The value of post-transplant monitoring of DSA in clinically stable renal transplant recipients.

CONCEPT RECOMMENDATIONS

Disclaimer: text is very preliminary and additional edits await the more definite recommendations after TLJ 3.0

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Abstract

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Abbreviations

aABMR	Active antibody mediated rejection
ABMR	Antibody mediated rejection
c.aABMR	Chronic active antibody mediated rejection
cABMR	Chronic antibody mediated rejection
CAN	Chronic allograft nephropathy
CDC	Complement dependent cytotoxicity assay
cg	Transplant glomerulopathy (Banff pathology consensus recognized lesion)
COMMIT	Consensus On Managing Modifiable risk In Transplantation working group
dd-cfDNA	Donor-derived cell-free DNA
dnDSA	*de novo* donor-specific antibody
DSA	Donor-specific antibody
gDSA	Intragraft donor-specific antibody
GRADE	Grades of Recommendation Assessment, Development and Evaluation
HLA	Human leukocyte antigen
IgG	Immunoglobulin G
MFI	Mean fluorescence intensity
MHC	Major histocompatibility complex
t	Tubulitis (Banff pathology consensus recognized lesion)
TCMR	T-cell mediated rejection
TLJ	Transplantation Learning Journey
RCT	Randomized controlled trial
SPI	Solid phase immunoassay
STAR	North-American Sensitization in Transplantation: Assessment of Risk working group
Subclinical DSA	DSA that has been noted in patients who otherwise do not show any sign of clinical dysfunction of the allograft, such as significantly increased proteinuria or decreased eGFR
QALY	Quality-adjusted life year

Introduction

The introduction of the complement-dependent cytotoxicity assay (CDC) in 1969 was the first step towards addressing the issue now known as antibody-mediated rejection (ABMR). (1) Means to investigate this entity were further expanded in later years by the introduction of novel techniques, amongst others, flow-cytometry and solid-phase immunoassays (SPI).

Yet this also seemed to concomitantly introduce new dilemmas, such as how to interpret SPI assay results in the face of a negative pretransplant CDC crossmatch or whether patients should be monitored for the incidence of donor-specific antibodies (DSA) to HLA post-transplantation. Also defining a positivity cut-off, defining the donor specificity of an antibody or even the definition of a relevant change in antibody titre are challenging. For the purpose of this consensus review, DSA are generally implied to be DSA to HLA, unless otherwise specified.

A consensus meeting in 2013 concluded that pretransplant monitoring of DSA through single-antigen bead SPI's could be of benefit in risk stratification. (2) Additionally, DSA monitoring in post-transplant patients could be of benefit in those with a dysfunctioning graft, as well as a screening modality at least once in the first year post-transplant in patients with a stable graft. The level of evidence was however not found to be sufficient for strong recommendations. Nevertheless, pre-transplant screening of DSA through SPI assays with single antigen bead (SAB) tests as immunological risk stratification technique seems standard practice in many transplant centers these days and a recent position paper by Bestard et al. (3) seems to consolidate this screening practice further. Post-transplant monitoring of DSA in graft dysfunction seems to be equally standard practice in case of clinical suspicion of ABMR. (4) However, standardized monitoring of DSA in renal graft recipients without overt signs of transplant dysfunction such as decrease in eGFR or increasing proteinuria, so called *subclinical DSA*, has not taken hold as standard of care in most transplant centers.

This lack of implementation is likely related to uncertainty regarding the clinical consequence and cost-effectiveness of monitoring for subclinical DSA. If the aim is early detection of underlying rejection, then one would for instance first have to prove that screening would detect sufficient rejection cases in an earlier stage on subsequent biopsy, that earlier treatment would improve patient outcome over detecting and treating cases with overt signs of allograft dysfunction, and that such a strategy is ultimately cost-effective. These issues were not addressed in the earlier consensus

paper and the lack of a defined clinical consequence could perhaps underlie the discrepancy in the clinical implementation of those proposed DSA monitoring guidelines.

The above makes it clear that the prerequisites for validity of a screening test are different from those of diagnostic tests. To appraise the validity of a screening test, Wilson & Jungner defined 10 criteria in 1964, which since then have been described as the gold standard for this purpose. (5) (Box 1)

The purpose of this consensus paper is to assess the value of protocollary post-transplant monitoring of (subclinical) DSA. Statements and recommendations will reflect the fulfillment or lack thereof of the relevant aforementioned criteria by Wilson & Jungner.

Additionally, potential gaps in knowledge will be identified and future research objectives will be stated.

1. The condition sought should be an important health problem.
2. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
3. There should be a recognizable latent or early symptomatic stage.
4. There should be a suitable test or examination.
5. The test should be acceptable to the population.
6. There should be an agreed policy on whom to treat as patients.
7. There should be an accepted treatment for patients with recognized disease.
8. Facilities for diagnosis and treatment should be available.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a “once and for all” project.

Box 1: Wilson & Jungner’s principles of screening

To formulate this consensus statement, the European Society for Organ Transplantation appointed a working group of European experts in renal transplantation in December of 2021 within the Transplantation Learning Journey (TLJ) 3.0. An additional evidence review team was appointed, which met with the working group to outline relevant literature search strategy. The evidence review team searched PubMed, Embase and Cochrane libraries through May 2022 to identify

relevant studies. The methodology of this project has been described extensively before [ref Cillo U et al. Transplant Int in press].

Recommendations based on this evidence are graded on strength of recommendation (1 or 2 for strong or weak recommendations respectively) and level of evidence (A, B, C, D for strong, moderate, low and very low respectively) according to the Grades of Recommendation Assessment, Development and Evaluation (GRADE) methodology (6)

The recommendations and guideline statements and the Wilson & Jungner criteria which they reflect are summarized in box 2.

Recommendations	GRADE Level	W&J Criterium
Efforts should be made to prevent late renal allograft loss, of which one of the leading causes is ABMR.	1A	1
Clinicians should note that DSA are associated with a high risk for development of rejection, primarily ABMR, and subsequent allograft loss.	1C	2
Upon detection of a DSA, efforts should be made to determine its pathogenicity and the impact on prognosis.	2C	3
DSA can signal for underlying microscopic injury, indicative of subclinical rejection, which can be identified through allograft biopsy.	1C	3
Development of dnDSA can signal for subclinical TCMR, which in turn could be related to underexposure to immunosuppression.	2D	3
Allograft biopsies in patients with subclinical DSA show lower ABMR chronicity scores compared to patients with allograft dysfunction.	2D	3
Efforts should be made to standardize testing and reporting of DSA, including information on MFI, their plausibility and possible cross-reactive antigens/epitopes.	Not graded	4
Whilst post-transplant monitoring of preformed DSA in patients with stable graft function might be helpful, additional clinical and laboratory parameters should also be considered when deciding if a biopsy should be performed.	2C	4
DSA MFI levels or complement binding ability (C1q, C4d, C3d) should not influence decision-making regarding whether a biopsy in patients with subclinical dnDSA should be omitted, but other non-invasive markers may increase predictive value in the future.	2C	4
We recommend optimization of maintenance therapy, including addressing non-adherence in patients who develop subclinical dnDSA. Additional treatment should only be considered after performing an allograft biopsy.	1C	5-7

Evidence regarding the cost-effectiveness of standardized monitoring of DSA in stable renal graft recipients is missing and future efforts should be undertaken to determine this.	2D	9
Monitoring for persistence or broadening of subclinical dnDSA repertoire should not be discontinued after a certain time post-transplant.	2C	10
The optimal DSA monitoring scheme has not been established and depends on factors such as immunological matching, DSA screening methods, and immunosuppression, but a pragmatic approach would be antibody monitoring at 3 to 6 months post-transplant and annually thereafter.	2C	10

Box 2: Summary of statements and recommendations

PICO 1:

Overarching question: Does late rejection pose a health problem?

Sub-PICO: In renal transplant recipients (P), is late rejection (I) a significant contributor to allograft attrition rates compared to other factors (C)?

Efforts should be made to prevent late renal allograft loss, of which one of the leading causes is ABMR. (1A)

Breakthroughs in maintenance immunosuppression during the latter part of the past century drastically increased kidney graft survival rates. (7-10) This was, however, realized mainly through increases in graft survival over the first year. Comparably less progress has been made in improving graft attrition rates beyond the first year during this era. Unfortunately, recent registry data analysis showed that this rate of progress has not increased since 2000 when accounting for evolution in donor and recipient characteristics. (11)

The major limiting factor in long-term death-censored graft survival appears to be antibody-mediated rejection (ABMR), in which DSA play an important role. (12) This entity has become the leading cause for overall death-censored renal allograft loss in recent decades. (13, 14)

It therefore seems indisputable that improving the rate of allograft loss due to ABMR is an important health issue in kidney transplantation and we recommend that efforts to improve long-term graft survival should be aimed at tackling this entity. In doing so, one has to be aware that any efforts

should be put into clinical context and balanced against the competing risk (for late allograft loss) of patient mortality.

