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The Italian External Quality Assessment (EQA) program on urinary sediment by microscopy examination: a 20 years journey

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Abstract

Objectives: In spite of the introduction of automated systems for urinary sediment analysis, microscopy examination remains the gold standard, and it is more than ever important to perform it with a good and reliable quality. External Quality Assessment (EQA) programs on urinary sediment are rare. The present paper provides an analysis of results from 2001 to date of the EQA Italian program which involves today 230 laboratories.

Methods: The program includes four surveys per year. Participants are asked the identification and clinical associations of urinary sediment particles, shown as phase contrast microscopy images in the website of the Center of Biomedical Research (CRB) (2 surveys), and the diagnosis of clinical cases presented by both images and a short clinical history (2 surveys). The results of each survey are then scored and commented. In 20 years, 298 images were presented: 90 cells (9 types), 23 lipids (5 types), 87 casts (21 types), 53 crystals (14 types), 22 microorganisms (5 types), and 23 contaminants (9 types). Moreover, 27 clinical cases, covering a wide spectrum of conditions with different degrees of complexity, were presented to participants.

Results: Identification: among urinary particle categories, the correct identification rate (obtained for each particle from the sum of correct + partially correct answers) was very high for micro-organisms (mean ± SD: 96.2 ± 3.5%), high for lipids (88.0 ± 11.8%) and crystals (87.0 ± 16.5%) followed, in decreasing order, by cells (82.1 ± 15.9%), casts (81.8 ± 14.8%), and contaminants (76.7 ± 22.1%). Clinical associations (n=67): the rate of correct answers was 93.5 ± 5.7% ranging from 75.0 to 100% for all but one clinical association (i.e., acute glomerulonephritis: 55.4%). Clinical cases: throughout surveys, due to the overall rate of particle misidentification, only 59.8 ± 17.1%, (range 32.5–88.7%) of participants achieved access to clinical diagnosis. Of these, 88.7 ± 10.6% (range 59.9–99.3%) were able to indicate the correct diagnosis.

Conclusions: Our program can be used as a tool to improve the identification of urine particles and the knowledge of their clinical meaning and to encourage specialists of laboratory medicine to correlate urinary findings with other laboratory data and the clinical history, an aspect that improves the value of the day by day work.

Keywords: external quality assessment programs; urinalysis; urinary sediment.

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Introduction

Due to the natural erosion of education in medicine and the exponential growth of knowledge, clinical professionals need to be lifelong learners. In particular, the increasingly pervasive automation in laboratory means that knowledge based on human activity, especially where morphological recognition is concerned, needs to be kept updated.

A field in which this reasoning can be applied is the urinary sediment examination – an integral part of urinalysis that requires an appropriate approach based on correct methodology, equipment, knowledge, experience and updating capability.

Today, automated systems – based either on automated intelligent microscopy or flow cytometry – have

improved the workflow in large laboratories, where high numbers of samples are analysed everyday. However, most pathological samples still require manual microscopy, which still represents the gold standard method for urine sediment examination [1, 2].

In addition to conventional Internal Quality Control (IQC) programs, External Quality Assessment Schemes (EQAS) represent a key tool for the improvement of laboratory quality and are mandatory requirements in accreditation programs in all fields of laboratory medicine [3]. EQAS on urinary sediment are rare [4–12].

The aim of this paper is to describe the results obtained in 20 years of activity of an EQAS on urinary sediment which has been going on in Italy since 2001 under the guidance of the Center of Biomedical Research (CRB), which is an EQA organisation with many programs in different fields of laboratory medicine (www.centroricercabiomedica.net) [13–17].

Materials and methods

The CRB Program was set up in 2001, as an Italian project on standardisation of urine analysis, by a promoting Committee which included the representatives of the three Italian societies of Laboratory Medicine – *Società Italiana di Biochimica Clinica e Biologia Molecolare Clinica (SIBioC); Società Italiana di Patologia Clinica e Medicina di Laboratorio (SIPMeL); Società Italiana di Nefrologia (SIN)*. From 2012 it was set up in collaboration with the Italian Urinalysis *Group: Gruppo Interdisciplinare Laboratorio e Clinica dell'Apparato Urinario (GIAU)*.

The aims of the program are: 1. to evaluate the capability of participants to identify the urinary sediment particles and their clinical associations; 2. to act as an educational tool for a diagnostic test that was (and is still?) usually scarcely considered both at a laboratory and a clinical level; 3. to stimulate improvement in the overall quality of urinary sediment examination.

