococcus aureus bloodstream infection (SA-BSI) is a major cause of morbidity and mortality in patients on hemodialysis, particularly those dependent on central venous catheters for vascular access. In the United States in 2014, *S aureus* was the most common bloodstream isolate from patients with BSI on hemodialysis, accounting for 30% of isolates.¹ This represents a decrease from previous years,² probably because of improvements in central venous catheter care^{3–5} and increasing prevalence of arteriovenous fistula or graft access in accordance with guidelines,⁶ although reporting practices have also changed. In the United Kingdom, though methicillin-resistant *S aureus*–BSI rates have been decreasing in the hemodialysis population, methicillin-susceptible *S aureus*–BSI rates are actually increasing since 2011 to 2.65 per 100 patient-years in 2015.⁷ As well as being common, these infections are potentially fatal; in patients on hemodialysis, the risk of death within 15 days of infection, or hospitalization for treatment of infection, is >8 times higher in SA-BSI than in BSI with other organisms.⁸ The 90-day mortality for SA-BSI in this population is significant, reported between 18.2% and 30.6%.^{9–11} The financial cost is also high, estimated at \$25,518 per methicillin-resistant *S aureus*–BSI and \$17,354 per methicillin-susceptible *S aureus*–BSI in patients on hemodialysis in the United States,¹⁰ with similar costs reported in Europe.¹¹ It is clear that these infections are still a major problem in this group.

The prevalence of *S aureus* nasal carriage is high (26%–31%) in patients on hemodialysis,^{12,13} and those who are colonized are particularly at risk of BSI.¹³ Intuitively, then, decolonization would be an effective way to prevent SA-BSI. However, decolonization is often unsuccessful¹⁴ and there is some evidence that resistance to topical antimicrobials is a problem in this population.^{15,16} As a result, there is a growing awareness of the importance of investigating SA-BSI prevention strategies other than decolonization. Vaccination has more potential for long-term protection, assuming a protective immune response can be achieved and sustained. In this context, the prospect of a vaccine to prevent SA-BSI has been the focus of increasing interest in recent years. An economic model of an *S aureus* vaccine in the population on hemodialysis predicted that such a vaccine would be cost-effective over a range of costs, vaccine efficacies, and prevalence rates

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of *S aureus* colonization.¹⁷ Here we discuss some of the challenges of developing an effective vaccine against SA-BSI for use in patients on hemodialysis.

Challenges in *S aureus* vaccine development

Numerous attempts to develop a vaccine against *S aureus* over more than a decade have been unsuccessful. Notable examples include StaphVAX (Nabi Biopharmaceuticals, Rockville, MD) and V710 (Merck, Kenilworth, NJ), both of which failed in phase 3 clinical trials. There are a number of reasons for these failures, but one of the critical issues has been the difficulty in defining correlates of protective immunity to *S aureus*.

StaphVAX consisted of *S aureus* capsular polysaccharides 5 and 8, the most common capsular polysaccharide types in clinical isolates, conjugated to a recombinant *Pseudomonas aeruginosa* exotoxin A. In murine studies, StaphVAX induced protective immunity, which correlated with capsular polysaccharide-specific antibody levels.¹⁸ Early human studies showed that the vaccine stimulated antibody production in healthy subjects as well as in patients on hemodialysis,¹⁹ with an initial phase 3 study showing protection against SA-BSI in patients on hemodialysis from 3 to 40 weeks after vaccination. However, efficacy was not sustained up to 1 year²⁰ and the decrease in efficacy appeared to correlate with decreasing antibody levels. A follow-up study showed that a booster administered to hemodialysis patients approximately 3 years after the initial dose succeeded in increasing opsonophagocytic antibody titers.²¹ In a subsequent phase 3 study²² in >3000 patients on hemodialysis, the vaccine also induced a robust antibody response. However, despite this, it failed to protect against SA-BSI over a 60-week follow-up period after either 1 or 2 doses.