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PICO 2:

Overarching question: Do we understand the natural history of rejection sufficiently to identify a latent stage?

Sub-PICO(s):

In renal transplant recipients with rejection (P), are DSA (I) a significant independent causative contributor to development of the rejection process (O) compared to those without DSA (C)?

In renal transplant recipient with rejection (P), are other factors (I) determined as significant independent cause for the development of the rejection process (O) compare to those without those factors (C)?

Clinicians should note that DSA are associated with a high risk for development of rejection, primarily ABMR, and subsequent allograft loss. (1C)

For screening to be successful, one should have an understanding of how covert pathological processes can develop into overt clinical graft dysfunction, as the aim is to identify the covert process before dysfunction occurs.

In the case of ABMR, the screening marker itself seems to be implicated in the underlying pathological process. This is apparent with pre-transplant DSA, considering the high risk of hyperacute rejection if transplantation proceeds despite a positive CDC-crossmatch. Modern practice precludes such transplantation without measures such as desensitization or paired kidney exchange programs. Though this is not the case in pre-transplant DSA which are only found through SPI assays. Nevertheless, a meta-analysis has implicated these pre-transplant CDC-crossmatch negative DSA as a significant risk factor for ABMR (RR, 1.98; 1.36–2.89) and allograft loss (RR, 1.76; 1.13–2.74). (15)

Regarding de novo DSA (dnDSA), a recent large meta-analysis implicated the development of dnDSA as a significant risk factor for notably cellular rejection [RR 2.92; 95% CI 2.16–3.94], acute ABMR [RR 9.66; 95% CI 6.79–13.73], chronic ABMR [RR 6.78; 95% CI 4.31–10.66] and allograft loss [RR 4.95; 95% CI 3.81–6.43] (16).

While these meta-analyses demonstrate a clear association of anti-HLA DSA with subsequent rejection and allograft loss, this does not necessarily infer a causal relationship.

However, the pathogenicity of HLA-DSA has been an extensively studied subject in recent years and a recent extensive literature review by Callemeijn et al. (17) has attempted to untangle association from causation. They assessed this proposed causal relationship between anti-HLA DSA and microvascular inflammation, which is typically associated with ABMR, through the Bradford-Hill criteria, which can be used as guide for causal inference in epidemiological research. This assessment indeed shows that most criteria are met. As there is a biological plausible explanation in that endoluminal interaction of circulating antibodies with donor endothelium allows for a direct effect, which has been demonstrated in murine models. (18) Here, rejection could be induced in cardiac transplants after passive transfer of anti-HLA DSA. In clinical studies, HLA-DSA are strongly and consistently associated with incidence of microvascular inflammation in several independent cohorts (15, 16, 19). Furthermore similar associations between anti-HLA DSA and ABMR have been

found in various types of organ transplants (12) and both preformed and dnDSA seem to be able to predict occurrence of ABMR (20, 21). Some Bradford-Hill criteria are not fully met. As there is no clear demonstrable biological gradient, considering that there is no clear relationship between antibody titre and occurrence of ABMR or graft failure. (22) Lastly, reversibility has not yet been convincingly demonstrated. While there were short term beneficial effects of plasma exchange and IVIG on acute ABMR, effects on more chronic or late ABMR are variable. (23) Nonetheless, there seems to be clear preclinical and clinical evidence of a causal relation between anti-HLA DSA and ABMR.

Yet despite this causal relationship, not all recipients with preformed DSA or dnDSA seem to progress to graft failure or even ABMR. (24, 25)

Mechanisms at the molecular level have been proposed to explain this phenomenon that would classify some DSA as indolent or even anti-inflammatory. This could be partly related to specific characteristics of the Fc fragment of IgG DSA or its IgG subtype, as outlined in previous reviews and studies. (26-30) Additionally, isotype switch has been proposed as an alternative protective explanation but this has not been corroborated. (31) Yet, multiple cellular pathways have been implicated in the development of ABMR, not all of which are dependent on binding of the Fc-fragment (27, 32). Some have hypothesized that in some patients, DSA may in fact be "accommodating" as their interaction with the endothelium leads to upregulation of complement regulatory proteins, instead of inflammatory ones. (33-35) This could be akin to the process commonly seen in ABO-incompatible transplants. Yet what ultimately determines which pathway, regulatory or inflammatory, is activated has not yet been fully uncovered. Lastly, there may be a role for regulatory T and B-cells. (36, 37)

It is thus clear that while a causal relationship between HLA-DSA and ABMR can be inferred, there is still much unknown regarding the underlying pathological mechanisms of this relationship.

Moreover, it must also be mentioned that not all patients with microvascular inflammation, indicative of injury attributed as being "antibody-mediated", have measurable levels of anti-HLA DSA. The entity known as HLA-DSA negative ABMR by definition suggests factors other than HLA DSA can mediate microvascular inflammation.

This could perhaps still be explained by HLA-DSA which are not measurable in assays on peripheral blood, as they could be locally produced in the allograft or they are fully adsorbed from the bloodstream into the allograft. (38) Though the latter of these hypotheses has not yet been

corroborated as only seven patients have ever been described with measurable DSA in the eluate of their allograft but not in serum analysis. (39, 40)

Alternatively, other causal factors may be at play in patients with HLA-DSA negative ABMR.

The role of non-HLA DSA has also previously been described and implicated as a causal factor (41-44), though much is still unknown regarding which non-HLA loci are particularly harmful and how mismatches in these loci eventually induce rejection in the graft.

Antibody-independent mechanisms could also be responsible for occurrence of microvascular inflammation. As NK-cells may induce this histological entity through a "missing self" mechanism when interacting with donor endothelium. (45, 46) Additionally, pre-clinical evidence has emerged showing that monocytes may also have direct allo-recognizing properties which could induce microvascular inflammation. (47, 48)

Lastly, there may a pivotal role for T-cells, as multiple studies have associated previous T-cell mediated rejection with development of DSA. (21, 49-51) This role of T-cells perhaps further questions the current dichotomized view on rejection (i.e. either TCMR or ABMR). As eloquently summarized by Callemeijn et al. (17), it does not explain the heterogeneity of kidney transplant rejection in terms of serology, molecular changes, immune infiltrate composition, treatment response, and the presence of mixed rejection.

This summary of studies shows that there are likely multiple individual pathways, not all of which are fully understood, that eventually lead to microscopic injury that is currently defined as ABMR by Banff'19 criteria, with certain amounts of crosstalk between them.

Nonetheless, regardless of the incompletely understood natural history of ABMR, anti-HLA DSA are still significantly associated with, and predictive of it and clinicians should be aware of this.

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PICO 3:

Overarching question: Are we able to identify latent rejection through DSA

screening before overt dysfunction occurs?

Sub-PICO(s):

In renal transplant recipients (P), is development of dnDSA or prevalence of preformed DSA (I) associated with subclinical rejection (O) compared to those without DSA (C)?

In renal transplant recipients with subclinical DSA (P), can allograft biopsy guided by DSA development/evolution (I) identify subclinical rejection in an earlier pathological stage (O) compared to biopsies in the event of more overt dysfunction (C)?

Upon detection of a DSA, efforts should be made to determine its pathogenicity and the impact on prognosis. (2C)

&

DSA can be a signal for underlying microscopic injury, indicative of subclinical rejection, which can be identified through allograft biopsy. (1C)

Seminal papers by Wiebe et al. (21, 52) have shown in a large single-center cohort of 506 patients with protocol biopsies at 6 months post-transplant and in case of dnDSA development, as well as indication biopsies that of 64 patients who developed dnDSA, 45 were subclinical patients. Moreover, development subclinical dnDSA was independently associated with increased risk of transplant glomerulopathy (and thus chronic ABMR), renal functional decline and allograft loss compared to patients with no DSA or graft dysfunction. This indicates that DSA development can precede overt rejection and clinical dysfunction of the graft and it can thus be a signal of a latent underlying pathological process. This latent rejection process has also been observed in more recent studies (Table 1).

Bertrand et al. (53) recently analyzed 123 patients with subclinical dnDSA in a large French retrospective multicenter cohort study with biopsies in case of dnDSA development and found that

41.5% of these patients had subclinical ABMR at biopsy. Interestingly, patients with subclinical DSA but absent ABMR had significantly lower five years allograft attrition rates than those with rejection and additionally had stable eGFR at five years post-transplant, as compared to significant functional decline observed in those with subclinical ABMR.

