Molecular Biology Testing for Non-Invasive Diagnosis of Allograft Rejection: KIDNEY

PICO 1: In kidney transplant patients with stable graft function, is dd-cfDNA a reliable diagnostic tool for subclinical acute rejection monitoring when compared with standard of care (eGFR/creatinine monitoring or surveillance biopsy)?

Population: adult/pediatric kidney transplant recipients with stable graft function
Intervention: single time point or serial monitoring of plasma dd-cfDNA, the optimal frequency of testing is also in question
Comparators: Renal function monitoring (serum creatinine/GFR), Surveillance biopsies
Outcome: Diagnosis of subclinical rejection, Effective treatment of subclinical rejection (resolution based on biomarker improvement or repeat biopsy)

Author: J. Friedewald/ Co-Author: S. Park

STATEMENT: We suggest that clinicians consider screening for *subclinical* antibody-mediated rejection in patients with stable graft function with serial blood dd-cfDNA measurements. dd-cfDNA alone does not appear to be a reliable tool for the detection of subclinical T-cell-mediated rejection. The optimal timing and frequency of screening have not been established and we suggest the use of this test in stable patients to avoid the need for surveillance biopsies.

Level of evidence: moderate
Level of recommendation: weak for

PICO 2: In kidney transplant patients with acute allograft dysfunction, is dd-cfDNA a reliable diagnostic tool for acute rejection monitoring when compared with standard of care (eGFR/creatinine monitoring or for cause biopsy)?

Population: adult/pediatric kidney transplant recipients with acute graft dysfunction
Intervention: Single time point or serial monitoring of plasma dd-cfDNA, The optimal frequency/timing of testing is also in question
Comparators: Renal function monitoring (serum creatinine/GFR), For Cause biopsies
Outcome: Diagnosis of clinical acute rejection

Author: J. Friedewald/ Co-Author: S. Park

STATEMENT:
We recommend that clinicians measure dd-cfDNA in the blood in patients with acute graft dysfunction to non-invasively assess the likelihood of rejection, particularly antibody-mediated rejection. Low levels of dd-cfDNA do not necessarily exclude the presence of T-cell-mediated rejection in the graft.

Analytical Considerations
Currently, the donor-derived fraction of cell-free DNA is the standard measurement. Some groups have advocated for using both the fraction of dd-cfDNA and the quantity of dd-cfDNA to improve the detection of clinical acute rejection. Additionally, all assays in the US are currently being run in one of several central/reference labs (currently 3 commercially available assays). Different methodologies involving the assay being run in individual hospital labs used in Europe may require further validation for clinical correlation.

Level of evidence: medium
Level of recommendation: moderate for

PICO 3: In kidney transplant patients with stable graft function, is blood gene expression profiling (GEP) a reliable diagnostic tool for subclinical acute rejection monitoring when compared with standard of care (eGFR/creatinine monitoring or surveillance biopsy)?

Population: adult/pediatric kidney transplant recipients with stable graft function
Intervention: Single time point or serial monitoring of plasma GEP, The optimal frequency of testing is also in question
Comparators: Renal function monitoring (serum creatinine/GFR), Surveillance biopsies
Outcome: Diagnosis of subclinical rejection, Effective treatment of subclinical rejection (resolution based on biomarker improvement or repeat biopsy

Author: O. Bestard/Co-Author: J. Sellares

STATEMENT: 1) We do not recommend implementing in clinical kidney transplantation the use of GEP to non-invasively diagnose the presence of on-going sub-clinical rejection yet. We strongly advocate the necessity to develop independent, prospective and interventional studies using GEP in PB for decision-making, to provide more robust evidence of the value of using GEP in PB to safely avoid surveillance biopsies.

2) An effort to further validate all technologies is highly warranted to establish consistent methods and thresholds to be used in clinical transplantation.
Level of evidence: mixed, moderate
Level of recommendation: weak against

PICO 4: In kidney transplant patients with acute allograft dysfunction, is blood gene expression profiling (GEP) a reliable diagnostic tool for clinical acute rejection monitoring when compared with standard of care (eGFR/creatinine monitoring or for cause biopsy)?

Population: adult/pediatric kidney transplant recipients with acute graft dysfunction (for cause biopsies)
Intervention: Single time point or serial monitoring of blood GEP, The optimal frequency of testing is also in question
Comparator: Renal function monitoring (serum creatinine/GFR), For-cause biopsies
Outcome: Diagnosis of clinical acute rejection, Effective treatment of rejection (resolution based on biomarker improvement or repeat biopsy)

Author: O. Bestard/Co-Author: J. Sellares

Recommendation:

1) We do not recommend yet implementing in clinical kidney transplantation the use of GEP to non-invasively diagnose or rule out the presence of ongoing acute graft rejection in patients displaying acute allograft dysfunction. We strongly advocate the necessity to develop independent, prospective and interventional studies using GEP in PB for decision-making, to provide more robust evidence of the value of using GEP in PB to safely avoid surveillance biopsies.