V710, a vaccine containing a single protein (iron-regulated surface determinant protein B), present in the majority of *S aureus* isolates, induced a lasting antibody response in initial studies in patients on hemodialysis²³ as well as in healthy adults.²⁴ Vaccine efficacy in animal models appeared to correlate with antibody levels.²⁵ However, in a phase 3 trial where V710 was administered preoperatively to patients undergoing cardiothoracic surgery, there was no significant reduction in postoperative invasive *S aureus* infection despite induction of anti-iron-regulated surface determinant protein B IgG antibodies.²⁶ Furthermore, among patients who did develop *S aureus* infection postoperatively, mortality was significantly higher in the V710 group than in the placebo group.²⁶ A *post hoc* subgroup analysis of prevaccination serum levels of a panel of cytokines demonstrated 100% mortality in 12 patients with undetectable interleukin-2 (IL-2) levels who received V710 and subsequently developed postoperative *S aureus* infection.²⁷ This was much higher than the mortality rate in similar patients who received placebo. IL-2 is important in stimulating T-cell differentiation; thus, these findings suggest that even in the presence of an antibody response, a protective immune response to *S aureus* cannot be generated without certain T-cell subsets.

Thus, although vaccine antibody responses correlate with protective immunity to other encapsulated pathogens, such as

Streptococcus pneumoniae, the same does not appear to be true of *S aureus*, as discussed further below. Notably, T-cell responses were not assessed prospectively in clinical trials of either of the vaccines discussed above.

The role of T cells in the immune response to *S aureus* infection

A growing body of work is highlighting the importance of T cells, particularly T-helper cells, in the protective immune response to *S aureus*.²⁸ In SA-BSI, effector T cells of the T-helper cell 1 (Th1) subtype are active and clonally expanded during infection,²⁹ suggesting that they are important in the immune response to these infections. Th1 cells activate macrophages through the release of the cytokine interferon- γ ²⁹ and macrophages phagocytose and destroy *S aureus*. Th17 cells are also important in the immune response to *S aureus* but appear to be more active in skin and soft tissue infection than in BSI. Patients with specific Th17 defects, such as those with autosomal dominant hyper-IgE syndrome, are prone to recurrent *S aureus* skin infections.³⁰ Th17 cells are important in controlling neutrophil recruitment to the site of infection; thus, Th17 deficiency prevents bacterial destruction by neutrophils, the first line of defense against *S aureus*. Interestingly, however, in a recent study involving 95 patients with SA-BSI, a higher ratio of Th17 to Th1 cytokines at a time point 2 to 4 days after infection demonstrated a modest association with mortality. In a subgroup analysis comparing 14 patients who died within 90 days of SA-BSI with a group of 14 matched survivors, an increasing ratio of Th17 to regulatory T cells over the course of the infection was also associated with mortality in immunocompetent but not immunocompromised patients.³¹ The reasons for this remain unclear, but the authors hypothesized that these findings represent the damaging effect of an overwhelming inflammatory response, against which immunosuppression may provide some degree of protection.

It appears, therefore, that protection against *S aureus* infection requires a robust T-cell response, particularly involving Th1 and Th17 cells, which are critical for controlling phagocytic cell responses and facilitating bacterial clearance, but may actually lead to adverse outcomes if responses are excessive or prolonged. Remarkably, experimental vaccines driving robust T-helper cell responses in murine models are capable of conferring protection in the complete absence of antibodies. A vaccine based on a fungal protein, agglutinin-like sequence 3 protein (Als3p), exhibiting structural and sequence homology with *S aureus* clumping factor A conferred protection from SA-BSI in B-cell-deficient mice but not in T-cell-deficient mice.³² In a follow-up study, this vaccine induced a Th1/Th17 response, with production of interferon- γ and IL-17A, leading to neutrophil recruitment, which correlated with protection against SA-BSI.³³ Furthermore, a vaccine consisting of nanoparticles loaded with *S aureus* clumping factor A was shown to induce an antibody-independent Th1- and Th17-biased response, which correlated with protective immunity to invasive *S aureus* infection in mice.³⁴

These results, coupled with the findings of the vaccine studies already discussed, have been instrumental in shifting the *S aureus* vaccine research focus to the T-cell response. There is now a sense that next-generation *S aureus* vaccines will need to induce protective cellular as well as humoral immunity. Ideally, an *S aureus* vaccine would drive both antibody- and cell-mediated immunity, which, combined, should lead to effective clearance of infection as shown in Figure 1. Whether this will be sufficient to protect against infection in particular patient cohorts, however, remains to be established.