Loupy et al. (54) showed in a large French single center prospective cohort study, with external validation, of 1001 patients with one year protocol biopsies that 13.1% of patients had subclinical TCMR and 14.2% of patients had subclinical ABMR. Their primary point of view was the protocol biopsy at 1Y posttransplant, including 317 for-cause biopsies, rather than prospective DSA monitoring, but all of the patients with subclinical ABMR had DSA. Interestingly, 78% of subclinical ABMR cases were related to pretransplant DSA, indicating that both pretransplant DSA and dnDSA can underlie a latent pathological process. Notably, patients with subclinical ABMR at one year protocol biopsy had a significantly lower eight year allograft survival probability of 56%, compared to 90% in the group without rejection.

Schinstock et al. (50) retrospectively analyzed a single center cohort of patients from Minnesota with 4, 12, 24 and 60 months with serial surveillance biopsies, but included also a number of indication biopsies and biopsies at dnDSA development. They found that of the 40 patients who were biopsied at the time of dnDSA development, 25%, 7.5% and 20% had underlying active ABMR, chronic ABMR and TCMR respectively. Interestingly, upon one year follow up biopsy post DSA detection, the prevalence of active ABMR and chronic ABMR had significantly increased to 52.9% and 38.2% respectively. Out of the patients with dnDSA, only those with histologic evidence of ABMR at DSA detection or on subsequent biopsy had increased incidence of graft failure. As 21% of patients with ABMR and DSA had eventual graft failure as compared to 0% of patients with DSA but absent ABMR. Although the follow-up time for this comparison was only a mean of 3.2 ± 2.0 years.

In contrast, a study by Yamamoto et al (55) reported from a smaller retrospective Japanese cohort study of 43 patients with dnDSA without graft dysfunction. They found 41.8% of patients had subclinical ABMR. Eight of 25 patients without subclinical AMBR at the index biopsy had a subsequent biopsy at two years post-index biopsy and *none* showed subsequent development of ABMR. Only one of these eight patients had deteriorating creatinine clearance and proteinuria, though this patient had recurrence of IgA nephropathy.

Parajuli et al. (56) showed in an American retrospective single center cohort study of 45 patients with indication biopsies and in case of dnDSA development that of 29 patients with subclinical dnDSA, 15 (51%) had underlying rejection. Of those rejections, 60% were AMR, but 20% and 20%

were TCMR and mixed rejection respectively. Patients with clinical rejection and DSA had much lower rates of ABMR at 14%, compared to 43% and 43% for respectively TCMR and mixed rejection. Waldecker et al (57). retrospectively studied 84 German patients with indication biopsies or in case of dnDSA development from a single centre and found that out of 50 patients with subclinical dnDSA, 44% had ABMR, 15% had TCMR, 12% had mixed rejection and 15% had borderline rejection. In clinical dnDSA patients, 50% had ABMR, 12% had TCMR, 26% had mixed rejection and 8% had borderline rejection, though these differences with subclinical patients were not significant.

Although not all of these studies were performed from the perspective of prospective DSA monitoring but some rather from the perspective of protocol or surveillance biopsies, these studies all indicate that subclinical DSA can be a signal for latent rejection in almost 50% of biopsies with ~ 10-20% of TCMR and 15-40% of ABMR. Though, as stated before, not all patients who develop DSA seem to lose the graft or even show declining allograft function.
The studies by Bertrand et al. (53), Yamamoto et al (55). and Schinstock et al (50). suggest that within patients with subclinical DSA and subclinical rejection, the histology might have important prognostic value in terms of pathogenicity and prognosis. This was corroborated by Parajuli et al (58) in a retrospective cohort of 587 patients without rejection at initial protocol *or* indication biopsies that there was no difference in five years allograft loss between DSA positive and DSA negative patients, albeit that de novo DSA positivity in patients with negative index biopsies was associated with subsequent rejection. This might suggest that the follow-up period might have been too short. Additionally, a study by Hayde et al (59). found that the rate of allograft loss was lower in DSA positive patients without histological features of rejection compared to patients with histological features. Interestingly, gene expression profiles of the kidney histology were comparable between the two groups in terms of aspects related to alloimmunity. However, the gene expression profile of whole blood showed increased gene transcripts related to alloimmunity in DSA positive patients with ABMR, but not in DSA positive patients without ABMR. These results seem to suggest that there might a local but not a systemic alloimmune response to the allograft of DSA-positive patients without histological signs of rejection. It was speculated that perhaps the initial local alloimmune response is necessary in order to develop a regulatory profile, though this has thus far not been corroborated.

Whilst DSA positivity may provide an initial prompt to further investigate the transplant recipient through an allograft biopsy, the allograft biopsy itself may provide additional prognostic information

beyond the DSA positivity or rejection diagnosis.

Kim et al. (60) showed in a prospective cohort study of 215 patients that while DSA was univariately associated with renal function decline, this was no longer statistically significant when analyzed with a multivariate model including microvascular inflammation and tubulitis.

Multiple other studies found significant associations between histological lesions as microvascular inflammation, transplant glomerulopathy and tubulitis, and allograft loss in patients with DSA, though these studies did not report whether this was independent from DSA prevalence. (52, 61, 62). In contrast, the iBox (63) shown that DSA as a prognostic factor contributes significantly to other markers of graft function such as proteinuria and eGFR in the overall group, but that histology contributed only modestly to prognosis and overall C-statistic. However, the histology contributed importantly to outcome in the subgroup with ABMR [ref]

These studies therefore suggest that subclinical DSA can not only signal underlying latent rejection diagnosis, but that the underlying pathology is also independently important for prognosis.

Study	Type of study	Total patients (n)	Total DSA+	Biopsied Patients with Subclinical DSA (n)	dnDSA/ preformed DSA	Time of biopsy	Subclinical aABMR (n) (%)*	Subclinical c.aABMR (n) (%)*	Subclinical cABMR (n) (%)*	Subclinical TCMR (n) (%)*	Mixed rejection (n) (%)*	No rejection (n) (%)*
Wiebe et al. (21)(52)	Retrospective Single center	508	64	45	dnDSA	6 months post-transplant At dnDSA detection Graft dysfunction	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
Bertrand et al. (53)	Retrospective Multicenter	123	123	123	dnDSA	At dnDSA detection	32 (26%)	19 (15.5%)	Not specified	Not specified	Not specified	No ABMR: 72 (58.5%)
Loupy et al. (54)	Retrospective Single center + external validation	1001	?	?	dnDSA + Preformed DSA	1 year post-transplant	142 (14.2%)**			132 (13.2%)**	Not specified	727 (72.6%)**
Schinstock et al. (50)	Retrospective Single center	771	54	40 biopsied at detection of DSA 34 biopsied 1 year post detection of DSA Not all subclinical	dnDSA	4, 12, 24, 60 months post-transplant at dnDSA detection Graft dysfunction	At dnDSA detection: 10 (25%) 1 year post dnDSA detection 18 (53%)	Not specified	At dnDSA detection: 3 (7.5%) 1 year post dnDSA detection 13 (38.2%)	At dnDSA detection: 8 (20%) 1 year post dnDSA detection 5 (14.7%)	Not specified	Not specified
Yamamoto et al. (55)	Retrospective Single center	899	95	43	dnDSA	At dnDSA detection	18 (42%)			Not specified	Not specified	No ABMR: 25 (58%)
Parajuli et al. (56)	Retrospective Single center	45	45	29	dnDSA	At dnDSA detection "Other indications"	9 (31%)			3 (10%)	3 (10%)	14 (48%)
Waldecker et al. (57)	Retrospective Single center	865	132	34	dnDSA	At dnDSA detection Graft dysfunction	11 (26%)	3 (9%)	1 (3%)	5 (15%)	4 (12%)	5 (15%)

***: Proportion of total patients (Since total subclinical DSA uncertain)*

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Development of dnDSA can signal for subclinical TCMR, which in turn could be related to underexposure to immunosuppression (2D)