Participants

The program is addressed to Italian central laboratories, both public and private, and to specialized laboratories of nephrological units. However, since 2004 also some Slovenian laboratories are participating in the program, with the official support of the Slovenian Association for Clinical Chemistry (SACC) and the Slovenian National External Quality Assessment Scheme (SNEQAS). The average number of participants in 20 years of activity was 284 ± 39 with the maximum number in 2009 (n=365) and the minimum in 2019 (n=224). The respondents to surveys are either one professional or more professionals supplying one common and shared answer.

Materials

Urinary sediment components are mainly unstable, especially in their original forms. This makes the use of such materials in external quality assessment programs almost impossible, thus from the beginning, we used photomicrographs of real urinary samples, first shipped to participants as paper images in colour and from 2006 presented in the website of the program.

Main features of the program

Period 2001–2011: The methods and results of the program, which in this period was under the responsibility and guidance of one of us (G.B.F.), a nephrologist with an expertise in urinary sediment and urinalysis [18–25], has been described in details elsewhere [6, 21, 22]. In this period, the descriptive identification of particles were evaluated as correct, partially correct, incorrect or no answer and scored accordingly (5, 3, 0, and –2 respectively).

"Partially incorrect" was scored when a particle was either correctly identified but not fully defined (e.g. calcium oxalate crystals without the specification whether they are mono- or bihydrated, or erythrocytes without the specification whether they are isomorphic or dysmorphic) or when a particle was partially misidentified (e.g. an erythrocytic cast defined as both erythrocytic and leukocytic cast).

Period 2012 to date: In 2012 the program was partly redesigned under the guidance of another author of the present paper (F.M.), who is an expert in urinalysis [26–29], and in collaboration with the GIAU [30–32]. Images, proposed from the coordinator of the EQA program (S.S.), were chosen if there was 80% or greater consensus of referee laboratories, which are members of GIAU.

In 2012 the program consisted of 4 surveys: two with 2 phase contrast microscopy images each, together with the microscopic field from which the particle was isolated and two other surveys, each one with one clinical case.

From the beginning of 2013 to date the program consists of 4 surveys/year which are organized as follows:

- 2 surveys, with the particles (4–8 for surveys) shown by phase contrast microscopy and, when appropriate, also by polarized light. Participants are asked to identify the particles and for some of them they are also asked to indicate a clinical association, chosen among 4 or 5 possible options proposed.
- 2 surveys, each one with a clinical case. Clinical cases consist of a brief clinical history, really occurred, which also include some key laboratory data and four phase contrast microscopy images of particles found in the urine sediment of the presented case. For clinical cases too the participants are asked to identify the particles shown and choose one possible diagnosis among 4–5 proposed.

From 2012 to 2014 the surveys continued to allow a free-text identification of particles, whereas from 2015 to date the participants are asked to identify the particles chosen among 10 options.

The score adopted to evaluate the identification of particles by the participants was the same as that used in the period 2001–2011 but, since the answer is linked to an option, from 2015 the answer classified as partially correct no longer exists. For clinical association the answer was considered and scored only if the particle was correctly identified. For clinical diagnosis (clinical cases) the answer was considered and scored only if all four particles were correctly identified.

For each survey, the CRB edits a report for each laboratory containing the judgement and the scores obtained together with a summary of all participants' answers and a comment on the images

shown, their main clinical correlates, the answers supplied by participants, together with an overview of the score obtained by all laboratories. Failing laboratories must analyse the reasons for the failure and start corrective action.

At the end of each annual cycle, CRB edits a report summarizing the laboratory's performances and scores together with an overview of the results obtained by all laboratories.

Moreover, at the end of each survey, the images presented, accompanied by a small comment, are uploaded to an Atlas, divided into categories and sub-categories, on the website of CRB. The Atlas, with the databank of the urine sediment images presented in the years represents an important resource for participants.

Particles and clinical cases studied

From 2001 to date, 298 images were presented, 110 of which within clinical cases: 90 cells (9 types), 23 lipids (5 types), 87 casts (21 types), 53 crystals (14 types), 22 micro-organisms (5 types), and 23 contaminants (9 types).

Some particles have been presented several times by means of similar but not identical images (Figure 1). For some particles, moreover, the images presented over time showed – for educational purposes – uncommon or atypical morphologies, as in the case of uric acid crystals (typical lozenges or spindle-like crystals) and triple-phospate crystals (typical "coffin lid" form and scissors or star-like crystals) (Figure 2). In the same period 27 clinical cases were presented to participants.

Results

The identification of particles

The correct identification rate in the period 2001–2011 was obtained for each particle from the sum of correct + partially correct answers, subsequently from correct answers only.

