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Review article

Can immune biomarkers predict infections in solid organ transplant recipients? A review of current evidence

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ABSTRACT

Despite improvements in graft survival, solid organ transplantation is still associated with considerable infection induced morbidity and mortality. If we were able to show that serious infection risk was associated with excessive suppression of immune capacity, we would be justified in "personalizing" the extent of immunosuppression by carefully monitored reduction to see if we can improve immune compromize without increasing the risk of rejection. Reliable biomarkers are needed to identify this patients at an increased risk of infection. This review focuses on the currently available evidence in solid organ transplant recipients for immune non-pathogen specific biomarkers to predict severe infections with the susceptibility to particular pathogens according to the component of the immune system that is suppressed. This review is categorized into immune biomarkers representative of the humoral, cellular, phagocytic, natural killer cell and complement system. Biomarkers humoral and cellular systems of the that have demonstrated an association with infections include immunoglobulins, lymphocyte number, lymphocyte subsets, intracellular concentrations of adenosine triphosphate in stimulated $CD4^+$ cells and soluble CD30. Biomarkers of the innate immune system that have demonstrated an association with infections include natural killer cell numbers, complement and mannose binding lectin. Emerging evidence shows that quantification of viral nucleic acid (such as Epstein Barr Virus) can act as a biomarker to predict all-cause infections. Studies that show the most promise are those in which several immune biomarkers are assessed in combination. Ongoing research is required to validate non-pathogen specific immune biomarkers in multi-centre studies using standardized study designs.

Contents

Abbreviations: CMV, cytomegalovirus; EBV, Epstein Barr virus; HHV6, human herpes virus 6; HHV 8, human herpes virus 8; PJP, *Pneumocystis jirovecii*; sCD30, Soluble CD30; VZV, varicella zoster virus.

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1. Introduction

An episode of infection for a solid organ transplant (SOT) recipient can result in increased mortality and serious morbidity, including an increased risk of allograft rejection [1–4]. While the underlying risk of admission to hospital for infection differs according to transplant type [5], SOT recipients overall do have a substantially higher requirement for admission and higher case fatality rates related to infection than the general population [6]. Consequently, prevention, diagnosis and treatment of infection have become key goals in the care of SOT recipients (Fig. 1).

One component of the risk of infection in individuals transplanted is the immunosuppressive regimen, often standardized at individual sites, but sometimes leading to quite markedly different immunological effects in patients. Despite the clear clinical benefit to accurately predicting in which patients infection or rejection will develop, or be likely to develop, there are no good clinical tools available [7]. The patients that develop both infection and rejection are a particularly important group because their optimal window of immunosuppression is narrowly set between that which protects them from rejection and that which leads inevitably to serious infection.

While immunosuppression may be seen as a balance between the risk of infection and of rejection, there are a number of reasons why a SOT recipient may develop both syndromes. Firstly, the clinical risk factors for infection and rejection may overlap. Secondly, the risk of infection and rejection may be increased as a consequence of reactive changes to the immunosuppressive regimen. For example, if a patient developed an infection, immunosuppression may be reduced thereby increasing the risk of rejection. Conversely, a patient with rejection may have their immunosuppression increased with a subsequent