As shown by Schinstock et al. (50), Parajuli et al (56). and Waldecker et al. (57), in addition to signaling ABMR, DSA can seemingly also signal underlying TCMR, which is in line with the thought that allogeneic responses may be a part of a rejection continuum. As they showed 10-20% of patients with subclinical DSA or at detection of DSA had TCMR. Unfortunately, no biopsies were performed in a DSA negative control group in these studies, making it difficult to be certain of the precise odds of DSA to signal TCMR risk. However, the association of T-cell mediated injury and dnDSA is well described as previous TCMR is an independent risk factor for the development of dnDSA (21, 49-51) . This association is hypothesized to be explained by sensitization of the B-cell compartment through inflammation induced by the T-cell alloimmunity. (64)
Since Wiebe et al. (21) correlated both TCMR hallmarks of tubulitis and interstitial inflammation with non-adherence in patients with dnDSA, it might be speculated that those dnDSA positive patients with TCMR reflect a specific subgroup of patients with underexposure to immunosuppression. These patients may additionally have worse prognosis, as Cherukuri et al. (65), showed that in a retrospective single center cohort of 294 patients, those DSA positive patients with underlying TCMR and non-adherence as determined by high CNI intrapatient variability have significantly worse four years allograft survival than adherent DSA positive patients with TCMR, 30% vs 75% respectively. Additionally, another study by Schinstock et al. (66) found in a multicenter cohort study of 113 dnDSA positive patients that non-adherent patients or those who had reduced immunosuppression have worse three years post-dnDSA detection allograft survival than adherent DSA positive patients on regular maintenance immunosuppression, 70% vs 87.8% respectively. Though they did not note whether these underexposed patients had more TCMR related lesions.
Unfortunately, no studies on the association of TCMR with DSA in renal allograft recipients with preformed DSA have been conducted. As such, it is not clear whether the assumptions for dnDSA hold true in these patients as well.

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Allograft biopsies in patients with subclinical DSA show lower ABMR chronicity scores compared to patients with allograft dysfunction. (2D)

As shown, studies in which biopsies have been performed in patients with subclinical DSA report a prevalence of ABMR in 41-44% of cases. (53, 55-57) Interestingly, the pathological process in these patients could show an earlier stage of disease, as a retrospective single center study of 143 ABMR patients by Parajuli et al. (67) found that the Banff sum chronicity and cg scores of patients with underlying ABMR at biopsy were lower in subclinical ABMR patients, compared to those with ABMR and dysfunctioning allografts. Additionally, Wiebe et al. (21) found that no patient with subclinical dnDSA had transplant glomerulopathy at biopsy.

This could indicate that patients with subclinical DSA present with more active ABMR (aABMR) instead of chronic active ABMR (c.aABMR) or chronic ABMR (cABMR).

However, the previously mentioned study by Waldecker et al. (57) was not able to show this

difference in respect to cABMR, though this could be related to the very small sample size of patients with cABMR. In respect to c.aABMR, they reported a greater proportion of patients with clinical dysfunction and dnDSA presented with c.aABMR as compared to those with subclinical dnDSA, 28% vs 7%. Though they unfortunately did not report whether this was statistically significant.

Nevertheless, the higher Banff sum chronicity scores and increased transplant glomerulopathy observed in subclinical ABMR would fit the theory postulated by Wiebe et al. (21) that ABMR initially presents as acute inflammation with gradually increasing chronic lesions.

This is also suggested in studies by Loupy et al. (54, 68) and Haas et al. (69) which found that patients with subclinical ABMR at three months and one year post-transplant have significantly more transplant glomerulopathy at follow up biopsies compared to those without rejection on index biopsies.

While these studies give some suggestion that patients with subclinical ABMR have less chronic forms of ABMR, the evidence is limited. We therefore recommend that more research be conducted to confirm this.

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PICO 4:

Overarching question: Are current DSA testing methods suitable for DSA screening and can certain DSA characteristics be used to further guide allograft biopsy decision making

In renal transplant recipients are current DSA assessment methods sufficient to reliably detect anti-HLA antibodies and its donor specificity

(Sub)Pico's:

In renal transplant recipients with subclinical DSA (P), can DSA characteristics (MFI, class, IgG subclass, complement binding ability) (I), reliably be used to identify patients without rejection (O) compared to allograft biopsy (C)?

Efforts should be made to standardize testing and reporting of DSA, including information on MFI, their plausibility and possible cross-reactive antigens/epitopes (Not graded)

In addition to attempting to further stratify the risk that subclinical DSA may incur through allograft biopsy, one should also be aware of the inherent limitations of testing of and reporting on DSA. Anti-HLA antibody detection and antigen/epitope specificity identification have never been as good

as today. HLA antibody assessment using solid phase assays including all major HLA loci are already recommended in the 2017 North-American Sensitization in Transplantation: Assessment of Risk working group (STAR) report. (70) Albeit beyond the scope of the present consensus report on DSA monitoring, efforts should be made to standardize anti-HLA antibody testing and interpretation to increase the clinical utility of the current methods. Non-HLA antibodies are beyond the scope of this consensus report. Initiatives such as the STAR working group (70, 71) are essential to clarify the expectations and limitations of current clinically used DSA detection methods. Standardization, within and between centers and between manufacturers is not only a prerequisite in clinical studies but also valuable to increase clinical utility in the follow up of individual patients.
Additionally, when reporting on DSA, crosstalk between the HLA-lab and the clinic is important. Clinicians need to receive comprehensive reports in a timely manner while being informed on the limitations of individual assays and results. Tissue-typers on the other hand need to understand the clinical course of a patient after transplantation. Whereas HLA labs are highly involved in the definition of acceptable and unacceptable antigens pretransplant, they are less involved in the posttransplant follow up of individual patients. To increase clinical utility (prognostic aspects) and validity (diagnosis) feedback should not only go from the lab to clinic but also vice versa resulting in both analytical and clinical reporting. This interaction is specifically needed to address the potential pitfalls of DSA screening in entity of DSA negative ABMR.

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Whilst post-transplant monitoring of preformed DSA in patients with stable graft function might be helpful, additional clinical and laboratory parameters should also be considered when deciding if a biopsy should be performed. (2C)

Development of dnDSA is a biomarker that could prompt a clinician to further investigate a patient for underlying pathology. Here we consider monitoring patients with subclinical preformed DSA. In these patients it might be more difficult to determine a prompt to decide on whether or not to biopsy. Though these antibodies may gradually disappear from the circulation and it could thus be argued that post-transplant persistence of preformed DSA could prompt a biopsy, since most studies indicate that persisting preformed DSA incur a higher risk of allograft loss and rejection than cleared DSA (20, 72-76), although some studies contradict this conclusion (60, 77). Additionally, studies comparing allograft loss in patients with cleared preformed DSA versus no preformed DSA give conflicting results. (20, 73, 78). Furthermore, no study has examined the specific predictive test characteristics of clearance of preformed DSA.

This indicates that while persistence of preformed DSA seems detrimental for transplant outcomes compared to those with cleared preformed DSA, it is currently not certain whether grafts in patients who clear preformed DSA have a survival disadvantage or suffer higher rates of rejection compared to grafts in regular non-sensitized patients.

There is currently little evidence that change in the MFI of preformed DSA in patients with stable grafts after the transplant has any predictive value. Although earlier studies showed that an early rise in DSA MFI was associated with early ABMR (79, 80), a more recent in depth analysis by Philpott et al. (81) of early (<1 month) post-transplant temporal evolution of DSA indicated that it was the speed of change in MFI, rather than eventual delta MFI, during the first month, that impacted allograft survival. They elegantly showed that patients with modulating preformed DSA (i.e. a rise then subsequent fall of MFI) had significantly better allograft survival than patients with sustained levels of preformed DSA (i.e. rising MFI and followed by sustained or stable MFI throughout). This would indicate that a random point measurement of DSA MFI level in the early post-transplant course would provide minimal predictive information, as high delta MFI compared to pre-transplant could still be associated with a DSA which is undergoing a modulating course and thus appears to incur less risk than a DSA which had a more stable course in MFI. In this study, biopsies were only performed in case of allograft dysfunction, so it is difficult to extrapolate these results to patients with stable graft function. Considering that the inter-laboratory variation of MFI can be as high as 62%, delta MFI alone should be interpreted with caution in the absence of other clinical parameters. (82) Consensus guidelines of the STAR working group are in line with this notion, as they state that any increase of MFI less than 50% is likely to be meaningless in otherwise relaxed situations. (70) Furthermore, even if the results of Philpott et al. could be extrapolated to subclinical patients, they

would only support careful monitoring in the first month post-transplant, as allograft survival was dependent on the type of evolution of DSA in that month. Unfortunately, no studies have analyzed associations between late evolution in preformed DSA MFI and transplant outcomes.

This leads to the conclusion that although patients with preformed DSA and stable grafts can have latent rejection, there is currently no evidence to support the notion that monitoring these DSA provides a prompt to initiate further investigation of the patient.

Instead, these patients might benefit from protocol biopsies, as advised by previous guidelines (2, 83), or, perhaps benefit from a screening strategy combining serum dd-cfDNA or alternative non-invasive biomarkers, as discussed in the next paragraph, to risk stratify the DSA and aid decision-making for conducting a biopsy.

