



Tissue pathway for native medical renal biopsies

July 2019

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Unique document number	G061
Document name	Tissue pathway for native medical renal biopsies
Version number	3
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Date active	July 2019
Date for full review	July 2024
Comments	This document replaces the 2013 publication with the same name. In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for consultation from 4 April to 2 May 2019. Responses and authors' comments are available to view following final publication of this tissue pathway. Dr Brian Rous Clinical Lead for Guideline Review

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Registered charity in England and Wales, no. 261035
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NICE has accredited the process used by the Royal College of Pathologists to produce its tissue pathways. Accreditation is valid for five years from 25 July 2017. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

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Foreword

The tissue pathways published by the Royal College of Pathologists (RCPATH) are guidelines that enable pathologists to deal with routine surgical specimens in a consistent manner and to a high standard. This ensures that accurate diagnostic and prognostic information is available to clinicians for optimal patient care and ensures appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

The guidelines themselves constitute the tools for implementation and dissemination of good practice.

The following stakeholders were contacted to consult on this document:

- UK Renal Pathology EQA membership
- the Renal Association.

No major organisational changes or cost implications have been identified that would hinder the implementation of the tissue pathway.

The information used to develop this tissue pathway was collected from electronic searches of the medical literature (PubMed database up to 2018), previous recommendations of the RCPATH, and local guidelines in the UK. Published evidence was evaluated using modified SIGN guidance (see Appendix A). Consensus of evidence in the tissue pathway was achieved by expert review. Gaps in the evidence will be identified by College fellows via feedback received from consultation. The sections of this tissue pathway that indicate compliance with each of the AGREE II standards are indicated in Appendix B.

A formal revision cycle for all tissue pathways takes place on a five-yearly basis. However, each year, the College will ask the author(s) of the tissue pathways, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the document needs to be updated or revised. A full consultation process will be undertaken if major revisions are required. If minor revisions are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the changes will be incorporated into the pathways and the full revised version (incorporating the changes) will replace the existing version on the publications page of the College.

The tissue pathway was reviewed by the Clinical Effectiveness department, Working Group on Cancer Services and Lay Governance Group and placed on the College website for consultation with the membership from 4 April to 2 May. All comments received from the Working Group and membership were addressed by the authors to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

This tissue pathway was developed without external funding to the writing group. The College requires the authors of tissue pathways to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness department and are available on request. The authors have declared no conflicts of interest.

1 Introduction

The medical renal biopsy forms an important part of the diagnosis and management of patients presenting with acute kidney injury, proteinuria/nephrotic syndrome, nephritic syndrome and chronic kidney disease. It is an invasive procedure associated with a risk of serious and potentially life-threatening complications. The decision of whether to perform a renal biopsy is based on a careful risk–benefit assessment. Once the decision to perform a renal biopsy has been made, it is essential that laboratory and diagnostic procedures are in place to optimise the clinical benefit obtained from the biopsy. The final diagnosis frequently depends on combining clinical, biochemical and serological data with that from light microscopy (LM), immunohistology and electron microscopy (EM). If any of these elements are lacking, it may not be possible to reach a diagnosis. The following recommendations are regarded as the minimum acceptable practice for medical renal biopsies. Much of the content of the tissue pathways represents custom and practice, and is based on the substantial clinical experience of the authors. Published evidence to support the recommendations has been identified by PubMed search and referenced where appropriate. The strength of supporting evidence for specific elements is indicated using modified SIGN guidance.

1.1 Target users and health benefits of this tissue pathway

The target primary users of the tissue pathway are trainee and consultant cellular pathologists and, on their behalf, the suppliers of IT products to laboratories. The secondary users are those clinicians who request and carry out renal medical biopsies (nephrologists and transplant surgeons), and those who commission renal services.