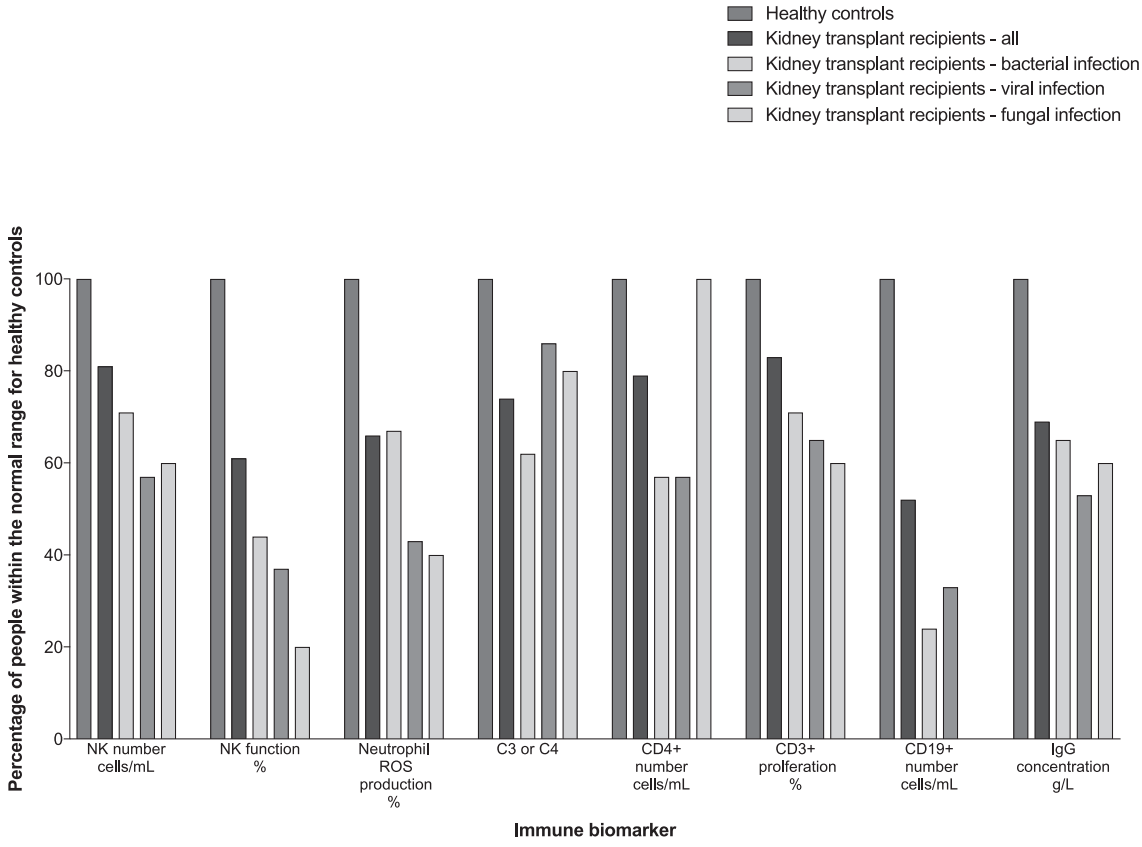

Fig. 1. The relative impairment of immune biomarkers according to type of infection in a cohort of kidney transplant recipients. Biomarkers were tested at baseline in 168 stable kidney transplant recipients (median 4.1 years post-transplant) and patients were followed for 2 years for the development of infection. Any infection resulting in hospital admission whereby a causative microorganism was isolated were included. Infections were classified into bacterial, viral and fungal. Results for immune biomarkers were compared with a cohort of laboratory controls, who were healthy with no known infectious or inflammatory conditions. The immune biomarker was classified as reduced if the result was below the 5th percentile of healthy controls.

increased risk of infection. Thirdly, an infectious episode itself has been reported to trigger allograft rejection through the development of heterologous immunity [4].

Cippa et al. attempted to disentangle the individual risks for infection and rejection in the first year after kidney transplant [7]. They performed a *post-hoc* analysis of a large cohort of kidney transplant recipients. They defined clinical risk factors for infection and rejection from the multivariable analysis and applied a risk weighting for both infection and rejection to each patient. Their model was able to discriminate between the groups and consequent external validation confirmed the applicability of the model in an independent cohort. This is one of the few studies that have demonstrated that clinical data can be used to stratify patients to predict infectious risk. Reliable biomarkers for the risk of infection would therefore be of great value as an adjunct to guide the clinician in adjusting the level of immunosuppression. Biomarkers could also be used in clinical trial design to personalize prophylaxis against infection and more precisely design an individual, risk-based immunosuppressive regimen [8].

Biomarkers to predict infection can be pathogen specific or non-pathogen specific. A non-pathogen specific biomarker is a biological assay with no specificity for a particular antigen or organism [8]. Pathogen specific biomarkers have been examined in several studies, whereby viral specific $CD4^+$ and $CD8^+$ lymphocyte responses have identified patients at high risk for cytomegalovirus (CMV) [9], Epstein Barr Virus (EBV) [10] and BK virus (BKV) [11].

This narrative review will focus on the currently available evidence for SOT recipients using non-pathogen specific immune biomarkers to predict severe infections. Whilst in clinical practice it is important that the risks for infection and rejection are not taken in isolation, risk factors for allograft rejection are beyond the scope of this review which will focus on infection risk alone.

We searched MEDLINE and EMBASE from their inception until the 1st July 2018. Pertinent articles were selected from the citations returned from the search. Literature searches included keywords and free text terms for solid organ transplantation, biomarkers, risk factors and the infectious outcomes of interest. Results were limited to human subjects and language of publication was restricted to English.

This review is categorized into immune biomarkers representative of the humoral, cellular, phagocytic, natural killer cell and complement system. This categorization is arbitrary, as host defence against infection is achieved through the combined effect of all arms of the immune system. However, this categorization could be of practical use for clinicians when selecting antimicrobial agents for empirical treatment of infection and infection prophylaxis. Table 1 presents the risk of susceptibility to particular pathogens according to the component of the immune system that is impaired [12–47]. Much of this data is derived from observational reports regarding patients with primary immune deficiencies. The risk of infection with a particular pathogen can be difficult to predict in transplant recipients because multiple components of the immune system are affected to varying degrees. There is little evidence directly comparing the relative contribution of each component of the immune system in mounting an effective response against different pathogens in SOT recipients. Table 2 illustrates the role of different components of the innate and adaptive immune system in the control of infectious pathogens and their relative contribution.

Immunosuppression following SOT is predominately aimed at suppressing cellular immune function in order to prevent allograft rejection. With suppression of cellular immune function, innate and humoral immunity play an enhanced role in defence against infection. Calcineurin inhibitors (CNIs) and mycophenolate mofetil are the cornerstone immunosuppressants for SOT recipients. Whilst they directly target T cell function they also suppress humoral and innate function, which might otherwise compensate for the reduction in cellular function [48,49]. In some patients, additional treatment targeted towards specific elements of the immune system are used, for example, anti-thymocyte globulin and rituximab which respectively deplete T cells and B cells. Monitoring CNI drug levels guides dosing. However, this is only a surrogate for the degree of effect on T cell function from treatment and rarely assessed directly. It is notable that other aspects of the immune system effectively go unmonitored.

1.1. Humoral immune biomarkers

Studies examining the association between biomarkers of the humoral immune system and infection are presented in Table 3.

Table 1
Defects in host immunity and associations with organisms.

