EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

Updating the European Urinalysis Guidelines

term 2018-2022

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THE ECLM- EUROPEAN URINALYSIS GUIDELINES 2000

The document to be updated

ECLM. European Urinalysis Guidelines.

(Kouri T, Fogazzi G, Gant V, Hallander H, Hofmann W, Guder W, editors).

Scand J Clin Lab Invest, Suppl 231, 60: 1-96, 2000

TFG: Urinalysis
TERMS OF REFERENCE

Background: The European Urinalysis Guidelines 2000 need to be updated at least with respect to the following:

- new diagnostic markers and infective agents
- development of automated particle counting
- current tools of specimen collection, techniques, possible preservation
- quality control processes, analytical performance specifications

Terms of reference:

- To revise the previous publication by evidence-based knowledge and publish a new European guideline for urinalysis
- To promote standardised and high-quality procedures that can improve clinical utilisation of laboratory tests and the development of new urinalysis technologies

TFG: Urinalysis
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Contents to be Updated

1. General Parts:
   - Medical needs, Patient preparation and Specimen collection
   - Hierarchy of Measurement Procedures
2. Chemistry
3. Particles
4. Bacteriology

NEW RECOMMENDATIONS BASED ON EVIDENCE

Gyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, for the GRADE Working Group. **GRADE:** an emerging consensus on rating quality of evidence and strength of recommendations. Brit Med J 2008; 336:924-6.

Topics to be Updated: Medical Needs, Diagnostic Use

IMPROVED SIEVING: Renal disease (KDIGO 2012, German guideline 2021]

Urine test strip (WBC, RBC, Pro, Nit) → Urine Albumin/creatinine ratio
+ plasma/serum creatinine → estimated GFR

Sensitive screening for specific patients (diabetes, hypertension) as before

REDUCED WORKLOAD: Urinary tract infections (UTI) (EAU 2021, German guideline 2017]

(1) Low-risk non-pregnant female cystitis patients with typical symptoms and without vaginal irritation may be diagnosed without specific laboratory tests by using a validated ACSS questionnaire (Acyte Cystitis Symptoms Score), available from: http://www.acss.world/downloads.html

(2) Midstream samples of OTHER symptomatic patients may be screened

by rapid examination (strip test) of urine, to exclude bacteriuria at 10^8 CFB/L (10^5 CFU/mL) (points-of-care), or

by automated counting to exclude bacteriuria at 10^7 CFB/L (10^4/mL) with a sensitivity of 90-95 % (in the laboratory as economically justified).

Sensitive cultures of high-risk patients should be performed as before, based on clinical request

Provisional Recommendations: Medical Needs and Requisition

Recommendations (1-2) **1 = Strong, 2 = Weak recommendation**	Gyatt GH, et al, for the GRADE Working Group. Brit Med J 2008; 336:924-6.	**Level of Evidence (A-D) ***
Urinalysis tests should be requested based on presentation of patients being at low or high risk for urinary diseases. The tests for particles, microbes, or chemical constituents in urine should be planned between laboratories and clinics, to maximise benefits against resource. (1)		B
Asymptomatic bacteriuria must not be generally sought to avoid unnecessary antimicrobials and multiresistant strains of uropathogens. (1)		A
General screening strategies for low-risk patients must not ignore targeted diagnostics for high-risk patients with life-threatening conditions. (1)		B
Electronic requisition and reporting of urinalysis tests are encouraged, based on local development of diagnostic algorithms and pre-planned emergency tests. Electronic requisition also facilitates transfer of key information between clinicians and laboratories. (1)		B

*Levels of Evidence: A = high, B= moderate, C= low quality of evidence, D = consensus by the experts

Topics to be Updated: Patient Preparation

Interaction with patients should be improved from objects of medical information to subjects who make decisions on their disease, based on the provided information.

In urine specimens, we believe in human interaction in increasing motivation of patients to improve collection their urine specimens (instead of getting repeatedly embarrassed with contaminated samples).