However, both of these methods are unrelated to the validity of DSA monitoring and these are therefore beyond the scope of this consensus review.

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DSA MFI levels or complement binding ability (C1q, C4d, C3d) should not influence decision-making regarding whether a biopsy in patients with subclinical dnDSA should be omitted, but other non-invasive markers may increase predictive value in the future (2C)

While development of subclinical dnDSA may prompt further investigation of the patient, it would be of interest to define other factors that would help further stratify the risk of underlying graft pathology. As this may prevent needless allograft biopsies in patients with subclinical DSA. Multiple studies have associated certain characteristics of DSA with worse outcomes, such as MFI level (sum of all DSA MFI or highest individual MFI) (52, 60, 84-88), certain IgG subclasses (28, 29, 89), or complement binding ability (C1q, C4d, C3d) (19). However, most studies do not provide information on the negative predictive value of these characteristics, which would be the parameter of interest in deciding on whether to omit a biopsy.

Unfortunately, few studies have been conducted which study these test parameters. Although Eskandary et al. (90) retrospectively studied 86 patients with subclinical DSA from a single center and associated highest MFI, sum of MFI and complement binding ability with underlying ABMR, the

respective individual C-statistics, which measure the accuracy in discrimination of the outcome, were moderate at best for each characteristic (Highest C-statistic: 0.77, 0.75, 0.65 respectively). Additionally, a combined model of maximum or sum of MFI and either C1q, C4d or C3d positivity did not significantly improve the predictive power of the base model of only the MFI.

When analyzing test parameters for a range of highest and sum of MFI, they found that while a higher cutoff of >5000 or >10000 enjoyed a higher specificity for ABMR (0.86 and 0.99 for both MFI characteristics), the sensitivity drastically reduced from 0.82, 0,84 to 0.34, 0.43 and 0.30, 0.27 respectively. When analyzing these test parameters with the average reported prevalence of underlying ABMR at detection of dnDSA (43%) without taking patients into account with only underlying TCMR, the negative predictive value is still low (MFI>5000 0.63, 0.67; MFI>10000 0.64, 0.65, for maximum MFI and sum of MFI respectively). This indicates at least 30% of underlying ABMR would be missed by preclusion of a biopsy based on MFI cutoffs >5000 in subclinical patients.

Another study by Viglietti et al. (91) performed similar analyses with allograft loss as outcome in 186 patients with both subclinical and clinical DSA. They found an equally moderate C statistic regarding maximum MFI in the total group of patients with post-transplant DSA (0.72). This was only marginally better in specifically dnDSA+ patients (0.75). No analysis regarding specific MFI cut-offs was performed.

While C1q binding was found to significantly increase the fit of the base model, the numerical increase in C-statistic was a marginal 0.028 in dnDSA+ patients. (0.751 to 0.779)

Interestingly, IgG3 positivity strongly increased the fit of the model with improvement of the C-statistic from 0.75 to 0.88. Yet this specific characteristic was predominately present in patients whose dnDSA was detected after development of allograft dysfunction. In patients whose dnDSA was detected as a part of regular annual screening, only 2% of patients were IgG3 positive, yet 74% and 57% of these patients had a form of ABMR at biopsy one and two years post-transplant respectively.

These studies indicate that while some test characteristics such as higher MFI or IgG3 positivity might increase the likelihood of underlying pathology in dnDSA positive patients with stable grafts, *absence* of these characteristics also definitely do not exclude it. Currently, it seems therefore that none of these studied DSA characteristics can be used reliably to preclude a biopsy in patients with subclinical DSA.

We therefore do not recommend utilizing these DSA characteristics as an aid in deciding if a biopsy of patients with subclinical dnDSA could be omitted.

Mention should be made of the additional prognostic value of non-invasive markers of allograft tissue damage such as donor-derived cell-free DNA (dd-cfDNA) or urinary chemokines in the prediction of ABMR in patients with subclinical DSA. A meta-analysis has implicated that ABMR causes release of dd-cfDNA into the circulation which results in 10-fold increase of the median fraction of dd-cfDNA as compared to transplant recipients without rejection. (92) Interestingly though, patients with TCMR had no significantly increased fraction of dd-cfDNA.

While these biomarkers themselves are unrelated to the validity of DSA screening, recent studies have shown additional prognostic value for specifically underlying ABMR when both methods are combined in a single model.

In regards to dd-cfDNA, Jordan et al. (93) found significantly higher amounts of dd-cfDNA in DSA positive patients with ABMR, compared to DSA positive patients without ABMR. Additionally, a dd-cfDNA fraction cut-off of 1% in serum provided a very good C-statistic of 0.86 in discriminating ABMR in DSA-positive patients, which corresponded with a negative predictive value of 83% and a positive predictive value of 81%.

Moreover, a study by Mayer et al, (94) who analyzed a subset of the cohort analyzed in the study by Eskandary et al. (90), found that a combined model of DSA MFI and dd-cfDNA had an excellent C-statistic of 0.92 in discriminating between ABMR and no ABMR in subclinical DSA positive patients. This was a significant improvement over models only using DSA MFI or only using dd-cfDNA. Though no positive or negative predictive value was provided for this combined model.

Finally, a recent study by Obrișcă et al. (95), showed that a combined model of dd-cfDNA fraction >1 and dnDSA MFI >2500 had excellent predictive performance for ABMR with positive predictive value of 0.94 and negative predictive value of 0.92.

In regards to urinary chemokine excretion, Rabant et al (96). showed that a combined model of urinary CXCL10 expression and DSA MFI improved the C-statistic of the base model of only the MFI from 0.72 to 0.82. Notably, the negative predictive value was reported as high at >90%.

Tinel et al. (97) analyzed a predictive model containing urinary CXCL9 and CXCL10 excretion, in addition to DSA MFI, eGFR and certain patient characteristics and reported a C-statistic of 0.81 in patients with stable grafts and 0.85 in patients with graft dysfunction. Notably, they reported that the model could help avoid 58 out of 100 unnecessary biopsies in patients with stable grafts, when taking a <10% risk of missing acute rejection for granted.

These studies indicate that non-invasive biomarkers in patients with subclinical DSA could perhaps be utilized in decision-making for performing a biopsy. However, it must be noted that the total DSA

positive population included in these studies was low and further validation is thus needed. Furthermore, not all transplant centers currently have access to such tests in routine diagnostics. Nonetheless, non-invasive biomarkers seem promising and we recommend more research be conducted to confirm its risk-stratifying properties in relation to subclinical DSA positivity.

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PICO 5:

Overarching question: Is treatment for patients with subclinical DSA or subclinical rejection defined?

SubPICOs:

In renal transplant recipients with subclinical DSA who have not yet been biopsied (P), is treatment of any kind (I) compared to no treatment (C) beneficial for transplant outcome (O) (allograft loss, clinical rejection risk)

In renal transplant recipients with rejection (ABMR or TCMR) (P), is treatment in the subclinical phase (I) more beneficial to transplant outcome (O) (allograft loss/kidney function) compared to treatment in case of overt dysfunction (C)?

We recommend optimization of maintenance therapy, including addressing non-adherence in patients who develop subclinical dnDSA. Additional treatment should only be considered after performing an allograft biopsy. (1C)

Optimization of maintenance therapy, which includes promoting adherence, reintroduction of steroids and maintaining tacrolimus trough levels >5 ng/mL, has been recommended in previous consensus statements for the treatment of ABMR and TCMR. (23) Additionally, Cherukuri et al. (65) showed the detrimental effects of non-adherence in DSA+ patients with TCMR.
Moreover, the consensus on managing modifiable risk in transplantation (COMMIT) working group has reported on non-adherence and underexposure to immunosuppression as pivotal risk factors for poor transplant outcomes. (98)
While not all patients with subclinical dnDSA have underlying rejection, development of dnDSA in itself has been heavily correlated in multiple studies to current underexposure to immunosuppression. (52, 65, 66, 99-102) This subsequently implies that while the DSA might not always signal for underlying microscopically observable rejection, it may indeed still signal underexposure to immunosuppression, which should be addressed. Studies showing that non-adherent/underexposed DSA positive patients have worse allograft survival than DSA positive patients with adequate exposure support this notion. (52, 66) We therefore recommend that all patients who develop subclinical dnDSA should be treated by optimization of maintenance therapy according to local protocols, regardless of underlying histology, if toxicity and side-effects allow for such optimization. The ultimate goal is to optimize graft survival which includes taking into account competing mortality risk from infections, malignancies, and other toxicities.
Some evidence has emerged regarding the effectiveness of conversion from a CNI based

immunosuppressive regime to regimes based on costimulation blockade through belatacept. (103) Perhaps optimization of maintenance therapy could entail this strategy, as it would effectively eliminate occult non-adherence due to the fact that belatacept is administered intravenously. Additionally, its immunological mode of action may be more fitted for patients who have already developed a dnDSA as it interrupts T-follicular helper - B-cell interaction and could thus decrease B-cell stimulation and reduce DSA formation. (104) Some studies have shown effectiveness of belatacept on DSA levels and on the (lower) incidence of ABMR in sensitized patients. (103-106) The incidence of TCMR was however significantly increased, especially in patients converted within the first year post-transplant.