Bacteria	Viruses	Fungi	Parasites
Humoral system (B cells and immunoglobulins) [11–18]			
Streptococcus pneumoniae	Enterovirus spp.		Giardia spp.
Haemophilus influenzae	Echovirus spp.		
Campylobacter spp.	Norovirus (chronic)		
Mycoplasma spp.			
Ureaplasma spp.			
Cellular system (T cells) [19–33]			
Mycobacteria tuberculosis	Herpes viruses (HSV, CMV, EBV, VZV, HHV6, HHV8)	Invasive filamentous fungal	*Toxoplasmosis*
Non-tuberculous mycobacteria	Polyoma virus (BK and JC)	*Pneumocystis jirovecii*	*Cryptosporidium* spp.
Nocardia spp.		*Cryptococcus* spp.	*Microsporidium* spp.
Streptococcus pneumoniae		*Candida spp. (mucocutaneous or invasive)*	
Listeria spp. and			
Salmonella spp.			
Phagocytic system (neutrophils, phagocytes, macrophages) [33–37]			
Staphylococcus aureus		Candida (mucocutaneous or invasive)	
Klebsiella spp.		Invasive filamentous fungi	
Serratia spp.			
Natural killer cell system [34,38–44]			
Non-tuberculous mycobacteria	Herpes viruses (HSV, CMV, EBV, VZV, HHV6, HHV8)	Invasive filamentous fungal	
Complement system [45–47]			
Neisseria meningiditis			
Streptococcus pneumoniae			
Haemophilius influenzae			

spp: species, HSV: herpes simplex virus, CMV: cytomegalovrius, EBV: Epstein Barr virus, VZV: varicella zoster virus, HHV6: human herpes virus 6, HHV 8: human herpes virus 8

Table 2
An overview of the interplay between various components of the immune system and their relative contribution to the control of infectious pathogens. This figure is based on data from case reports and cohort studies.

Immune system components	Function and interaction with other immune system components	Relative contribution of components of the innate and adaptive immune system in control of infectious pathogens				
		Bacteria	Mycobacteria	Fungi	Viruses	Parasites
NK cells	Direct cytotoxicity Cytokine activation of macrophages Cytokine activation of T cells	+	++	++	+++	+
Monocytes/Macrophages/Granulocytes	Phagocytosis of pathogens Recruitment and activation of T lymphocytes Cytokine activation of NK cells	+++	++	+++	++	+++
Complement	Opsonization of pathogens Lysis of pathogens Recruitment of phagocytes	+++	+	+	+	+
T cells	Assistance with maturation of B cells into immunoglobulin producing plasma cells and memory B cells Direct cytotoxicity Activation of macrophages to kill intracellular organisms	++	+++	+++	+++	+++
B cells and immunoglobulins	Presenting antigen to T cells Immunoglobulin production Opsonization of pathogens Activation of complement Antibody neutralization of pathogens Direct binding to phagocytes	+++	+	+	++	+

+++: strong contribution, ++: moderate contribution, +: weak contribution.

Table 3
Associations between humoral biomarkers and infections ins solid organ transplant recipients.

Year	Biomarker	Recipient organ type (number)	Study design Follow up (years)	Timing of biomarker measurement	Results
2006 [56]	IgG, IgA, IgM	Heart (38)	Prospective 1.4	Pre-transplant and post-transplant day 7 and month 1	After adjustment for CMV sero-status, IgG pre-transplant and post-transplant day 7 were associated with infection (RR 3.69 and RR 11.21; respectively).
2008 [57]	IgG, IgA, IgM	Liver (46)	Prospective 0.5	Pre-transplant and post-transplant day 7 and month 3	Pre-transplant IgG and IgA hypergammaglobulinemia were associated with infection (RR: 2.78 and 2.77, respectively).
2012 [55]	IgG, IgM, IgA	Kidney (290)	Prospective 1	Pre-transplant and post-transplant month 1 and 6	Hypogammaglobulinaemia at month 1 was a risk factor for overall infection and bacterial infection month 1–6. Hypogammaglobulinaemia at month 6 was a risk factor for overall infection and bacterial infection month 6–12.
2008 [54]	IgG	Kidney (152)	Prospective 1	Pre-transplant and post-transplant month 3 and 12	Hypogammaglobulinaemia pre-transplant and month 3 was associated with increased risk of infection.
2013 [53]	IgG	Lung, Liver, Kidney, heart (1756)	Meta-analysis 0.2- to 6.5	Various time points over 1 year post-transplant	Severe Hypogammaglobulinaemia (IgG <400 mg/dL) during the first year post-transplant was associated with overall infections, CMV (OR: 2.4), *Aspergillus* spp. (OR 8.19), other fungal (OR: 3.7), and respiratory infections (OR: 4.8), and all-cause mortality (OR: 21.9).
1996 [58]	IgG, IgM, IgA IgG subclasses	Kidney (36)	Prospective Early post-transplant period	Post-transplant week 5	Lower IgG1 subclass in patients with infection compared with non-infected patients.
2018 [59]	IgG, IgA, IgM, C3,C4, titers of antibodies to pneumococcal polysaccharide antigens (IgG, IgA, IgM), CMV antibodies, serum B-cell activating factor	Lung (82)	Prospective 0.5	Pre-transplant and post-transplant day 7 and month 1	IgG post-transplant day 7 was associated with CMV disease and fungal infection (OR 8.15 and RR 8.03; respectively). Lower IgM antibody against pneumococcal polysaccharide antigens post-transplant day 7 was associated with bacterial (OR 3.96).
2018 [60]	IgG, IgA, IgM, C3,C4, titers of antibodies to pneumococcal polysaccharide antigens (IgG, IgA, IgM), CMV antibodies, serum B-cell activating factor	Heart (170)	Prospective 0.5	Pre-transplant and post-transplant day 7 and month 1	Low IgG and low C3 post-transplant day 7 were associated with severe infection and bacterial infection (OR 7.40 and 12.37; respectively). Low IgG antibody against pneumococcal polysaccharide antigens post-transplant day 7 and day 30 were associated with bacterial infection (OR 14.82).