From 2001 to date, 298 images were presented, which showed 63 elements of urinary sediment. Among urinary particle categories, the correct identification rate (mean ± SD, range) was very high for micro-organisms (96.2 ± 3.5%, 89.1–100), high for lipids (88.0 ± 11.8%, 55.5–99.7) and crystals (87.0 ± 16.5%,16.9–100) followed, in decreasing order, by cells (82.1 ± 15.9%, 10.9–100), casts (81.8 ± 14.8%, 9.2–99.3) and contaminants (76.7 ± 22.1%, 20.9–99.6). The identification rates for each type of particle are reported in Table 1 and Figure 3.

For cells, the higher correct identification rate (>90%) was for dysmorphic erythrocytes (~94%) and leukocytes (~92%), while it was the lowest for the macrophage (~49%). The correct identification rate for renal tubular epithelial cells (RTECs) was 76.5 ± 10.6% (range 52.9–93.3, n=16).

In the period 2001–2014, when participants had to describe the particles, for some of them, such as erythrocytes and transitional epithelial cells, the terminology used was often incomplete, without specification whether the erythrocytes were isomorphic or dysmorphic and transitional epithelial cells were from superficial or deep layers of the uroepithelium. In these cases the rate of partially correct answers may be relevant.

Lipids were correctly identified in a percentage ranging from ~85% for cholesterol crystals to ~92% for aggregates of lipid droplets.

Among casts, the correct identification rate was very high for casts containing crystals (94.0 ± 3.5%, 91.5–96.4, n=2), high (>85%) for cellular (85.9 ± 10.4%, 51.6–99.3, n=29), and granular (85.2 ± 12.9%, 60.5–98.4, n=11) casts, followed, in decreasing order, by waxy (83.6 ± 8.6%,

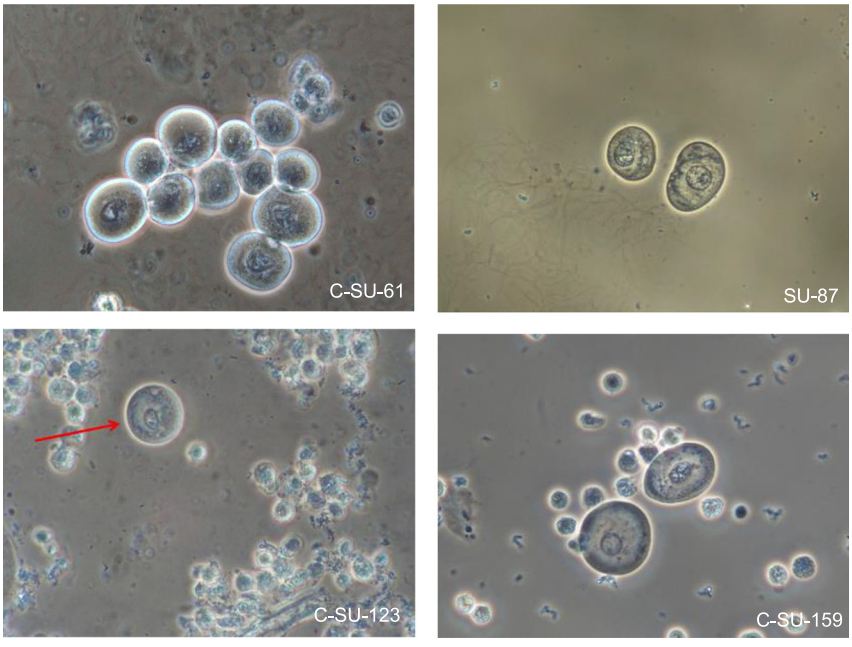

Figure 1: Four images of superficial transitional epithelial cells (phase contrast microscopy 400×).