We therefore recommend more research be conducted on the role of costimulation blockade as a means to optimize maintenance therapy in patients with subclinical DSA.

In regards to further pre-emptive treatment of patients with subclinical dnDSA, evidence is lacking. Only one small cohort study has been identified, in which patients with subclinical DSA were treated with bortezomib, plasmapheresis (PP), IVIG and corticosteroids without performing a biopsy to confirm rejection. (107)

While this study showed that patients who achieved DSA clearance had more stable two year allograft function compared to those with persistent DSA, no control group was included and thus it cannot be concluded that improvement in outcome was due to the treatment.

Furthermore, irrespective of efficacy, subjecting all patients with subclinical dnDSA to such a strong and broadly targeting immunosuppressive regimen might be difficult to justify, considering that 15-48% of this population have no underlying observable histological injury and thus appear to have good allograft survival. (50, 56, 57)

Lastly, subclinical DSA provide a signal for increased risk of various types of rejection. Identification of the type of rejection through a biopsy will ensure that patients with underlying cell-mediated rejection are not unnecessarily subjected to therapy aimed at antibodies and vice versa.

We therefore do not recommend additional pre-emptive treatment of patients with subclinical dnDSA, over and above optimization of maintenance therapy, without performing an additional allograft biopsy.

Whether a DSA screening program in subclinical patients is acceptable for this population largely depends on whether the proposed benefits of earlier treatment outweigh the projected risks of case

finding and whether subsequent treatment can improve prognosis.

The risk of DSA screening itself is negligible and the risk that renal allograft biopsies pose seems acceptable to many in the field. While bleeding related complications are not uncommon, the rate of serious complications is well below 0.5%, indicating that this is a safe procedure in most patients. (108, 109) Though certain comorbidities might increase this risk and thus the clinician should evaluate this per individual patient.

Nevertheless, these low risks still need to be weighed against the potential benefits of such a biopsy. We will discuss the benefits of treatment as guided by biopsy below, though it should be stressed that clinical judgement should always be employed to determine if individual patients are in fact eligible for these treatments before deciding to perform such biopsies.

For preformed DSA, the decision to biopsy subclinical patients appears unguidable by sole monitoring of these preformed DSA, therefore the proposed benefits of early treatment in these patients cannot be attributed to the monitoring strategy itself. Thus, only the proposed benefits of early treatment of subclinical patients with dnDSA will be evaluated.

Patients with underlying subclinical TCMR have the best evidence for gained benefit, as the basis for treating cell-mediated rejection is well-established. In regards to subclinical TCMR specifically, a literature review by Mehta et al. (110) showed that most available studies (111-113) at the time showed that untreated subclinical TCMR leads to worse graft function. (Table 2)

In addition to these studies, Choi et al. (114) showed in a retrospective study of 304 patients with two weeks post-transplant protocol biopsies that patients with untreated early subclinical TCMR had significantly lower ten years allograft survival compared to non-rejectors (62.3% vs 96.2%).

Rush et al. (115) showed in a randomized trial of 72 patients that treatment of early subclinical TCMR as detected by protocol biopsy at one, two, three and six months post-transplant leads to lower chronicity scores, less late rejections and more stable and lower creatinine levels at two years post-transplant than patients who were only biopsied at 6 months post-transplant. Another RCT by Kurtkoti et al. (116) showed similar results in regards to lower creatinine levels at 6 and 12 months.

While these older studies could be criticized that they were conducted before the tacrolimus era and are thus less applicable to current practice, recent studies also suggest that treatment may have beneficial effects. For instance, studies by Loupy et al. (54) and Hoffman et al. (117) showed no significant difference in delta creatinine, odds of 50% eGFR loss or allograft survival between subclinical TCMR patients treated standardly with pulse steroids and a control group without TCMR at protocol biopsy.

An additional recent study by Seifert et al. (118) utilizing protocol biopsies at 3 and/or 6 months in 120 pediatric patients, showed that untreated subclinical borderline TCMR patients had decreased freedom from a composite endpoint of death censored graft loss and acute rejection at 5 years post-transplant compared to patients without inflammation at biopsy. However, this was not observed in a subcohort who received treatment (at the discretion of the attending physician), in whom there was no difference in the composite endpoint compared to those without inflammation. This suggests that treating subclinical borderline rejection may be beneficial. In contrast, subclinical cases in which inflammation met BANFF criteria for TCMR were all treated in this study, but still had significantly increased risk of meeting the composite endpoint compared to cases without inflammation. However, due to the retrospective nature of this study, the absence of a control untreated subclinical TCMR group, and with few cases having >2 year follow up, it is difficult to make too many conclusions from this finding.

The study by Choi et al (114) showed that allograft loss was mainly attributed to chronic allograft nephropathy (CAN). Other studies also associated untreated TCMR with development of CAN. (119-121). This term has long been dismissed by Banff pathology consensus as it did not encompass any attempt to attribute etiology of disease process. However it is now recognized that antibody mediated injury is an important contributor of what was then known as CAN (122), so it could be speculated that early intervention in subclinical TCMR leads to less antibody mediated injury, or perhaps even prevents it. Though this cannot definitively be determined from the results published by these older studies.

There are currently no guidelines on the treatment of subclinical TCMR. A recent systematic review and meta-analysis by Ho et al. (123) showcases the effectiveness of treatment, but also the wide variety of treatment regimens that are employed throughout different transplant centers. This is likely related to the scarcity in RCTs on this topic. Previous research suggests that a maintenance immunosuppression regimen consisting of tacrolimus and mycophenolate mofetil or analogues is optimal for reducing the risk of chronic histological injury. (114, 121, 124) This is likely in line with the current recommendation on optimization of maintenance immunosuppression.

Rush et al. (115) and others (54, 116, 117, 125) showed the effectiveness of a short-term steroid pulse.

Nonetheless, the effectiveness of treatment seen in the meta-analysis by Ho et al. (123) on patients with subclinical TCMR simultaneously shows that there is still room for improvement, as histological response rates are not optimal and the known complications of steroid pulses are well-described.

More randomized trials are urgently needed to improve our understanding of optimal treatment of subclinical TCMR.

Study	Type of study	Total patients (n)	Total subclinical TCMR (n) or (%)	Time of Biopsy	Treatment of subclinical TCMR	Outcome
Nankivell et al. (111)	Retrospective Single center	961	6.9% of all biopsies TCMR 23.4% of all biopsies B-TCMR (number of patients not provided)	1, 2 weeks 1, 3, 6, 12 months post-transplant Annually thereafter	Methylprednisolone in 22.9% of TCMR and 12.3% of B-TCMR	Biopsies taken >3 months post-transplant with either subclinical TCMR or B-TCMR both associated with higher ci and ct scores at 1 year biopsy. Persistent TCMR associated with more significant decline in eGFR at 2 years
Moreso et al. (112)	Retrospective Single center	372	74 subclinical TCMR 65 subclinical TCMR + CAN	Protocol biopsy during initial 6 months post-transplant "For cause"	None	Incidence of CAN in patients with subclinical TCMR vs without: 47% vs 37% (P<0.05) 15 years DCGS lower in patients with CAN + TCMR compared to no rejection (RR 1.86 [1.11 - 3.12])
Scholten et al. (113)	RCT	126 1:1 TAC vs CsA	At 6 months: 7.4% TCMR and 23.4% B-TCMR At 12 months 14.3% TCMR 24.5% B-TCMR	Protocol biopsy at 6 and 12 months post-transplant At graft dysfunction	None	Less subclinical TCMR in TAC group. Subclinical TCMR at 6 months associated with CAN grade >2 Subclinical TCMR not associated with creatinin clearance at 2 years
Choi et al. (114)	Retrospective Single center	304	40	Day 14 Post-transplant	None	10 years graft survival subclinical TCMR vs no rejection: 62.3% vs 96.2% (p<0.05)
Rush et al. (115)	RCT	72 1:1 early biopsies vs later biopsy	In early biopsy group: Subclinical TCMR at 1, 2, 3, 6 months: 43%, 32%, 27%, 15% In late biopsy group: Subclinical TCMR at 6 months: 32%	Protocol biopsy at 1, 2, 3, 6, 12 months vs Protocol biopsy at 6, 12 months	Pulse steroids for all subclinical TCMR	Significantly higher amount of patients with ci + ct scores ≥ 2 in control group vs early biopsy group 24% vs 6% (p<0.04) Significantly higher creatinin at 2 years in control group vs early biopsy group 183 ± 22 µmol/L vs 133 ± 14 µmol/L (p<0.05)