IV: intravenous, CMV: Cytomegalovirus, RR: relative risk, OR: odds ratio.

1.2. B cells

B cell numbers are frequently reduced following SOT [49–51]. While there is evidence that enhanced humoral immunity before transplantation, such as increased memory class-switched B cells, can identify heart transplant recipients at low risk of infection [52], studies specifically linking B cell numbers and their kinetics to infectious outcomes post-transplantation are lacking.

1.3. Immunoglobulins

Hypogammaglobinemia is common in SOT recipients and a number of prospective studies have demonstrated that pre-transplant or early post-transplant hypogammaglobulinemia is associated with an increased infectious risk [49,50,53–58]. Florescu et al. performed a meta-analysis examining the risk of infection in SOT recipients with hypogammaglobulinemia in the first year post-transplant [53]. Pooled data from 18 studies revealed an increased risk of infection and death in those with severe hypogammaglobulinemia (<400 mg/dL). However, this risk was not identified in patients with mild hypogammaglobulinemia. Immunoglobulin subclass deficiencies (IgG1) may be also be associated with infectious outcomes [58].

1.4. Seroresponses to vaccination

There are limited data assessing other measures in humoral competence (such as vaccine responses) that link *in vitro* measurements with infectious outcomes. Recent studies by Sarmiento et al. have reported that kinetics of IgA or IgM anti-pneumococcal polysaccharide antigens may have a role in predicting post-transplant infections in heart and lung transplant infection [59,60]. An Australian study demonstrated that seroresponses to annual influenza vaccination were very poor and were not associated with the development of all cause sinopulmonary infection. (In press Transplant Proceedings).

1.5. Cellular immune biomarkers

Studies examining the association between biomarkers of the cellular immune system and infection are presented in Table 4.

Table 4
Association between cellular immune biomarkers and infections in solid organ transplant.

Year	Biomarker	Recipient organ type (number)	Study design / Follow-up (years)	Timing of biomarker measurement	Results
2012 [64]	T-lymphocyte subsets kinetics	Heart (48) Kidney (42)	Retrospective 1	Various time points in the first 8 months post-transplant	Heart transplant recipients with OIs had lower $CD4^+$ and $CD8^+$cell numbers than those without infections. Kidney transplant recipients with OIs had lower $CD8^+$ cell numbers than those without infections.
2015 [65]	$CD4^+$ cell number and $CD8^+$ cell number	Lung (83)	Retrospective 1	Various time points in the first 12 months post-transplant	A nadir $CD4^+$ cell number < 200 cells/μL in the first 3 months post-transplant predicted a higher frequency of viral OI in the subsequent 6-month period.
2009 [62]	Total lymphocyte count	Liver (63)	Prospective 2	Pre-transplant	Pre-transplant total lymphocyte count was associated with infection (OR: 10.1).
2014 [66]	Total lymphocyte count	Liver (276)	Retrospective 5	Pre-transplant	Pre-transplant lymphopenia <500 cells/mm^3 was associated with CMV (HR: 5.5) and non-CMV invasive infection (HR: 1.6).
2014 [62]	Peripheral blood lymphocyte subsets	Kidney (304)	Prospective 1	Pre-transplant and post-transplant months 1 and 6	Recipients who did not receive anti-thymocyte globulin, $CD8^+$ cell number < 0.100 x10^3mm/μL was an independent risk factor for OI (HR: 3.55). Recipients who received anti-thymocyte globulin, a $CD4^+$ cell number < 0.050 × 10^3 cell/μL showed negative predictive values of 0.92 for the subsequent occurrence of overall OI and CMV disease.
2006 [63]	$CD4^+$ cell number	Kidney (20) All HIV positive	Prospective 3	Various time points over 3 years post-transplant	Annualized risk of infection while $CD4^+$ cell number < 200 cells/μL was over 10 times that when $CD4^+$ > 200 cells/μL.
2012 [88]	T cell proliferation to antigen and mitogen stimulation	Heart (12) Controls (8)	Prospective 1	Pre-transplant and post-transplant month 3	Month 3 post-transplant $CD3^+$ cell and $CD8^+$ cell proliferative responses to mitogen were lower in infected patients than those without infection.
2010 [77]	sCD30	Kidney (586)	Prospective 5	Pre-transplant	Low level sCD30 (<120 U/mL) was associated with an increased risk of pneumonia.
2008 [79]	sCD30	Kidney or Simultaneous kidney/pancreas (92)	Prospective 2	Pre-transplant	Low level sCD30 (<90 U/mL) was associated with a decreased risk of infection.
2007 [78]	sCD30	Heart (100)	Prospective 2	Pre-transplant	Low level sCD30 (<90 U/mL) was significantly associated with an increased risk of infection.
2006 [76]	sCD30	Heart (100)	Prospective 1	Pre-transplant	Low level sCD30 (<90 U/mL) was associated with an increased risk of infection.
2017 [85]	sCD30	Kidney (100)	Prospective	Pre-transplant and post-transplant month 1, 3 and 6	Higher sCD30 levels a per-transplant were associated with increased risk of bacterial infection (HR 4.65).
2012 [82]	iATP	Liver, lung, heart, kidney (2013)	Meta-analysis	Various time points	The pooled estimates for iATP in identification of infection risk were poor (sensitivity 0.58, specificity 0.69, positive likelihood ratio 2, negative likelihood ratio of 0.39, diagnostic odds ratio 7.41).
2012 [83]	iATP	Liver (651)	Systematic review <0.1 to 4.2	Various time points	The pooled estimates for iATP in identification of infection risk were good, (sensitivity 0.84, specificity 0.75, positive likelihood ratio of 3.3 and an area under the receiver operator curve of 0.82).
2006 [80]	iATP	Kidney, heart, simultaneous kidney/pancreas, liver, small bowel (504)	Meta-analysis	Various time points	Patients with an iATP <25 ng/mL were 12 times more likely to develop an infection than a recipient with a stronger immune response.