1.2 Generic issues relating to staffing, workload and facilities

The following recommendations should be met for a general level of acceptable practice:

- the laboratory should have sufficient pathologists, biomedical scientists and clerical staff to cover all of its functions. In general, staffing levels should follow the workload guidelines of the RCPATH.
- optimally, two or more pathologists in a unit should be competent in the reporting of renal biopsies, to provide cover for periods of leave. It is recognised that in some smaller units only one pathologist may have specialist expertise, and in such cases cover for periods of leave should be arranged with renal pathologists in other units.
- all pathologists reporting renal biopsies should:
 - participate in audits
 - participate in the RCPATH's continuing professional development (CPD) scheme
 - participate in the national UK renal pathology external quality assessment (EQA) scheme
 - have access to specialist referral opinions on a regional network or national basis.
- the maximum workload for a full-time renal pathologist will depend on the case mix of the biopsies, but should not be greater than 1,200 renal biopsies per year. An evidence-based minimum workload is not clearly defined. However, pathologists must bear in mind their diagnostic experience, ongoing CPD activity and EQA outcomes in assessing their ability to maintain an acceptable level of reporting expertise. When the renal workload is low (<200 biopsies/year), no more than two pathologists should be involved in providing the service. When it is very low (<100 biopsies/year), passing the renal workload to a larger unit should be considered, as maintaining an acceptable level of expertise may be difficult if only small numbers of biopsies are reported.

- the laboratories handling renal biopsies should:
 - be equipped to allow the recommended technical procedures to be performed safely
 - be accredited by United Kingdom Accreditation Service (UKAS) or equivalent.
- workload data should be recorded and monitored in a format that facilitates determination of the resources involved.
- reports should be held on an electronic database that has facilities to search and retrieve specific data items, and that is indexed according to SNOMED T, M, D and P codes or SNOMED CT.

2 Laboratory protocols

2.1 Laboratory facilities

- In addition to routine LM, there must be access to immunohistology (immunofluorescence [IF] and/or immunoperoxidase [IP] techniques) and EM. EM facilities may be off-site.
- Laboratories handling renal biopsies should participate in the UK National EQA Scheme for renal stains and the UK National EQA Scheme for immunocytochemistry.

2.2 Specimen submission and dissection

- Optimally native renal biopsies should be examined under a dissecting microscope and divided while fresh. In circumstances when this is not possible (for example if the renal unit and laboratory are in different hospitals), the specimen can be transported in suitable fixatives for LM and EM, and buffer/transport medium if frozen tissue for IF is required.
- Wherever practicable, a sample of cortex large enough to contain at least one glomerulus should be fixed for EM.

2.3 Staining

- Minimum LM stains for native renal biopsies are: haematoxylin and eosin with at least two levels, stains for basement membranes (periodic acid-Schiff and methenamine silver), stain for connective tissue and vessels (such as elastic van Gieson or other trichrome), and a stain for amyloid.
- A minimum number of six levels is recommended. The optimum number of levels that should be examined depends in part on the diagnoses being considered; it is higher for conditions characterised by focal lesions (such as the distinction of minimal change nephropathy from focal segmental glomerulosclerosis).

[Level of evidence – C.]

2.4 Immunohistology

- The use of immunohistology is recommended in all cases.
- The minimum routine panel for the investigation of glomerular disease is: IgG, IgA, IgM, C3 and C1q, in addition to kappa and lambda light chains for adult renal biopsies.
- Immunohistological method:

- IP in paraffin sections has the advantage of providing a permanent record of the findings but is frequently difficult to report as a result of high background staining of plasma and matrix proteins. If this method is used, then laboratory protocols should be optimised to minimise background staining. Pathologists should become familiar with their laboratory's results and interpret the local slides accordingly.
- The demonstration of light chain restriction in glomerular deposits is usually possible by IF staining of frozen sections, but is frequently unsuccessful using IP stains in paraffin sections. A method of IF using pronase-digested paraffin sections may increase the sensitivity of detection of light chains.¹ This method may also assist in the diagnosis of masked immunoglobulin deposits, in which there is false-negative staining on IF.² If there is a clinical suspicion of a light chain-related pathology and IF on frozen sections is negative, then IF on paraffin sections should be carried out.

[Level of evidence – D.]

- The demonstration of linear glomerular basement membrane (GBM) positivity for IgG in anti-GBM disease is frequently difficult using an IP method in paraffin sections, and this diagnosis cannot be excluded on the basis of this method.

[Level of evidence – D.]

- Other antibodies, including those recognising IgG4, amyloid A, PLA2R, uromodulin, myoglobin and viruses known to infect the kidney, should be available for use if indicated.
- Antibodies that should be available but may have to be sourced by referral to specialist laboratories include THSD7A (a membranous glomerulonephritis antigen),³ DNAJB9 (a marker of fibrillary glomerulonephritis),⁴ fibronectin, type III collagen, specific collagen type IV alpha chains and specific amyloid proteins.