Documentation of the urine concentration is needed with all measurements from single-voided urine specimens to allow interpretation of diuresis, with one of the following ways:

- density (specific gravity or weight; relative volumic mass), osmolality, or
- reference measurand, used to calculate measurand-to-reference ratio

  (e.g. albumin-to-creatinine)

Provisional Recommendations: Patient Preparation

Recommendations (1-2)	Level of Evidence * (A-D)
Interaction with patients should be improved to become subjects in decision-making on their disease. This would result in improved motivation to learn collection their urine specimens in detail, and reduction of contaminated, low-quality samples (1).	C
Laboratories should maintain educational material bank and continuous co-operation with their clinical units to improve preanalytical processes, including preparation of patients to deliver high-quality urine specimens. (1)	B
Urine concentration should always be combined with the measurements of single-voided samples, expressed as measure of urine concentration (relative density, osmolality, conductivity), or a reference quantity with a measurand-to-reference ratio, e.g. albumin-to-creatinine ratio. (1)	B

*Levels of Evidence: A = high, B= moderate, C= low quality of evidence, D = consensus by the experts

Topics to be Updated: Specimen Collection

Measurand-to-reference ratios (e.g., albumin-to-creatinine ratio) of single-voided samples are better than timed collections to detect or follow-up of proteinuria in clinical routine.

Order of draw from primary containers to vacuum tubes is suggested

Specifications for successful preservation are given, and preservatives reviewed for basic urinalysis, bacterial culture, and quantitative chemical measurements, to stimulate verifications as required by the new IVDR and MDR regulations.

Order-of-Draw from a Urine Specimen

Order of draw from the primary container to be used in filling the secondary containers is proposed to be:

(1) initial one tube without preservatives to test the practice of filling

(2) tubes for microbial tests

– first tubes without preservatives, then tubes with preservatives

(3) tubes for chemistry tests

– tubes without preservatives not used in step (1), then tubes with preservatives

Provisional Recommendations: Specimen Collection

Recommendations (1-2) 1 = Strong, 2 = Weak recommendation	Level of Evidence (A-D) *
Mid-stream urine specimens are strongly recommended for single voided urine, because of the lower level of contamination to various measurements as compared to first-void specimens. (1)	A
Remarkable effort (*not only unidirectional information*) should be carried out to reduce contamination rates to the desired 10%, or to a minimum of 15% at 10^7 CFB/L (equivalent to 10^4 CFU/mL) in bacterial cultures of spontaneously voided urine specimens. (1)	B
Measurand-to-reference ratios from single-voided samples are recommended to replace timed urine collections because of their lower incidence of non-conformities. Verification of the intended measurand to a new patient group is needed before clinical application. (1)	A
Preservation of urine specimens should be evaluated against the given specifications, using the intended measurement procedures. (1)	C

*Levels of Evidence: A = high, B= moderate, C= low quality of evidence, D = consensus by the experts

Topics to be Updated: Chemistry

Diagnostic use of traditional strip tests was reviewed with new citations.

Internal quality control: Performance reflectometers should be followed by primary (quantitative) reflectance signals at the dynamic 1+ to 2+ range of concentrations.

Significance of specific measurements of both glomerular and tubular marker proteins in high-risk patients is reinforced with new data on progress of incipient nephropathies.

Analytical performance specifications (APS) for proteinuria measurements are suggested to be derived from reference change values, $D_K = z * \sqrt{2} * u_{TOT}$

Reference change value, or critical difference D_K between two measurements, proposal for analytical performance specification (APS)

$$D_K = z * \sqrt{2} * u_{TOT}$$

z = Gaussian statistic, typically z=1.96 is used with 2α < 5% and (1-β) = 50%,
but an increased sensitivity (1-β) = 85% at z=3, or 98% at z=4 should be considered

u_{TOT} = total uncertainty of measurements, including biological, preanalytical and analytical uncertainty; it contains both imprecision and bias

$u_A^2 = u_{TOT}^2 - (u_{BIOL}^2 + u_{PRE}^2)$, where the allowable u_A = APS

E.g., for urine albumin, an $u_A \leq$ 18-36 % is needed to detect a D_K = 200 % (using z=3, or z=4)
corresponding to a change in urine albumin concentration 30 mg/L to 90 mg/L
that differentiates normoalbuminuria from moderate albuminuria