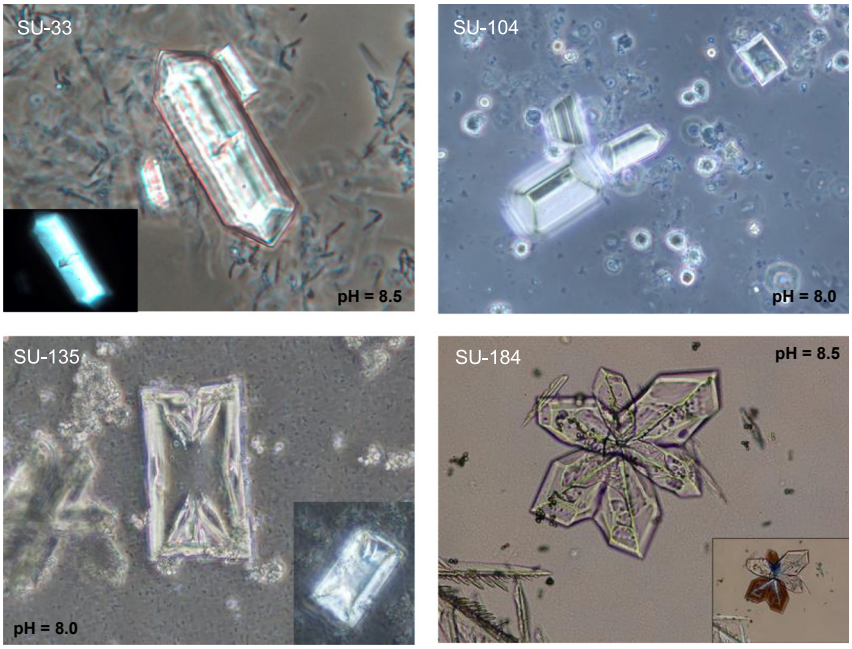

Figure 2: Four images of triple-phosphate crystals with typical "coffin lid" form (SU-104) and uncommon morphologies: prisms (SU-33 and SU-135) or star like crystals (SU-184), (phase contrast microscopy 400×).

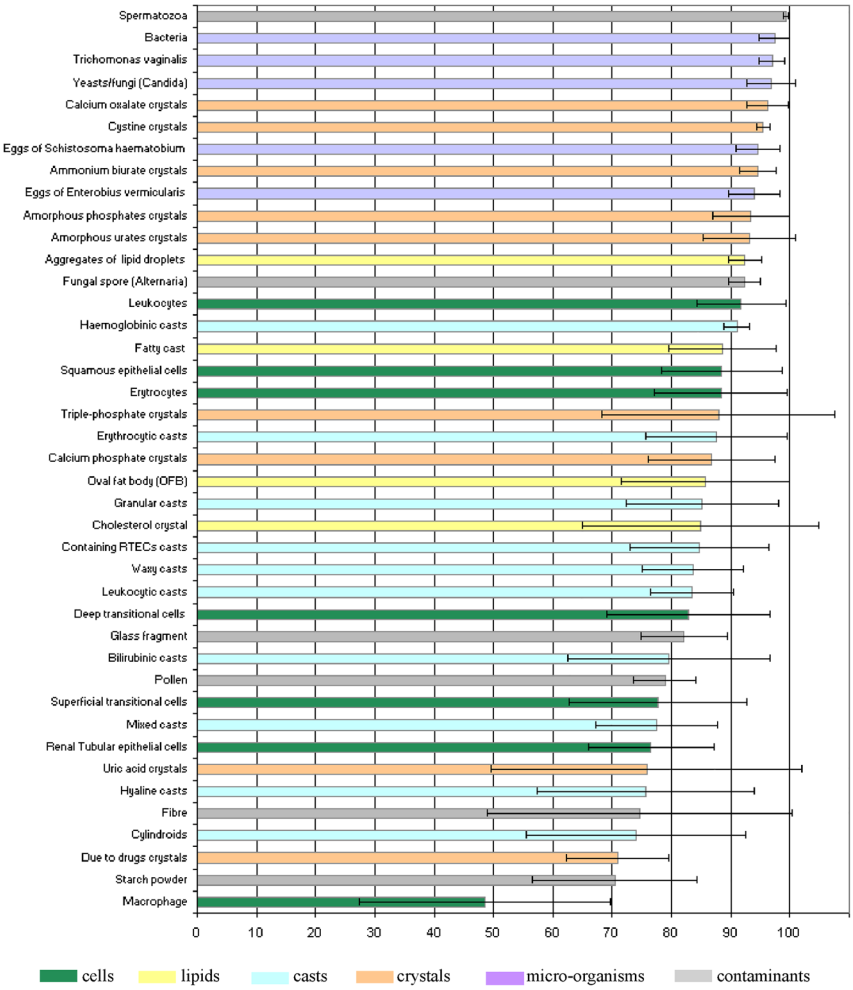

Figure 3: Correct identification rates of the shown particles (mean % ± SD).

Table 1: Identification rates of the particles presented. The identification rates are reported as mean ± SD.