Progress in *S aureus* vaccine development

The majority of *S aureus* vaccine candidates currently in development contain multiple antigens, with the aim of stimulating a broad immune response, including cell-mediated immunity. Table 1 summarizes *S aureus* active immunization candidates currently or recently in clinical trials. Only 2 of these (numbers 3 and 5 in Table 1, being developed by NovaDigm and Pfizer, respectively) appear to be actively recruiting to clinical trials at present. Other candidates are in preclinical trials, and some of these have had encouraging results and have induced T-cell immunity in mice.^{43,44}

Patients on hemodialysis: clinical trial subjects for an *S aureus* vaccine?

A suitable clinical trial cohort for a future *S aureus* vaccine should be at high risk of SA-BSI, but also identifiable prospectively as being at risk, to allow time for a protective immune response to develop after vaccination. Patients on hemodialysis generally meet these criteria. Patients with end-stage kidney disease would be most likely to benefit from an *S aureus* vaccine if it was administered before commencing hemodialysis. These patients are also at long-term risk of SA-BSI and available for long-term follow-up. Thus, they are perhaps the most suitable population in which to demonstrate continued protective efficacy of a vaccine. However, before progressing to clinical trials, there is a requirement to look more closely at immune responses in hemodialysis patients rather than extrapolating data from healthy subjects. Patients on hemodialysis, with their underlying chronic disease, often accompanied by multiple comorbidities, are inherently immunocompromised. This affects their ability to respond to vaccines and has implications for developing an *S aureus* vaccine for use in this group.

Immune defects in patients on hemodialysis

Independently of hemodialysis, chronic kidney disease (CKD) has long been recognized as a state of immunodeficiency⁴⁵ in

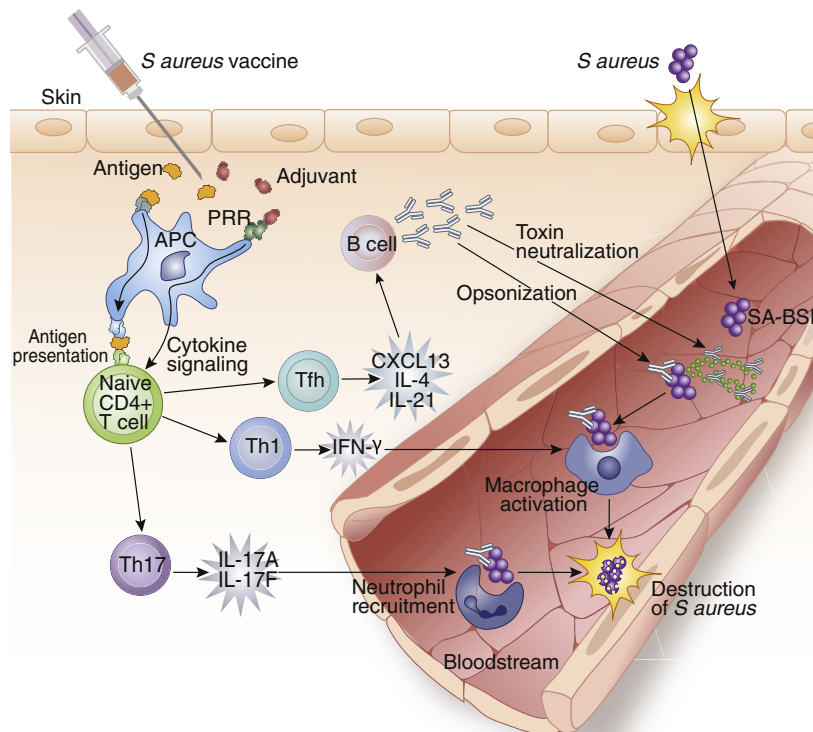


Figure 1 | Potential correlates of immunity for an effective *Staphylococcus aureus* vaccine. The ideal *S aureus* vaccine would comprise appropriate antigens and adjuvant capable of driving both antibody and T-cell responses. Antibodies are required to neutralize secreted toxins and facilitate phagocytosis by opsonization of the bacteria. The induction of memory T-helper cell 1 (Th1) and/or T-helper cell 17 (Th17) cell responses would in turn recruit and activate phagocytes, leading to the destruction and removal of the organism. Induction of follicular T-helper cells (Tfh) is also desirable to promote antibody responses. APC, antigen-presenting cell; CXCL, chemokine ligand; IFN- γ , interferon- γ ; IL, interleukin; PRR, pattern recognition receptor; SA-BSI, *Staphylococcus aureus* bloodstream infection.