OI: opportunistic infection, CMV: Cytomegalovirus, EBV: Epstein Barr Virus, HSV: Herpes Simplex Virus, VZV:Varicella Zoster Virus, HHV6: Human Herpes Virus 6, PCP: *Pneumocystis jirovecii*, CT scan: Computerised Tomography scan, sCD30: soluble CD30, IV: intravenous, spp.: species, iATP: intracellular Adenosine Triphosphate, HR: Hazard ratio, OR: odds ratio.

1.6. Lymphocyte subsets (total lymphocyte count, $CD4^+$ and $CD8^+$ cells)

Monitoring of the absolute numbers and kinetics of lymphocyte subsets (such as total lymphocyte number, $CD4^+$ cell number, $CD8^+$ cell number, $CD4^+$ cell nadir and CD4:CD8 ratio) to predict infections in SOT recipients has been to predict infection post-transplant [61–66]. $CD4^+$ and $CD8^+$ lymphopenia were associated are associated with the development of opportunistic infections such as *Pneumocystis jirovecii* (PCP), herpes viral and fungal infections. The majority of studies have used $CD4^+$ cell number monitoring before or early post-transplant and there are very few studies that have examined the association between $CD4^+$ cell number and infection beyond the first post-transplant year.

1.7. Soluble CD30 (sCD30)

CD30 is a cell surface maker that expressed by activated T cells [67,68]. CD30 is a member of the tumour necrosis factor receptor superfamily and its soluble form (sCD30) is released by CD4+ and CD8+ T cell clones. It appears to have a role in the regulation between T helper 1 (Th1) and T helper 2 (Th2) responses and may be a biomarker for Th2 polarized T cell responses. As such, it has been studied as a biomarker of cellular immunity (Table 3) [69,70]. Membrane bound CD30 can be proteolytically cleaved to generate the soluble form of CD30 (sCD30), which can be measured in serum or plasma by Enzyme Linked Immunosorbent Assay [8,71–75]. Trials that have examined the relationship between sCD30 and infections have found discordant results, hence the utility of this biomarker remains to be defined [76–79]. Fernandez-Ruiz et al. recently reported that high levels of sCD30 pre-transplant are associated with an increased risk of post-transplant bacterial infections but not other types of infections [68]. The authors propose that this relates to the immunomodulatory role of sCD30 which by deviating immune response towards Th2 reduces anti-bacterial immunity by inhibiting production of cytokines and reducing macrophage killing [68].

1.8. Intracellular concentrations of Adenosine triphosphate in stimulated $CD4^+$ cells (iATP)

The ImmuKnow immune cell function assay (Cyclex Inc., Columbia, MD, USA) is a commercial test developed to measure T cell activation, as a surrogate marker of T cell function. This assay detects iATP production from activated $CD4^+$ cells. After $CD4^+$ cells are incubated with the mitogen phytohaemagglutinin, iATP production is measured by chemiluminescense. iATP production is categorized as weak, moderate or strong. Weak responses are indicative of excessive immunosuppression and an increased risk of infection [80,81].

Since the tests' introduction, there have been numerous studies correlating iATP with rejection and infection. Two meta-analyses and one systematic review have been performed to examine the value of iATP in predicting infection, with discordant findings [82]. The largest study performed by Ling et al., found the test lacked sensitivity and specificity and concluded that the current evidence suggested that iATP is not able to identify individuals at risk of infection or rejection [80,82,83]. Vittoraki *et al* demonstrated the test was not reproducible for a single patient at different time points [84]. They found that of 128 kidney transplant recipients, 43% exhibited fluctuations in their iATP levels among the three T cell function zones (weak, moderate and strong). In this same study, because the majority of kidney transplant recipients and controls tested in the moderate range, the authors determined that they were not able to support this assay as an immune monitoring test in clinically stable renal transplant recipients. Suviolahti et al. demonstrated that there were differences in iATP results depending on the timing of testing in relation to the time blood was drawn [85]. They studied 152 transplant patients and 18 healthy controls and found that iATP levels were lower in 1-day-old blood compared with fresh blood, concluding that that fresh blood should be used for assessing iATP to obtain the most accurate results [85]. Recently, iATP has been identified as a potential biomarker for the prediction of CMV disease [86]. One of the only studies to change immunosuppressive regimens based on an immune biomarker was a randomized, parallel, blinded, interventional trial comparing the outcomes of adult liver transplant recipients whose immunosuppressive therapy was managed by standard practice compared to adjusting therapy based on iATP responses (interventional group) [87]. iATP testing was measured at several time points post-transplant with tacrolimus doses reduced by 25% when iATP values were <130 ng/mL iATP (low immune cell response) and increased by 25% when values were >450 ng/mL iATP (strong immune cell response). The 1-year patient survival was higher (95% *vs* 82%; $p < .01$) and the incidence of infections was lower (42.0% *vs.* 54.9%, $p < .05$) in the intervention arm relative to the standard care group. The difference in infections was due to a reduced incidence of bacterial (32% *vs* 46%; $P < .05$) and fungal infections (2% *vs* 11%; $p < .05$). iATP levels did not correlate with rejection in this study.