2.5 Electron microscopy

- The need for EM should be assessed on the basis of LM appearances. However, the majority of native renal biopsies with suspected glomerular disease are investigated in this way unless a definitive diagnosis is made on LM. If EM is required, this should be available within two weeks.

[Level of evidence – D.]

- If EM technical services are being provided remotely by a specialist unit, then the semithin sections from the EM block and the digital EM images should be provided to the pathologist responsible for reporting the renal biopsy. Diagnostically important lesions might be visible by LM in the semithin sections from the EM block but absent from the paraffin sections.

3 The renal biopsy report

- The LM, immunohistology and EM from a single case should ideally all be reported by the same pathologist. Reporting each in isolation may result in serious misdiagnosis.
- The pathology report should provide a summary of the clinical history, gross description of the specimen, details of tissue sampling for IF, LM and EM, and include a summary/comment at the end.^{5,6} If the clinical information provided is clearly deficient, then the requesting clinician should be contacted, or the diagnostic limitations resulting from the lack of clinical information made clear in the pathology report. The microscopy report should refer specifically to:
 - glomeruli

- tubules
 - interstitium
 - vessels
 - immunohistology
 - EM.
- For inflammatory renal disease, in addition to the diagnosis, the report must include indications of disease activity (grade) and chronicity (stage).⁷ For certain types of glomerulonephritis, the use of internationally accepted classifications is recommended. These include the recent revisions of the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) classification of lupus nephritis⁸ and Oxford classification of IgA nephropathy.⁹

[Levels of evidence – B–D.]

- If the adequacy of the biopsy is thought to cast significant doubt on the reliability of the interpretation, this should be stated explicitly.
- In addition to a written report, discussion of the case with a nephrologist is frequently of clinical value. This will often allow a more specific diagnosis than might have been apparent on the biopsy alone, and it may direct supplementary studies that may be required on the biopsy. The timeliness of the verbal and written reports should be appropriate to the clinical urgency.

4 On-call renal biopsy services

- If an on-call service is offered for out-of-hours urgent renal biopsies, this should be staffed only by pathologists that contribute to the routine renal pathology service or have been specially trained to report urgent renal biopsies.
- Urgent renal biopsy reports should be provided on the basis of paraffin sections produced on a rapid processing schedule, not frozen sections.
- Remote reporting of digital slides is appropriate for urgent specimens if the pathologist is trained in digital reporting of renal biopsies and the platform used has been validated for this purpose.

5 Criteria for audit

As recommended by the RCPATH as key performance indicators (see *Key performance indicators – proposals for implementation*, July 2013, <http://www.rcpath.org/profession/quality-improvement/kpis-for-laboratory-services.html>):

- histopathology cases are reported, confirmed and authorised within seven and ten calendar days of the procedure
 - standard: 80% of cases must be reported within seven calendar days and 90% within ten calendar days.

With agreement of service users, variance from the standard key performance indicators for renal biopsies is appropriate. In certain cases, issuing a provisional report, before all immunohistochemistry and EM is available and before multidisciplinary team discussion, results in more clinically ineffective reports (including inappropriate therapy). With this agreement, it is recommended that 80% of cases should be reported within two weeks.

- Standard: 80% of EM specimens should be reported within two weeks of requesting EM sections and images.

6 References

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Appendix A Summary table – explanation of grades of evidence
(modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	<p>At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target population</p> <p>or</p> <p>A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target population.</p>
Grade B	<p>A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target population</p> <p>or</p> <p>Extrapolation evidence from studies described in A.</p>
Grade C	<p>A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target population</p> <p>or</p> <p>Extrapolation evidence from studies described in B.</p>
Grade D	<p>Non-analytic studies such as case reports, case series or expert opinion</p> <p>or</p> <p>Extrapolation evidence from studies described in C.</p>
Good practice point (GPP)	<p>Recommended best practice based on the clinical experience of the authors of the writing group.</p>

Appendix B AGREE II guideline monitoring sheet

The tissue pathways of the Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this tissue pathway that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Introduction
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	Introduction
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword and Introduction
12 There is an explicit link between the recommendations and the supporting evidence	2–4
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	2–4
16 The different options for management of the condition or health issue are clearly presented	2–4
17 Key recommendations are easily identifiable	2–4
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	2–4
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	5
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interests of guideline development group members have been recorded and addressed	Foreword