Urine sediment particle	n	Correct + partially correct	Incorrect	n answers	n Labs
CELLS (n=90, 9 types)		**82.1 ± 15.9**	**17.3 ± 15.4**	**0.6 ± 1.0**	**255 ± 40**
Erythrocytes (n=23)		88.4 ± 11.2	11.1 ± 11.1		260 ± 38
Isomorphic RBCs	9	87.1 ± 10.4	12.5 ± 10.3		262 ± 44
Dysmorphic RBCs	5	94.0 ± 5.6	5.7 ± 5.5		276 ± 42
Acanthocytes	5	80.3 ± 16.5	18.7 ± 16.5		259 ± 25
Dysmorphic RBCs + acanthocytes	4	93.8 ± 2.7	5.9 ± 2.8		230 ± 13
Leukocytes	14	91.8 ± 7.6	8.1 ± 7.5		259 ± 41
Macrophage	6	48.5 ± 21.1	49.0 ± 19.8		278 ± 49
Renal tubular epithelial cells	16	76.5 ± 10.6	22.8 ± 10.1		243 ± 35
Superficial transitional epithelial cells	14	77.7 ± 15.0	21.6 ± 14.9		247 ± 31
Deep transitional epithelial cells	7	82.9 ± 13.8	16.5 ± 13.6		269 ± 48
Squamous epithelial cells	10	88.5 ± 10.1	11.4 ± 10.1		252 ± 55
LIPIDS (n=23, 5 types)		**88.0 ± 11.8**	**11.5 ± 11.4**	**0.5 ± 0.9**	**260 ± 47**
Aggregates of lipid droplets	3	92.4 ± 2.7	6.5 ± 2.6		264 ± 40
Oval fat body	6	85.8 ± 14.2	13.5 ± 13.4		257 ± 47
Fatty cast	9	88.6 ± 9.0	11.1 ± 9.0		253 ± 57
Cast containing cholesterol crystals	1	95.3	4.3		258
Cholesterol crystal	4	84.9 ± 20.0	14.6 ± 19.3		277 ± 49
CASTS (n=87, 21 types)		**81.8 ± 14.8**	**17.7 ± 14.8**	**0.5 ± 0.8**	**258 ± 45**
Hyaline	8	75.6 ± 18.3	23.4 ± 17.7		249 ± 49
Granular (n=11)		85.2 ± 12.9	14.3 ± 12.8		268 ± 34
Finely granular	6	88.3 ± 12.3	11.5 ± 12.2		279 ± 27
Coarsely granular	5	81.4 ± 13.9	17.7 ± 14.1		255 ± 39
Waxy	11	83.6 ± 8.6	15.9 ± 8.9		256 ± 47
Cellular (n=29)		85.9 ± 10.4	13.7 ± 10.4		257 ± 44
Erythrocytic	8	87.6 ± 11.9	12.0 ± 12.0		253 ± 41
Leukocytic	6	83.5 ± 7.0	16.2 ± 6.4		281 ± 47
Containing RTECs	12	84.7 ± 11.8	14.7 ± 12.0		244 ± 37
Erythrocytic + RTECs	1	83.0	16.6		263
Leukocytic + RTECs	2	93.3 ± 0.1	6.8 ± 0.1		288 ± 97
Pigmented (n=13)		81.4 ± 15.2	18.1 ± 15.0		258 ± 50
Bilirubinic (n=9)		79.6 ± 17.0	20.0 ± 16.6		248 ± 50
Bilirubinic + RTECs	4	89.1 ± 15.7	10.6 ± 15.1		222 ± 23
Bilirubinic (granular or waxy)	5	71.9 ± 15.0	27.6 ± 15.0		270 ± 57
Haemoglobinic	3	91.0 ± 2.2	8.2 ± 1.5		285 ± 61
Myoglobinic	1	69.4	30.2		268
Containing crystals (n=2)		94.0 ± 3.5	6.1 ± 3.5		217 ± 28
Granular containing acid uric	1	91.5	8.5		236
Containing monohydrated Ca oxalate	1	96.4	3.6		197
Mixed (n=10)		77.5 ± 10.2	21.8 ± 10.2		249 ± 46
Hyaline-granular	4	75.5 ± 10.3	23.6 ± 10.7		240 ± 36
Granular-waxy	1	67.8	31.4		361
Granular-erythrocytic	4	79.6 ± 11.4	19.9 ± 11.3		236 ± 16
Granular containing RBCs and an OFB	1	87.1	12.5		225
Cylindroids (n=3)		74.0 ± 18.5	26.0 ± 18.5		294 ± 69
Hyaline-granular	1	83.8	16.2		291
Containing RBCs	2	69.1 ± 23.3	31.0 ± 23.3		296 ± 98
CRYSTALS (n=53, 14 types)		**87.0 ± 16.5**	**12.4 ± 16.2**	**0.6 ± 1.4**	**260 ± 44**
Uric acid (n=8)		75.8 ± 26.2	23.7 ± 26.2		264 ± 40
“Rhomboid and diamond” shape	7	84.2 ± 11.9	15.3 ± 11.8		268 ± 41
“Stick” shape	1	16.9	82.7		237
Calcium oxalate (n=11)		96.3 ± 3.5	3.1 ± 3.0		256 ± 39
Monohydrated	5	93.8 ± 3.3	5.2 ± 3.0		256 ± 28
Bi-hydrated	6	98.5 ± 1.7	1.3 ± 1.8		256 ± 50
Triple-phosphate (n=10)		87.9 ± 19.7	12.0 ± 19.7		247 ± 46
“Coffin lid or prism” shapes	7	99.3 ± 0.5	0.5 ± 0.5		255 ± 53