Provisional Recommendations: Chemistry

Recommendations (1-2) 1= strong, 2= weak	Level of Evidence * (A-D)
Multiple (multiproperty) test strips are recommended as screening tools for low-risk patient populations because of their use in emergency diagnostics and cost-efficiency. (1)	A
Performance of strip tests must be verified against quantitative measurement procedures, and monitored with control solutions at their limits of positivity. (2)	B
Conventional strip tests are NOT recommended for urine diagnostics of high-risk patients, due to their insensitivity to renal damage or to bacteriuria at low colony counts. (1)	A
Sensitive detection of renal disease in high-risk groups requires sensitive measurements of albumin, and a tubular marker in urine, such as α1-microglobulin, quantitated as analyte-to-creatinine ratios, or from timed urine collections in special needs. (1)	B

*Levels of Evidence: A = high, B= moderate, C= low quality of evidence, D = consensus by the experts

Topics to be Updated: Particles

Revision of urine particle differentiation at Basic and Advanced levels

Automated particle counting procedures were reviewed,

with added value of automated bacteria screening

Different performance levels = Hierarchies (1-3) of urine particle analysis were updated

Analytical performance specifications of urinary particle analysis were summarised, as available from published documents

Hierarchy of Procedures = Levels of Accuracy in Urine Particle Analysis

Level 3: Advanced comparison level

- Kouri T, Györy A, Rowan RM, and the ISLH Task Force. ISLH Recommended Reference Procedure for the Enumeration of Particles in Urine. Lab Hematol 2003; 9:58-63

Level 2: Routine quantitative level

Automated quantitative counting

Visual quantitative counting and differentiation

- Urine sediment counted in a chamber (concentration with a precise volume)
- Chamber counting of uncentrifuged specimens (no concentration, with a precise volume)
- Standardised urine sediment under a coverslip (concentration factor-> volume)

Level 1: Ordinal scale level

- Non-standardized urine sediment, reporting at ordinal scale (0, 1+, 2+, 3+)

Provisional Recommendations: Particles

Recommendations (1-2) 1 = strong, 2 = weak recommendation	Level of Evidence * (A-D)
Laboratories should clearly describe their basic and advanced differentiation and reporting of urinary particles. (1)	A
Automated particle analysers need to be verified before implemented into routine, based on the published performance specifications (against level 3 procedures), as repeated in these guidelines. (1)	B
Laboratories should decide and verify one of the routine (level 2) procedures of visual microscopy for their routine particle analysis. (1)	A

*Levels of Evidence: A = high, B= moderate, C= low quality of evidence, D = consensus by the experts

Topics to be Updated: Bacteriology

Methods (= measurement procedures) used for bacterial cultures:

addition of automated processing of urine (inoculation, incubation, reading)

media: chromogenic agar as the *primary* medium, blood agar no more as routine

bacterial identification revised (MALDI-TOF MS, ASM Handbook *2016* as reference)

- chromogenic agar 60%, MALDI-TOF MS, 40%, biochemistry e.g. for *E.coli /Shigella*

Update of the list of bacteria responsible for UTI

proposed addition of *Aerococcus* spp and *Actinotignum schaalii* as level 2 pathogens

Fastened reporting and restriction of recommended antimicrobials for clinical use (EUCAST)

Provisional Recommendations: Bacteriology

Recommendations (1-2) 1= strong, 2=weak	Level of Evidence * (A-D)
Chromogenic agar is strongly recommended as a first line agar medium to identify *Escherichia coli* (most frequent uropathogen) easily, quickly and inexpensively (no need for a panel of tests to define the species). (1)	B
Bacterial identification using Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) is strongly recommended into medium-sized and large laboratories (> 100 specimens/day), to improve patient prognosis with (i) Accuracy and reliability of identification to the species level, and (ii) Shortened delay of reporting (from 36-48 h to 8-24 h) (1)	A
New species *Aerococcus spp* and *Actinotignum schaalii* are proposed into the list of Class 2 uropathogens (2)	B

*Levels of Evidence: A = high, B= moderate, C= low quality of evidence, D = consensus by the experts

Steps of Progress in 2022

The preliminary version for reviewing is planned to be ready in January 2022

Scientific and practical reviewers are welcome from:
Professionals within EFLM societies, and ESCMID (considering endorsement),
Other medical professionals (laboratory specialists), and
Representatives of IVD Sponsors

The official review is given by the Chair of Committee of Science (Prof Eric Kilpatrick) according to the EFLM procedures, a wish for a deadline May-June 2022.

Voting for acceptance by the EFLM national members according to the EFLM Procedures
Official publication (Guideline is a Type 1a document) in the CCLM, to be submitted by the end of the year 2022.