Table 1 | Clinical trial status of *Staphylococcus aureus* vaccine candidates

No.	Vaccine composition; pharmaceutical company (Reference)	Phase completed	Publication date	Population	Outcome	Status of vaccine research
1	HI, SpA5, mSEB, MntC recombinant proteins and aluminum phosphate adjuvants; Chengdu Olymvax Biopharmaceuticals (Chengdu, China) ³⁵	1	NA	Healthy adults aged 18–65 yr	Not published to date	Phase 1 studies completed; results not published to date (ClinicalTrials.gov identifiers NCT02820883 and NCT02804711)
2	STEBVax: recombinant staphylococcal enterotoxin B with alum adjuvant; Integrated BioTherapeutics (Rockville, MD) ³⁶	1	2016	Nonpregnant healthy adults aged 18–40 yr	Appeared to be safe and immunogenic, inducing functional toxin-neutralizing antibodies	Phase 1 completed (ClinicalTrials.gov identifier NCT00974935). Current status not clear
3	NDV-3: recombinant <i>Candida albicans</i> protein, homologous to the cell wall protein of <i>S aureus</i> , with an alum adjuvant; NovaDigm (Brookline, MA) ³⁷	1	2012	Healthy adults aged 19–47 yr	Generated significant antibody rise as well as a memory T-cell response as demonstrated by IFN- γ and IL-17 production	Recruitment for a phase 2a study in STAT3-mutated hyper-IgE syndrome suspended (ClinicalTrials.gov identifier NCT02996448). Recruitment in progress for a phase 2 study to prevent nasal <i>S aureus</i> colonization in military recruits (ClinicalTrials.gov identifier NCT03455309)
4	<i>S aureus</i> capsular polysaccharides CP5 and CP8 conjugated to a tetanus toxoid, mutated Hla, and clfA; GlaxoSmithKline (Brentford, UK) ³⁸	1	2015	Healthy adults aged 18–40 yr	No safety concerns identified, induced a robust antibody response	Phase 1 completed (ClinicalTrials.gov identifier NCT01160172). Current status not clear
5	SA3Ag/SA4Ag: CP5, CP8, recombinant clfA and/or manganese transporter protein; Pfizer (New York, NY) ^{39–41}	1/2	2017	Healthy adults aged 65–85 yr	Functional immune responses demonstrated	Recruitment in progress for a phase 2b study in adults undergoing elective spinal fusion procedures (ClinicalTrials.gov identifier NCT02388165)
6	Recombinant <i>S aureus</i> α -toxoid and a recombinant PVL subunit; Uniformed Services University (Rockville, MD)/Nabi Biopharmaceuticals ⁴²	1/2	2016	Healthy adults aged 18–55 yr	Well-tolerated, neutralizing antibody produced up to day 84	Phase 1/2 completed (ClinicalTrials.gov identifier NCT01011335). Current status not clear

clfA, *Staphylococcus aureus* clumping factor A; CP, capsular polysaccharide; HI, a fusion protein consisting of hemolysin A and IsdB (iron-regulated surface determinant protein B); Hla, staphylococcal hemolysin A; IFN- γ , interferon- γ ; IL-17, interleukin-17; MntC, manganese transport protein C; mSEB, mutagenized staphylococcal enterotoxin B; NA, not available; PVL, Pantone-Valentine leukocidin; SpA, staphylococcal protein A; STAT3, signal transducer and activator of transcription 3.

association with abnormal immune activation. Clinically, this manifests as higher infection-related mortality rates in patients with CKD than in the general population.⁴⁶ In addition, CKD frequently complicates underlying diseases that increase susceptibility to infection or require immunomodulatory therapy. There is considerable evidence that patients with end-stage kidney disease on hemodialysis are further immunosuppressed. Data from the United Kingdom indicate that infection was the cause of 21% of deaths in patients on dialysis in 2017.⁴⁷ In the United States, 17.7% of all hospitalizations in patients on hemodialysis in 2013 to 2015 were due to infectious diseases.⁴⁸ The physical insult of repeated breaches of the skin's barrier undoubtedly contributes to the high risk of infection in these patients, but disturbances in innate and acquired immunity are also involved,⁴⁹ including abnormalities in both B-cell- and T-cell-mediated adaptive immunity.⁵⁰ Impaired T-cell immunity in patients on hemodialysis is of particular relevance if these patients are to be considered for next-generation *S aureus* vaccines, which may require induction of an effective T-cell response to confer protection.