Table 1: (continued)

Urine sediment particle	n	Correct + partially correct	Incorrect	n answers	n Labs
"Scissor or star-like" shapes	3	61.2 ± 15.1	38.7 ± 14.9		229 ± 9
Calcium phosphate (n=6)		86.7 ± 10.7	12.9 ± 10.1		250 ± 31
Crystals	3	89.6 ± 8.3	10.4 ± 8.3		243 ± 42
Plate	3	82.4 ± 16.1	16.8 ± 15.0		260 ± 5
Amorphous urates	2	93.1 ± 7.8	7.0 ± 7.8		279 ± 19
Amorphous phosphates	4	93.4 ± 6.5	6.4 ± 6.6		243 ± 40
Ammonium biurate	4	94.6 ± 3.1	4.6 ± 3.4		281 ± 62
Cystine	2	95.5 ± 1.1	4.4 ± 1.3		251 ± 20
Bilirubin	1	58.4	41.6		197
Due to drugs (n=5)		70.9 ± 8.7	26.7 ± 7.3		301 ± 65
Amoxicillin	2	72.6 ± 14.3	26.7 ± 13.2		276 ± 112
Ciprofloxacin	1	68.2	31.5		327
Indinavir	2	70.7 ± 9.4	24.4 ± 2.4		313 ± 44
MICRO-ORGANISMS (n=22, 5 types)		**96.2 ± 3.5**	**3.7 ± 3.5**	**0.1 ± 0.2**	**245 ± 42**
Bacteria	5	97.4 ± 2.6	2.6 ± 2.6		246 ± 54
Yeasts/fungi (Candida)	7	96.8 ± 4.1	3.2 ± 4.1		253 ± 43
Trichomonas vaginalis	3	97.0 ± 2.2	3.0 ± 2.2		233 ± 37
Eggs of Schistosoma haematobium	4	94.6 ± 3.7	5.3 ± 3.6		254 ± 52
Eggs of *Enterobius vermicularis*	3	93.9 ± 4.3	6.0 ± 4.1		224 ± 25
CONTAMINANTS (n=23, 9 types)		**76.7 ± 22.1**	**21.3 ± 20.6**	**2.1 ± 2.8**	**244 ± 35**
Starch powder	4	70.5 ± 13.9	27.7 ± 14.6		273 ± 47
Fibre (n=9)		74.6 ± 25.7	23.2 ± 22.9		236 ± 27
Cloth fibre	2	94.6 ± 3.9	5.5 ± 3.9		279 ± 18
Vegetable and cellulose fibre	6	64.0 ± 25.5	32.8 ± 22.4		223 ± 12
Muscle fibre	1	98.2	1.3		230
Pollen	2	78.9 ± 5.2	15.5 ± 2.2		230 ± 0
Fungal spore (Alternaria)	2	92.3 ± 2.6	7.1 ± 1.7		272 ± 74
Spermatozoa	2	99.4 ± 0.4	0		227 ± 1
Glass fragment	3	82.1 ± 7.3	16.7 ± 7.4		235 ± 30
Pseudocast	1	22.7	73.8		229

RBCs, erythrocytes; RTECs, renal tubular epithelial cells; OFB, oval fat body.

66.2–93.2, n=11), pigmented (81.4 ± 15.2%, 57.0–98.6, n=13), mixed (77.5 ± 10.2%, 61.8–88.5, n=10) and hyaline (75.6 ± 18.3%, 41.0–95.1, n=8) casts. Cylindroids were correctly identified in a rate of ~74%.

Among the pigmented casts the highest correct identification rate was for haemoglobinic casts (~91%) while the lowest was for myoglobinic casts (69%).

Among crystals, the correct identification rate was very high (>90%) for calcium oxalate (96.3 ± 3.5%, 88.7–100, n=11), cystine (95.5 ± 1.1%, 94.7–96.2, n=2), ammonium biurate (94.6 ± 3.1%, 91.1–98.3, n=4), amorphous phosphate (93.4 ± 6.5%, 83.8–97.8, n=4) and amorphous urates (93.1 ± 7.8%, 87.5–98.6, n=2).