1.8.1. T cell proliferation

T cell proliferation can be measured *in vitro* through the use of mitogen or antigen stimulation [88]. A small study in heart transplant recipients demonstrated lower proliferative responses to mitogen in those that developed infection compared to those without infections [88].

1.8.2. Phagocytic biomarkers (neutrophils, phagocytes, macrophages)

Absolute neutrophil count and duration of neutropenia are powerful predictors of infection in haematopoietic stem cell transplants [89], but there are less data regarding the risk of infection of in SOT recipients. Egger et al. examined the use of polymorphonuclear leukocyte functional tests as predictive makers for infection shortly after surgery [90]. They found that levels after transplant surgery of the neutrophil derived enzyme, elastase over 100 mg/L, followed by a drop in polymorphonuclear leukocyte migration, were a marker for impending infection. Measurement of neutrophil phagocytic capacity and reactive oxygen species generation have also been performed in kidney transplant patients and shown to be predictive of infection when included in a composite immune score [49,50].

1.8.3. Natural killer (NK) cell biomarkers

NK cells are innate immune cells that are capable of immediate defence against pathogens and cancer. NK cells do not require antigen specific recognition of their targets, rather are activated by generic stress signals [91,92]. NK cells are important in the control of viral infections and NK cell deficiency predisposes to viral infection, in particular herpes virus [93,94]. Calcineurin inhibitors used in SOT can reduce NK cell function [48,95–97]. *In vitro* studies have demonstrated a decrease in NK cell degranulation and interferon gamma release with increasing doses of tacrolimus and cyclosporine. Several studies have examined the association between NK cell number and infections in SOT recipients. A recent publication by Fernandez-Ruiz et al..... described an association between low NK cell number one month post-liver transplant and opportunistic infections, such as CMV disease [44]. The same authors demonstrated that low NK cell numbers are predictive of both invasive fungal and herpes zoster infections in SOT recipients [44,98]. Blazik et al. [50], Hutchinson *et al* [49], Sarmiento *et al* [99] and Fernandez-Ruiz *et al* [100] included NK cell number as part of a composite score to predict infections in SOT recipients. Recent data suggests that certain NK cell subsets, (for example cd94/NKG2C^{bright} activating lectin-like receptors) have a role in the control of CMV infection in kidney transplant recipients [101]. Additionally, Dendle *et al* reported that NK cytotoxic function was a significant predictor of infection in stable kidney transplant recipients [102].

Table 5
Associations between biomarkers of the complement system and infections in solid organ transplant recipients.

Year	Biomarker	Recipient organ type (number)	Study design	Timing of biomarker measurement	Results
2006 [56]	C3 and C4	Heart (38)	Prospective 1.4	Pre-transplant and post-transplant day 7 and month 1	At month 1, C3 was lowest in patients who developed infections.
2008 [58]	C3 and C4	Liver (46)	Prospective 0.5	Pre-transplant and post-transplant day 7 and month 3	C3 hypocomplementemia as associated with infection (RR: 3.0).
2008 [55]	MBL	Kidney (152)	Prospective 1	Pre-transplant and post-transplant month 3 and 12	Low MBL at month 3 was associated with sepsis and viral infections.
2013 [104]	C3 and C4	Kidney (270)	Prospective 1	Pre-transplant and post-transplant month 1 and 6	Low C3 at month 1 was associated with overall infection and bacterial infection month 1–6 Low C3 at 6 months was associated with bacterial infection month 6–12.
2008 [106]	MBL	Simultaneous kidney/pancreas (152)	Retrospective 1	Pre-transplant	Urosepsis was more common in patients with low baseline MBL (<400 ng/mL) compared with those with greater MBL levels. No influence of MBL on the occurrence of wound infections and CMV disease.
2005 [105]	MBL MBL genotype polymorphisms were determined in liver donors and recipients	Liver (49)	Prospective	Pre-transplant and post-transplant month 12	The presence of MBL variant alleles in the MBL gene of the donor liver, but not in the recipient, was associated with an incidence of clinically significant infections.

IV: intravenous, CMV: Cytomegalovirus, MBL: Mannose binding lectin, RR: relative risk.

1.8.4. Complement biomarkers

The complement system has an important role in opsonization of infective pathogens and activation of the adaptive immune system. Table 5 summarizes studies examining the association between biomarkers of the complement system and infectious outcomes in SOT [54,99,103–106]. Reduced levels of complement, measured within one month of kidney, heart and liver transplant are associated with an increased risk of infections in the first post-transplant year [99,103,104]. When foreign antigen is presented, complement can be activated by the classical, the lectin and the alternate pathways. Functional assessment of the lectin pathway can be performed by measurement of serum mannose-binding lectin (MBL), which activates the pathway through binding to a broad range of microorganisms [107]. Genetic polymorphisms that lead to decreased MBL production have been identified [105] and recent data demonstrated that liver transplant recipients of MBL-deficient liver transplants have a higher risk of bacterial infections, pneumonia and bacterial-infection related mortality [108]. Three studies have identified an association between reduced MBL pre-transplant and an increased risk of infection post-transplant [54,105,106].