Impaired vaccine-induced immunity in patients on hemodialysis

In general, patients on hemodialysis have impaired immune responses to vaccines. Vaccines highly dependent on the antibody response, such as pneumococcal polysaccharide vaccines, do elicit protective antibody titers in patients on hemodialysis, but titers decline more quickly over time than in healthy controls.^{51,52} As expected, patients on hemodialysis with poor initial antibody responses to pneumococcal polysaccharide vaccine are at higher risk of pneumococcal disease.⁵³ It is unclear what factors are involved in preventing an adequate response in these patients but B-cell lymphopenia is known to occur in CKD, in part owing to apoptosis.⁵⁴ This may also explain the observed high failure rates of tetanus and diphtheria vaccines in patients on hemodialysis, which act by stimulating antibodies that neutralize the relevant toxins.^{55,56} The pneumococcal conjugate vaccine is also associated with an antibody response that decreases quickly over time in patients on hemodialysis.⁵⁷ Although a large retrospective study showed an association between pneumococcal vaccination and lower mortality risk in patients on hemodialysis,⁵⁸ there is a lack of good quality evidence to correlate serological responses to pneumococcal vaccination with clinical outcomes in patients on hemodialysis.

Compared with healthy people, patients on hemodialysis have low response rates to the hepatitis B vaccine, as determined by postvaccination titers of antibody to hepatitis B surface antigen; factors such as advanced age and diabetes mellitus make vaccine failure more likely in this population.⁵⁹ Although vaccine immunogenicity can be increased by increasing the number of doses and revaccinating with a different product in nonresponders,⁶⁰ vaccine responses remain suboptimal in patients on hemodialysis. Interestingly, a high CD4+ to CD8+ ratio in patients on hemodialysis is

associated with a good antibody response to the hepatitis B vaccine⁶¹ whereas poor response correlates with an impaired antigen-specific IL-2-producing effector memory CD4+ T-cell response.⁶² The inactivated influenza vaccine is also poorly immunogenic in patients on hemodialysis. This vaccine relies on the induction of both a Th1-dominated memory CD4+ response and a CD8+ response⁶³ to confer protective immunity. Of note, in a cohort of elderly subjects not undergoing dialysis, low prevaccination interferon- γ to IL-10 ratios have been found to correlate clinically with low vaccine efficacy.⁶⁴ Thus, in patients on hemodialysis, it appears that impaired T-cell immunity may lead to a blunted response to some vaccines. This could pose significant problems for a potential *S aureus* vaccine requiring an effective T-cell response.

Impaired T-cell immunity in patients on hemodialysis

Studies have consistently demonstrated low levels of total lymphocytes, including T cells and T-helper cells, in patients on hemodialysis and patients with end-stage kidney disease who have not yet commenced hemodialysis as compared with healthy controls.^{65–73} However, it is more difficult to find consensus on alterations in T-cell subsets in this population. Cytotoxic (CD8+) T cells have been reported as significantly lower in patients on hemodialysis than in healthy controls in some studies,^{65,71} but others have found no differences in numbers or proportions.^{66,73,74} A skewing of the effector T-cell response toward Th2 predominance has been reported in a study,⁷⁵ whereas elsewhere, Th1 responses were found to be more pronounced.⁷⁶ Reduced IL-17-producing CD4+ T cells have been observed in patients on hemodialysis in one study,⁷⁰ whereas another reported the opposite finding, a higher proportion of Th17 cells.⁶⁹ Similarly, with regard to regulatory T cells, many studies found no differences between patients on hemodialysis and healthy controls^{66,67,69,77} but others have variously reported high⁷⁸ and low⁷⁹ regulatory T cells in patients on hemodialysis. Several studies have, however, demonstrated low IL-2 levels in patients on hemodialysis as compared with healthy controls.^{65,73,74} Although patients on hemodialysis have been reported to have more IL-2 receptors than do healthy controls,^{72,73} these receptors appear to have a decreased ability to respond to IL-2.⁷² Defects in IL-2 will impair proliferation and differentiation of all T-cell subsets. In addition, expression of CD28 (a coreceptor for T-cell activation) and the T-cell activation marker CD69 are reduced in patients on hemodialysis as compared with healthy controls, further suggestive of impaired T-cell function in these patients.^{80,81}