The elevated SD for uric acid and triple-phospate crystals, are due to the surveys in which they have been presented with uncommon morphologies: shape of sticks form for uric acid and scissor or star-like form for triple-phospate.

Crystals due to drugs are those with the lowest correct identification rate (70.9 ± 8.7%, 62.5–82.7, n=5).

The five types of micro-organisms presented were always correctly identified by participants (from ~94% for eggs of *Enterobious vermicularis* to ~97% for Bacteria).

For contaminants the correct identification rate is very varied depending on the type of contaminant: the higher correct identification rate (≥95%) was for spermatozoa, muscle fibre and cloth fibre, the lowest for vegetable fibre (~64%).

Figure 4 represents the trend (mean ± SD) of the percentage of correct identification of particles per year. From 2001 to 2005 = 78.1 ± 5.3% (n=64); from 2006 to 2010 = 86.3 ± 4.6 (n=56); from 2011 to 2015 = 81.6 ± 4.8% (n=88); from 2016 to 2020 = 88.3 ± 1.1% (n=90).

The clinical association

For the evaluation of clinical associations, we changed our approach over the years, so that it is not possible to compare the results obtained in the early years, with

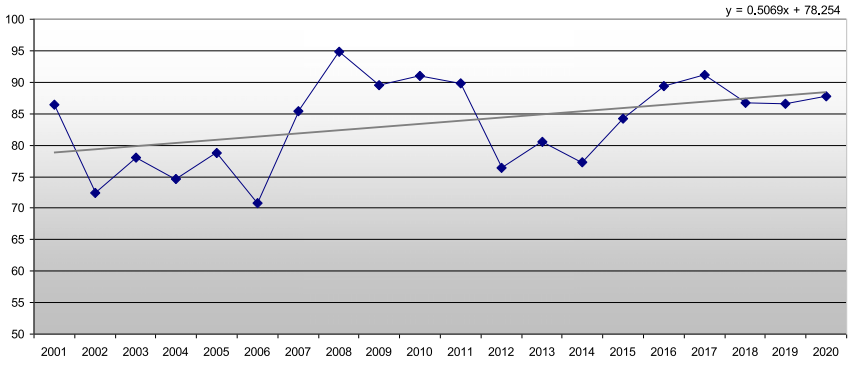

Figure 4: Trend (mean ± SD) of the percentage of correct identification of particles per year.
Linear regression: y=0.5069x + 78.254.

descriptive answers, with those obtained since 2004, when multiple choice answers were introduced.

From 2004 a total of 67 clinical associations were requested to participants. A mean of correct clinical association rate was 93.5 ± 5.7% ranging from 74.8 to 100% for all but one clinical association (i.e., acute glomerulonephritis: 55.4%, associated with cast containing renal tubular epithelial cells) (Table 2).

Among urinary particle categories, the correct clinical association rate (mean ± SD) was very high (>95%) for cells (96.1 ± 4.6%) and crystals (95.2 ± 3.3%), high (>90%) for micro-organisms (94.6 ± 4.2%), contaminants (93.6 ± 10.3%) and lipids (90.8 ± 7.2%). The lowest correct clinical association rate was for casts (89.5 ± 10.0%).

The clinical cases

For each survey presenting a clinical case, variable percentages of participants were able to correctly identify the whole set of particles shown. Thus, due to the overall rate of particle misidentification, only 59.8 ± 17.1%, (range 32.5–88.7%) of participants achieved access to clinical diagnosis.

Only seven cases (n=3, 4, 7, 20, 22, 25 and 27) had a rate >75% of participants with access to clinical diagnosis while for four cases (n=6, 12, 14, and 26) the rate of participants which identified all the particles was <40%. For these cases the sediment elements more misidentified were hyaline-granular cast for case 6, renal tubular epithelial cells for case 12, macrophage for case 14 and bilirubin crystal for case 26, with a rate of correct answers of 55.1, 60.7, 54.5 and 58.4% respectively. The results concerning clinical diagnoses are shown in Table 3.

Among the participants able to correctly identify all urine particles, 88.7 ± 10.6% (range 59.9–99.3%) supplied a correct clinical diagnosis, whilst 10.7% ± 10.7% (range 0–40.1%) supplied incorrect diagnoses and 0.6 ± 0.7% (range 0–2.7%) did not answer.