Study	Type of study	Total patients (n)	Total subclinical TCMR (n) or (%)	Time of Biopsy	Treatment of subclinical TCMR	Outcome
Kurtkoti et al. (116)	RCT	102 1:1 Protocol biopy vs only indication biopsy	Protocol biopsy group at 1, 3 months: 17.3%, 12%	Protocol biopsy at 1, 3 months post-transplant vs Indication only	Pulse steroids for subclinical TCMR Subclinical B-TCMR not treated	Serum creatinin significantly higher at 6 and 12 months in control group vs protocol biopsy group At 6 months: 137 ± 35 µmol vs 113 ± 29 µmol (P<0.001) At 12 months: 134 ± 36 µmol vs 106 ± 29 µmol (P<0.001)
Loupy et al. (55)	Retrospective Single center + External validation	1001	132	Protocol biopsy at 1 year	Pulse steroids	No significant difference in 8 year allograft survival or 8 year eGFR between subclinical TCMR vs no rejection
Hoffman et al. (117)	Retrospective Single center	192	56	Protocol biopsy at 3, 12 months	Pulse steroids (Banff 1A/B) or thymoglobulin (Banff ≥ 2A)	No significant difference in delta creatinin between 3 and 24 months or odds of 50% decline in eGFR between 3 months and final follow up between subclinical TCMR vs no rejection
Seifert et al. (118)	Retrospective Single center	103	37	Protocol biopsy at 3, 6 months	Increased maintenance immunosuppression, pulse steroids or thymoglobulin at discretion of physician	Significantly higher 5 years freedom from composite endpoint of acute clinical rejection or allograft loss in no rejection vs untreated subclinical B-TCMR (p<0.001) No significant difference in 5 years composite endpoint between treated subclinical B-TCMR vs no rejection Significantly higher 5 years composite endpoint in no rejection vs treated subclinical TCMR

In regards to treating patients with subclinical dnDSA without underlying observable rejection at allograft biopsy, Matignon et al. (126) treated patients with IVIG in a small randomized trial. They did not find any significant difference in regards to allograft survival or subsequent rejection in the group randomized to IVIG compared to a historical control group. No other studies have been conducted which examined treatment of patients with subclinical dnDSA without underlying observable rejection at biopsy.

Table 2: Summary of studies on outcome of treated and untreated subclinical TCMR
CAN: Chronic allograft nephropathy; ci: Interstitial fibrosis; ct: Tubular atrophy; CsA: Ciclosporin; DCGS: Death-censored graft survival RCT: Randomized controlled trial; TAC: Tacrolimus; TCMR: T-cell mediated rejection B-TCMR: Borderline TCMR
(Continues on next page)

Table 2 (continued): Summary of studies on outcome of treated and untreated subclinical TCMR
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In respect to treating patients with subclinical dnDSA and underlying ABMR, the evidence is less substantial than for subclinical TCMR. As stated before, some evidence suggests that these patients present with lower chronicity scores and less transplant glomerulopathy, indicating less chronic forms of ABMR.

Management of ABMR is dependent on the subtype, as has been extensively reviewed in a recent consensus paper by Schinstock et al. (23) This concluded that there is very little evidence of efficacy of current treatment protocols for chronic ABMR in patients with dnDSA, although IL-6 inhibition has shown some promising results and is currently being studied in a large multicenter phase III RCT. (127) Additionally, evidence is emerging on the effectiveness of costimulation blockade and anti-CD38 therapy in these patients, the latter of which is currently being investigated in a phase II RCT in the form of felzartamab. (103, 128)

Nevertheless, (early) active ABMR with dnDSA might be responsive to treatment regimens consisting of PP, IVIG and maintenance treatment optimization, albeit with a low amount of supporting evidence. (Recommendation level 3C, 3C and 1C respectively)

This implies that there could be some benefit for finding and treating patients with more acute and early forms of ABMR before they present late with clinical dysfunction and more chronic lesions. Three retrospective studies seem to support this. (Table 3) Parajuli et al (67). showed similarly good post-biopsy allograft survival in treated subclinical ABMR patients treated with IVIG and PP, as compared to protocol biopsied dnDSA positive patients without rejection. Additionally, treated subclinical ABMR patients had significantly better allograft survival than DSA negative patients with indication biopsies or patients with treated clinical ABMR. Importantly, there was no difference in outcome between subclinical ABMR based on preformed DSA (type 1) vs dnDSA (type 2). However, it must be noted that the post-biopsy follow-up time in patients with subclinical ABMR was relatively low at 31.0 ± 15.8 months.

Orandi et al (129). showed that patients with mostly type 1 subclinical ABMR treated by PP and in some situations rituximab or eculizumab had no significantly different rate of 5 years death-censored allograft loss compared to ABMR negative matched controls, whereas untreated patients had significantly more 5 years death-censored graft attrition rates

In addition, Yamamoto et al (55). described some beneficial effects of PP and rituximab in 8 out of 18 (44%) of patients with subclinical type 2 ABMR whereby DSA levels reduced significantly or histological injury stabilized upon rebiopsy.

In contrast, the large retrospective multicenter study by Bertrand et al. (53) and retrospective single-

center study by Loupy et al. (54) found that allograft survival in treated subclinical ABMR patients was still significantly worse than patients without rejection. Though only 39% of patients with subclinical ABMR in the study by Loupy et al. (54) received specific treatment for subclinical ABMR and no analysis was performed comparing the treated and untreated group.

Regardless, it is apparent that more robust research on the effectiveness of treatment of subclinical early ABMR is warranted. Still, the overall risk-benefit balance seems to be in favor of screening of DSA. Considering the evidenced projected benefit that patients with subclinical dnDSA and underlying TCMR stand to gain and the risks of a biopsy seems to be acceptable for most.

Study	Type of study	Total patients (n)	Total subclinical ABMR (n) or (%)	Type 1 or Type 2 ABMR	Time of Biopsy	Treatment of subclinical ABMR	Outcome
Parajuli et al. (67)	Retrospective single center	220	25 (all treated)	Type 1 and 2	Detection of dnDSA Protocol biopsies in case of pretranplant DSA 50% rise in MFI Graft dysfunction	≤ 3 months post-transplant: Pulse steroids, IVIG, PP ≥ 3 months post-transplant: Pulse steroids, IVIG, situationally RTX	No significant difference in 5 years DCGS between treated subclinical ABMR and no rejection Significantly better 5 year DCGS in treated subclinical ABMR than clinical ABMR and than DSA- indication biopsies No significant difference in DCGS between type 1 or type 2 subclinical ABMR
Orandi et al. (129)	Retrospective single center	2097	77 (41 treated)	Uncertain Mostly type 1	Protocol biopsies at 1,3,6, 12 months post-transplant in HLA or ABOi incompatible transplants	PP + Situationally RTX or eculizumab	No significant difference in 5 years DCGS between treated subclinical ABMR and ABMR free matched controls (74.9% vs 86.6%, p=0.20) Significantly worse 5 DCGS in untreated subclinical ABMR vs ABMR free matched controls (76.3% vs 90.6%, p<0.01)
Yamamoto et al. (55)	Retrospective single center	43	18 (all treated)	Type 2	At dnDSA detection	Plasmapheresis and RTX	Significant decrease of MFI in 6 out of 18 patients Within 10 patients with rebiopsy, 4 had improvement or no change in graft histology
Bertrand et al. (53)	Retrospective Multicenter	123	51 (19 treated)	Type 2	At dnDSA detection	A combination of IVIG/PP/RTX	Significantly worse 8 year DCGS in subclinical ABMR patients vs no rejection. No significant difference in 8 year DGCS between treated and untreated subclinical ABMR
Loupy et al. (54)	Retrospective single center + External validation	1001	142 (56 treated)	Type 1 and Type 2	Protocol biopsy at 1 year post-transplant	IVIG, PP, RTX	Significantly worse 8 years graft survival probability in subclinical ABMR vs no rejection (56% vs 90%, p<0.0001) Significantly faster decline of eGFR over 8 years in subclinical ABMR vs no rejection (p not provided) No analysis in regards to treated vs untreated subclinical ABMR

Table 3: Summary of studies on outcome of subclinical ABMR with or without treatment
ABMR: Antibody-mediated rejection; DCGS; Death-censored graft survival; DSA: Donor-specific antibody; dnDSA: de novo DSA; eGFR: Estimated glomerular filtration rate; IVIG: Intravenous immunoglobulins; MFI: Mean fluorescence intensity; PP: Plasmapheresis; RTX: Rituximab;

References:

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PICO 6:

Overarching question: Is there any evidence of cost-effectiveness of standardized DSA monitoring and treatment of found cases?