1.9. Combinations of immune biomarkers

Several studies have assessed the correlation of a composite immune score with post-transplant infections (Table 6) [49,50,99,100,109,110]. Five of the six studies have demonstrated a significant association. It is

Table 6
Associations between composite immune biomarker scores and infections in solid organ transplant recipients.

Year	Immune biomarkers	Organ type	Study design	Timing	Results
			Follow-up (years)		
2003 [49]	Lymphocyte subsets, mitogen-induced T-cell proliferative responses, neutrophil phagocytic capacity and reactive oxygen species generation. Score based on 1 point allocated if test less than 10th centile of healthy controls.	Kidney (152) Simultaneous kidney/pancreas (14)	Retrospective 5	Score performed cross-sectionally >12 months post-transplant	The patients with a higher immune biomarker score had a higher infection score.
2005 [50]	Lymphocyte subsets NK cell number, T cell proliferation IgG, IgM, IgA Neutrophil phagocytic capacity and reactive oxygen species generation. Score based on 1 point allocated if test less than 10th centile of healthy controls.	Kidney (70)	Prospective 5	Score performed cross-section ally >6 months post-transplant	The score was the only risk factor that was associated with infection. The score predicted major and opportunistic infections but not minor infections
2012 [99]	NK cell number, IgG, IgA, IgM Immunoglobulin subclasses, C3, C4 Score based on hazard ratios for each single immune test	Heart (133)	Prospective 1	Pre-transplant and day 7 and 30 and month 12.	Day 7 post-transplant low IgG2, NK cell number and C3 were predictors of infection after adjustment for total IgG levels.
2014 [109]	IgG C3 and C4 NK cell number $CD4^+$ cell number	Heart	Prospective 1	Post- transplant	Score was predictive of severe infection.
2016 [110]	Positive CMV serology plus at least one of: $CD4^+$: $CD8^+$ ratio < 1 and/or CD8+ count number > 700 cells/mm^3	Kidney (486)	Prospective 1	Pre-transplant	Score was predictive of both opportunistic infection and severe bacterial infection (HR: 2.9 and 2.3, respectively).
2016 [100]	Positive CMV serology plus at least one of: $CD4^+$: $CD8^+$ < 1 and/or $CD8^+$ cell number < 0.850×10^3 cells/uL	Kidney (435)	Prospective 1	Pre-transplant and various time points post-transplant	Score was not predictive of either OI or severe bacterial infection.

NK: natural killer, CMV: cytomegalovirus, VZV: varicella zoster virus, IV: intravenous, OI: opportunistic infection, *PCP: Pneumocystitis jirovecii*, HRHhazard ratio, spp.: species.

difficult however, to compare these studies directly due to differences in study designs and immune components included in the scores. The study performed by Blazik et al.. in kidney transplant recipients was the only study to examine a composite score beyond the first post-transplant year [50]. This study and that of Hutchinson et al. also differed from others in that they were the only studies to include neutrophil and T cell functional assays [49,50]. Importantly, both were performed prior to the widespread usage of tacrolimus and mycophenolate mofetil and need to be validated in the modern era of immunosuppression. In two separate cohorts of heart transplant recipients it was demonstrated that decreased levels of serum complement and natural killer cells add to the predictive value of total IgG levels for severe infection in heart transplant recipients [99,109]. Crepin et al. and Fernandez-Ruiz *et al* each performed a prospective study in kidney transplant recipients using CMV serostatus, $CD4^+$:$CD8^+$ ratio and $CD8^+$ absolute number in a composite score. Crepin *et al* found an association with the score and infection but Fernandez-Ruiz *et al* did not [100,110].

Mian *et al* performed a prospective cohort study of 137 SOT recipients using an immune monitoring assay to predict infections during the first year posttransplant [111]. The assay tested interferon gamma responses to stimulation of the innate (Toll-like receptor 7 ligand) and adaptive (anti-CD3+ antibody) immune system. The assay predicted and increased risk of infections, with patients with low IFN-γ values being at the highest risk of subsequent infection.

1.10. Biomarkers using quantification of viral nucleic acid

Measurement of viruses through quantification of their DNA in plasma or serum can be used to predict the risk of other infections in SOT recipients [112,113]. Viral replication in SOT recipients depends on a number of factors that should be taken into account when using viremia as a non-pathogen specific biomarker. Since some of the viruses proposed for use as non-pathogen specific biomarkers can also cause infection in transplant recipients, it can become difficult to determine whether increasing viral replication represents a biomarker for the level of immunosuppression or early infection with the virus itself. In addition, donor-recipient sero-status is predictive of viral infection and disease for CMV, EBV and BKV. The type of transplant can influence viral reactivation, and this may be virus and transplant specific. For example, BKV establishes latency in the reno-urinary tract and has a markedly higher risk of reactivation in kidney transplant recipients compared with other SOT recipients [114]. Certain immunosuppressive medications can influence viral replication [115].