2) An effort to further validate all technologies is highly warranted to establish consistent methods and thresholds to be used in clinical transplantation.

Level of evidence: low
Level of recommendation: weak against

Analytical Considerations

Multiple research studies have investigated the value of GEP in PB to noninvasively diagnose the presence of immune-mediated graft injury, either defined as any type of AR, TCMR or ABMR using different technological platforms. The aim of these biomarkers basically relies on trying to avoid unnecessary kidney allograft biopsies (for cause or per protocol).
Most robust studies have used retrospective multicenter cohort studies to discover different gene signatures and validated in retrospective sample cohorts or biorepositories to develop probabilistic dichotomous locked gene expression signatures to infer either High or Low risk of subclinical and/or clinical rejection. The fundamental diagnostic value of all GEP biomarkers relies on the consistently high negative predictive values reported with poor specificity and PPV.
However, few, small, independent and blinded prospective studies have been conducted. Interventional, prospective, independent multicenter studies are highly warranted. Some studies have suggested that a combination of biomarkers (GEP and dd-cfDNA) may increase their predictive value, therefore such studies should be also considered.

PICO 5: In kidney transplant patients with stable graft function, is urinary chemokine monitoring a reliable diagnostic tool for subclinical acute rejection monitoring when compared with standard of care (eGFR/creatinine monitoring or surveillance biopsy)?

Population: adult/pediatric kidney transplant recipients with stable graft function
Intervention: Single time point or serial monitoring of urine chemokines, The optimal frequency of testing is also in question
Comparator: Renal function monitoring (serum creatinine/GFR), Surveillance biopsies
Outcome:Diagnosis of subclinical rejection, Effective treatment of subclinical rejection (resolution based on biomarker improvement or repeat biopsy)

Author: D. Anglicheau/Co-Author: C. Tinel

Recommendation:
We recommend the monitoring of urinary chemokines CXCL9, or CXCL10, or a combination of both, to identify kidney transplant recipients at high risk of any type of clinical acute rejection (TCMR or ABMR), who could benefit from an allograft biopsy to confirm diagnosis.

We recommend the monitoring of urinary chemokines CXCL9, or CXCL10, or a combination of both, to identify unstable kidney transplant recipients at low risk of any type of clinical acute rejection (TCMR or ABMR), in whom other causes of graft dysfunction should be explored before performing an allograft biopsy.

The urinary chemokines CXCL9 and/or CXCL10 are non-specific inflammatory cytokines whose increase has been reported both in the course of TCMR and ABMR. We suggest that the urinary chemokines CXCL9 and/or CXCL10 should not be used to discriminate between TCMR and ABMR phenotypes.

Level of evidence: moderate
Level of recommendation: weak for

PICO 6:In kidney transplant patients with acute allograft dysfunction, is urine chemokine measurement a reliable diagnostic tool for clinical acute rejection monitoring when compared with standard of care (eGFR/creatinine monitoring or for cause biopsy)?

Population: adult/pediatric kidney transplant recipients with accute allograft dysfunction
Intervention: Single time point or serial monitoring of urine chemokines, the optimal frequency of testing is also in question
Comparator: Renal function monitoring (serum creatinine/GFR), For-cause biopsies

Outcome:Diagnosis of clinical acute rejection, Effective treatment of rejection (resolution based on biomarker improvement or repeat biopsy)

Author: D. Anglicheau/Co-Author: C. Tinel

Recommendation:
We suggest the monitoring of a combination of CXCL10 alone or a combination of CXCL9 and CXCL10, to identify kidney transplant recipients at low risk of any type of subclinical rejection (TCMR or ABMR), for whom a surveillance biopsy might not be necessary.

Analytical considerations

Major strengths for urinary chemokine-based predictions are the direct link between the biomarker and the underlying pathological mechanism, the reliance on multiple measurements in some longitudinal studies, the consistency across different measurement techniques, across different populations (American, European, Asian), across various ages (paediatrics and adult populations). Additionally, urinary chemokines are highly stable in urine samples and offer strictly noninvasive, widely implementable noninvasive monitoring with an acceptable medico-economical weight.
Some limitations for urinary chemokine-based predictions are the variable cutoffs according to the techniques, and their confounding by underlying clinical conditions such as urinary tract infection or BKV infection.

Level of evidence: moderate
Level of recommendation: weak for