The complexities of the underlying disease pathology associated with CKD likely have divergent effects on T-cell function; however, the hemodialysis procedure itself also affects T-cell activation and the production of inflammatory cytokines.^{68,82} The proportion of CD4+ T cells undergoing apoptosis is significantly higher immediately after the hemodialysis procedure than before,⁶⁸ while the duration of hemodialysis dependency has been shown to correlate with an increased percentage of apoptotic CD3+ and CD4+ T cells.⁶⁸

An increase in regulatory T cells (CD25+) with a concomitant decrease in activated T cells (CD69+) is also seen after the hemodialysis procedure, with an associated increase in IL-10 production.⁸² The mechanisms underlying these effects are not clear, but it is speculated that when T cells come into contact with the dialyzer membrane, this may subsequently lead to T-cell death, or in some cases stimulate an immunosuppressive IL-10 response.

Defects in T-cell numbers and function observed in patients on hemodialysis are reflected in their increased susceptibility to infectious diseases in which T-cell immunity plays an important defensive role. Acquisition of hepatitis B infection was a major risk for patients on hemodialysis in the past, and their risk of developing chronic infection was observed to be higher than that of the general population.⁸³ Although antibodies are important in preventing initial hepatitis B infection, CD4+ and CD8+ T cells become important once the virus is established in hepatocytes.^{84,85} The incidence of tuberculosis is also high in patients on hemodialysis,⁸⁶ and T cells (particularly Th1 cells), in association with macrophages, are crucial to the control of tuberculosis. The T-cell-dependent response to testing with purified protein derivative in tuberculosis-infected patients on hemodialysis is often poor,⁸⁷ while interferon- γ release assays are more sensitive but still suboptimal.⁸⁸

As detailed above, studies looking at T-cell number and function in patients on hemodialysis have yielded conflicting results, probably because of differences in laboratory and dialysis methods and control groups as well as small patient numbers. Many of these studies do not provide technical details of their hemodialysis procedures, and the effect of hemodialysis on T-cell number and function appears to vary with procedural differences⁷³ and the composition of the dialysate.⁶⁵ Synthetic rather than cellulose membranes are now standard, and high-flux dialysis, facilitating removal of middle molecules, has become the norm. These changes have led to improvements in T-cell function in patients on hemodialysis,⁸⁹ with reduced morbidity and mortality, partly because of lower infection rates. The use of high-flux rather than low-flux dialysis membranes is also associated with an improved response to hepatitis B vaccination.⁹⁰ Marked improvements have been brought about in dialysate and water quality, now regulated by international standards.^{91–93} In recent years, there has been a move toward hemodiafiltration for renal replacement therapy, with consequent significant reduction in mortality.⁹⁴ Interestingly, hemodiafiltration appears to be associated with a shift from a Th1 to a Th2 response as compared with conventional hemodialysis.⁹⁵ Thus, abnormalities observed in historic studies may not necessarily represent the cellular immune phenotypes of patients currently on hemodialysis. There is clearly a requirement for further study in this area, with larger patient numbers and using standard methods that represent the hemodialysis procedures and laboratory methods in use today.

Conclusions

It is certain that patients on hemodialysis would benefit significantly from an *S aureus* vaccine. However, these patients have distinctive clinical and immunological characteristics that differentiate them from healthy populations. T-cell-mediated immunity is impaired in patients on hemodialysis, and they exhibit suboptimal responses to vaccines, including those heavily dependent on T-cell responses. These factors mean that patients on hemodialysis may be poor responders to an *S aureus* vaccine that targets T-cell-mediated immunity; this problem will need to be overcome when developing a vaccine for use in this population. The design of next-generation *S aureus* vaccine trials in patients on hemodialysis or any other patient cohort remains a challenge, because of a lack of well-established correlates of immune protection. However, there is some evidence that expansion of appropriate effector T cells coupled with effective phagocytic cell responses in conjunction with a robust antibody response (Figure 1) may be key to vaccine efficacy. Critically, however, T-cell responses in patients on hemodialysis remain poorly understood and further profiling of immune responses to *S aureus* vaccines in patients on hemodialysis is therefore required to facilitate well-designed clinical trials in this cohort.

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AUTHOR CONTRIBUTIONS

RMM conceived the topic for review. The manuscript was drafted by RC and revised by all authors. All authors approved the final version of the manuscript.

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