1.11. Epstein Barr Virus

EBV DNAemia is common among SOT recipients ranging from 17% to 70% [112,113,116–121]. Morton et al. studied 499 kidney transplant recipients recruited between one month and 33 years post-transplant and followed with serial measurements of EBV DNA [121]. EBV DNAemia prevalence and persistence appeared to increase, rather than fall, with time from transplant. The majority of studies linking clinical outcomes with EBV DNAemia use post-transplant lymphoproliferative disorder as the outcome measure. However, more recently studies have used serial measurements of EBV DNAemia to assess infection risk in SOT recipients [112,113,120]. These studies show that a high EBV viral load or persistent EBV infection is associated with an increased risk of severe infection [112,113,120]. A study of 62 lung transplant recipients showed that detectable EBV DNAemia within 6 months post-transplant was associated with an increased rate of overall and opportunistic infections and that mean peak EBV DNAemia was higher in those with later overall infection and opportunistic infection [120]. Another study of 383 kidney transplant recipients showed EBV DNAemia was associated with opportunistic infection but not bacterial infection or CMV [113]. San Juan et al. found that in liver, heart and lung transplant recipients, high level and persistent EBV DNAemia was associated with tumours, severe and opportunistic infections [112]. Current guidelines recommend screening for EBV DNAaemia in high-risk recipients for one year after transplantation for the purpose of early detection of EBV-related post-transplant lymphoproliferative disorder [122].

1.12. Cytomegalovirus

CMV infection and disease is arguably the most important infection in SOT recipients. Established CMV disease is immunomodulatory and places patients at risk of subsequent infections and rejection. There are a number of CMV specific biomarkers in use in research settings that can be used to predict CMV disease [123]. The majority of these strategies rely on measurement of CMV specific $CD8^+$ cells. The use of CMV DNAemia as a non-specific biomarker for all-cause infection is problematic. Firstly, donor-recipient sero-status is a key determinant of CMV DNAemia and will affect the likelihood of infection independent of other factors. Secondly, measurement of CMV DNAemia is influenced by the use CMV antiviral prophylaxis. Thirdly, the appearance of high level CMV DNAemia generally warrants antiviral treatment making it difficult to measure longitudinally.

1.13. Human Herpes Virus 6 and 7

129 liver transplant recipients were randomized to real-time monitoring of HHV-6 and HHV-7 viremia by PCR at regular intervals or to undergo usual care, with the primary outcome being a composite of adverse events indirectly attributable to viral reactivation (including opportunistic infection, graft rejection and severe hepatitis C virus recurrence). There were no differences in the cumulative incidence of the primary outcome between the “monitoring” and “no-monitoring” groups at 1 year or 5 years [124].

1.14. Torque Teno virus

Torque Teno viruses (TTV) are small non-enveloped viruses that are non-pathogenic in humans [125]. There is emerging interest in the use of TTV as a non-specific biomarker of immunosuppression as they have a prevalence of up to 90% in healthy and immunocompromised individuals [126]. In SOT recipients, there have been studies that have demonstrated a correlation between the intensity of immunosuppression and TTV DNAemia [126–129]. A recent study prospectively quantified TTV viremia in the peripheral blood of 169 kidney transplant recipients. Patients who developed infections in the 14 months of follow-up had higher TTV levels compared to patients without infection. Logistic regression demonstrated independent association between TTV levels and infection. [130]

1.15. BK virus

BKV is an important pathogen, especially in kidney transplant recipients. Although BKV DNAemia is widely considered a marker of over-immunosuppression there are no specific studies linking BKV DNAemia to other infections. Further research is required into the association between BKV and all-cause infectious outcomes.

2. Conclusion

Better biomarkers useful to identify SOT recipients at an increased risk of infection are required so that strategies aimed at reducing the risk of infection can be well tested. The majority of studies that have used clinical factors to guide reductions in immunosuppression have resulted in unacceptably high rates of allograft rejection [1,131–133].

This review has summarized currently available evidence from studies that have used immune biomarkers to predict infection in SOT recipients. The current available evidence is insufficient to support the use of

any one single or composite panel of diagnostic tests or algorithms to guide the clinician in tailoring the immunosuppressive regimen optimally for a given transplant recipient [134]. There is high quality evidence that severe hypogammaglobulinemia predisposes to infection, so monitoring of immunoglobulin concentrations does appear worthwhile. There is moderate quality evidence that monitoring of lymphocyte subsets can predict infection making this simple test another feasible method of identifying patients at high risk of infection. The quality of evidence for the remaining biomarkers is low and mostly derived from single centre studies. The studies have differed in terms of study design, immunosuppressive regimens, follow up, infectious outcomes and clinical parameters. Furthermore, the relative contribution of CMV to total infections has differed markedly. There are very few studies that have validated the use of biomarkers in different transplant cohorts and those that did found inconsistent results [100,110]. Studies that have utilized composite immune scores have been the most promising, however the presence of co-linearity, functional overlap and redundancy of immune biomarkers needs to be considered [49,50,99,100,109,110,135,136]. Emerging evidence for the use of monitoring of viruses for non-pathogen specific infections is interesting but is yet to be tested in combination with immune biomarkers.

SOT recipients represent a unique group of patients in which to study immune biomarkers because although they are prescribed similar medications, there are widely variable degrees of immunosuppression and susceptibility to infection between individuals. Due to the changing epidemiology of SOT recipients, with less early graft loss and prolonged survival, increased research is required to develop robust tests to reflect the individual's level of immunosuppression or immune function. Ideally the tests should use standardized definitions and be validated in multiple transplant centres. The demographic trend towards older SOT recipients with increasing immune senescence may mean that CNI monitoring may be assaying a pathway (activation of naïve donor specific T- cells) that is of less importance than it was in previous eras. It might be that quantification (direct or indirect) of other aspects of immunity may be a better guide to functional immunity in such populations. Clearly, biomarkers that can predict both infection and rejection would be the most useful for clinicians. Furthermore, immune biomarkers found to be predictive of infection in SOT recipients, may be relevant to other immunocompromized patients and this requires further research.

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