In renal transplant recipients (P), has monitoring of DSA (I) been shown to be cost-effective compared to no monitoring (C)?

Evidence regarding the cost-effectiveness of standardized monitoring of DSA in stable renal graft recipients is missing and future efforts should be undertaken to determine this. (2D)

While the assessment of the balance between medical risks and benefits of early case finding may determine that a screening program is medically justified, this assessment does not necessarily determine whether it is cost-effective. As transplant centers have finite resources, DSA screening should be economically balanced. Unfortunately, evidence on cost-effectiveness of DSA screening is very scarce.

Only one DSA monitoring cost-effectiveness modelling study has been performed by Kiberd et al. (130) They found that costs per increased quality-adjusted life year (QALY) could range from $127.000 to $444.000, depending on the estimated efficacy of treatment. Though this model suffered from low evidence assumptions, as it assumed a range of treatment induced mortality rates and allograft loss risk reduction percentages, none of which were based on existing literature. Moreover, the model did not account for the fact that costs saved by not screening and treating early would still partly be spent later on treating patients when they do present with clinical dysfunction. This means that the presented costs per QALY are likely an overestimation, especially considering that most of the projected costs were attributed to the treatment of found cases, instead of DSA screening itself.

It therefore seems that it is currently not determinable whether DSA screening in clinically stable patients is cost-effective and further research is definitely warranted. Hopefully the UK-based randomized OuTSMART trial, which is nearing completion, on the effectiveness of DSA screening will provide more evidence on cost-effectiveness. (131)

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PICO 7:

Overarching questions: How frequent and until what time should DSA

monitoring be conducted? Should monitoring be continued indefinitely? If not, until what time or event should monitoring be continued?

SubPICOs/questions?

Is the incidence rate as a function of time post-transplant defined?

In renal transplant recipients who have developed dnDSA (P), is development of additional dnDSA (I) associated with worse transplant outcome (O), compared to no additional dnDSA (C)?

In renal transplant recipients who have developed dnDSA (P), is disappearance of the dnDSA (I) associated with better transplant outcomes (O) compared to persistence (C)?

In renal transplant recipients (P), are clear risk categories (I) defined for the risk of development of dnDSA (O) compared to those without those risks (C)?

In renal transplant recipients (P), are certain monitoring frequencies (annually, biannually, etc) (I) associated with better transplant outcomes (O) compared to other monitoring frequencies (C)?

Monitoring for persistence or broadening of subclinical dnDSA repertoire should not be discontinued after a certain time post-transplant (2C)

As new cases of subclinical rejection accumulate over time post-transplantation, DSA screening cannot be a one-time effort. Though the longevity of the monitoring strategy should be reflected by the a priori chance of development of dnDSA over time.

Unfortunately the dnDSA incidence rate is not fully clear, as the incidence rate in the literature widely varies from a steady rate of 1.5 to 5.4% per year in low-immunological risk patients. (52, 132-134) Others report a higher incidence in the first year ranging from 3.2% to even 20% in the first year with a lower steady yearly rate thereafter ranging from 0.8% to 4.3% per year. (50, 135, 136)

A recent large study by López del Moral shows that of 400 patients with dnDSA, 20% were found within the first year, 60% within five years and 85% within ten years post-transplant. (137) The large variance in incidence is likely partly reflective of differences in population, ethnic differences related to immunosuppressive exposure, and/or matching algorithms of organ allocation organizations. Nevertheless, most studies do indicate that incidence does not reduce significantly after one year post-transplant. This subsequently implies that any time-limited monitoring strategy, although less costly, would be medically arbitrary and would miss new subclinical cases that occurred after screening ceased. However, it must be noted that no prospective studies on efficacy of monitoring strategies on transplant outcomes have been conducted to confirm this and further research is therefore warranted.

Another point of contention is whether monitoring should be continued for persistence of dnDSA or for development of additional dnDSA after newly developed dnDSA has already been encountered. A retrospective study by DeVos et al. showed that an isolated positive dnDSA result in stable renal graft recipients has comparable risk of allograft loss and acute rejection to patients without DSA. (138). A study on risk of isolated DSA in lung transplants shows similar results. (139)

Additionally, DeVos et al. found that patients with >60% positive DSA measurements in at least 3 separate assessments are more likely to progress to allograft loss than those with <60% positive measurements.

The recent study by López del Moral et al. (137) showed that dnDSA which eventually disappear, either temporarily or permanently, are associated with a lower rate of allograft loss than those who persist. Additionally, they showed that development of multiple dnDSA (a broader repertoire) is associated with worse allograft survival, though this association was no longer statistically significant in multivariable analysis.

In contrast to the previous studies, Kim et al. found that resolved dnDSA was not in fact associated with more freedom from a 50% eGFR loss. (60)

These studies, while somewhat conflicting, overall seem to suggest that newly developed dnDSA which eventually disappear are less likely to be associated with subsequent allograft loss. In addition, persisting dnDSA seem detrimental for allograft survival. Lastly, additional dnDSA may develop, which could be cause for an additional allograft biopsy.

We therefore recommend that monitoring should not be discontinued upon development of dnDSA.

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The optimal DSA monitoring scheme has not been established and depends on factors such as immunological matching, DSA screening methods, and

immunosuppression, but a pragmatic approach would be antibody monitoring at 3 to 6 months post-transplant and annually thereafter. (2C)

Another dilemma entails the intensity of monitoring. In an ideal world, development of dnDSA would be noted immediately. But this would require a frequency of monitoring that is unlikely to be feasible. Centers which perform routine DSA monitoring seem to do so annually, although some perform one or more additional measurements in the first year post-transplant. (50, 53, 56)
Some might argue that the intensity of monitoring should be determined by the immunological risk, although the list of different risk factors associated with development of dnDSA is vast, making it difficult to define uniform risk categories. (140)
Though monitoring intensity stratification based on HLA matching might be easy to establish. It logically follows that recipients of a completely HLA-identical donor kidney should have no risk of developing DSA to HLA. Though completely HLA-identical transplants are rare. Most DSA appear to be aimed at HLA-DQ (141), though López del Moral et al. (137) showed that the proportion of patients with a full HLA-DQ match who developed dnDSA was comparable to those with a full HLA-B or HLA-DR match, indicating that other HLA loci mismatches should not so easily be disregarded. However, more recent evidence regarding molecular eplet HLA mismatching has emerged, whereby low DQ/DR eplet mismatching was found to carry a negligible risk for development of DQ or DR dnDSA. (100, 102) Those with moderate or high levels of mismatches had substantially higher hazard ratios for dnDSA development compared to those with low level mismatch, 15.4 and 23.8 respectively. This could indicate that low levels of total eplet mismatch load could be a reason to lower DSA monitoring intensity or even omit it. However, this risk-stratification technique has thus far not been corroborated in regards to class I DSA. Nonetheless, monitoring intensity based on eplet or molecular mismatch risk stratification seems promising and we recommend further research be conducted to confirm the validity of this method.
Currently, no study has been conducted which compares outcomes of monitoring strategies. Notwithstanding, the study by Parajuli et al (67). shows that patients with subclinical dnDSA who are detected and treated by a strategy consisting of screening after 6 months and annual screening thereafter have good outcome, indicating that more intensive monitoring may be unnecessary. Additionally, a monitoring interval greater than one year might be ill-advised, as studies in untreated subclinical ABMR or TCMR show more chronic lesions within one year post-diagnosis as well as

significantly more one year allograft loss in untreated subclinical TCMR. (68, 69, 114, 115) This may indicate that patients detected beyond one year from inception of the dnDSA may be more difficult to treat.

Lastly, considering the fact that multiple studies have indicated increased incidence of development of dnDSA in the first year post-transplant, it might be advisable to perform an additional measurement within 3 to 9 months post-transplant. (50, 135-137)

It thus appears from current low-level evidence that until more robust immunological risk-stratification methods are validated, monitoring strategies consisting of an annual screening with an additional screening within the first three to nine months post-transplant may seem pragmatic, though more research is warranted.

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