A <70% rate of correct diagnosis was observed for case 20 (urine contamination from genital secretions) and for case 23 (nephrotic syndrome), which obtained a rate of 64.5 and 59.9%, respectively.

Discussion

In this paper we describe the Italian EQA program on the urinary sediment and the results achieved from 2001 to date. In our opinion the program, which now involves about 230 laboratories distributed all over Italy with also an extension to Slovenia, shows several interesting aspects.

The part of the program on the identification of particles showed that the results were satisfactory only for micro-organisms and common lipids and crystals, while cells, casts and contaminants were less known (Table 1). Among cells, one of the least known is macrophage, whose significance in the urine, however, is not yet entirely clear [33, 34]. Among erythrocytes, acanthocytes obtained the lowest score (~80%) and their misidentification may represent a problem because they are considered the most reliable marker of glomerular bleeding [21].

Of higher concern was the poor identification of renal tubular epithelial cells (RTECs), which are a marker of tubular damage and are important, together with renal tubular cell casts and granular casts, to identify patients with acute tubular necrosis [35, 36].

For lipids, cholesterol crystals not always were correctly recognized by the participants, in spite of the fact that they are, together with aggregated of lipid droplets, fatty casts and oval fat bodies the hallmark of the urinary sediment of patients with the nephrotic syndrome [21].

For casts, some clinically important types are misidentified in about one third of cases, as bilirubin cast [37]. Also, hyaline casts, very common in the sediment of healthy subjects, such as in renal pathologies in combination with other types of casts [38], were little known.

Table 2: Answers concerning the clinical association.

Urinary sediment particle	n	CORRECT clinical association (chosen among 4–5 options)	Answers, %		
			Correct	Incorrect	n answers
Cells	**13**		**96.1 ± 4.6**	**3.6 ± 4.4**	**0.4 ± 0.5**
Dysmorphic erythrocytes	1	Glomerular haematuria	98.4	1.2	0.4
Superficial transitional cells	1	Cystitis	95.5	4.0	0.5
Deep transitional cells	3	Damage to the deep layers of the uroepithelium	98.4 ± 1.1	0.9 ± 0.5	0.6 ± 0.7
Renal tubular cells	5	Acute tubular necrosis	99.0 ± 0.4	1.0 ± 0.4	0.0
Macrophages	2	Active glomerulonephritis	88.2 ± 2.1	11.2 ± 1.1	0.7 ± 0.9
Transitional + squamous cells + leukocytes	1	Infection of the urinary tract	88.5	11.0	0.5
Lipids	**8**		**90.8 ± 7.2**	**7.9 ± 6.2**	**1.4 ± 1.5**
Oval fat bodies	1	Nephrotic syndrome	93.5	6.0	0.5
Fatty cast	4	Glomerular nephropathy associated with proteinuria >3.5 g/24 h	91.7 ± 3.1	6.9 ± 2.7	1.4 ± 1.5
Cholesterol crystal	3	Severe proteinuria/nephrotic syndrome	89.9 ± 13.2	8.4 ± 11.3	1.7 ± 1.9
Casts	**20**		**89.5 ± 10.0**	**9.3 ± 10.1**	**1.2 ± 1.6**
Hyaline cast	1	Intense physical exercise, kidney diseases, heart failure, etc.	75.0	25.0	0
Waxy cast	1	Active glomerulonephritis	94.8	5.2	0
Granular-waxy cast	1	Renal disease with deterioration of renal function	90.3	7.3	2.4
Erythrocytic cast or cylindroid	3	Haematuria of glomerular origin/active glomerulonephritis	93.6 ± 3.5	3.9 ± 3.1	2.5 ± 1.4
Leukocytic cast	2	Active proliferative glomerulonephritis	88.9 ± 6.9	8.8 ± 4.5	2.3 ± 2.4
Cast containing RTECs	3	Acute tubular necrosis	88.1 ± 1.0	11.8 ± 1.2	0.1 ± 0.2
Cast containing RTECs	1	Acute glomerulonephritis	55.4	44.6	0.0
Haemoglobinic cast	2	Haematuria of renal origin (glomerular)/active lupus nephritis	86.8 ± 6.4	10.3 ± 2.9	3.0 ± 3.5
Bilirubinic cast	4	Jaundice associated with increased conjugated bilirubin/hepatorenal syndrome/cirrhosis	96.1 ± 3.4	3.4 ± 3.2	0.5 ± 1.1
Epithelial-bilirubinic cast	2	Hepatorenal syndrome associated to tubular damage	97.2 ± 0.0.7	2.1 ± 1.0	0.7 ± 0.3
Crystals	**15**		**95.2 ± 3.3**	**3.4 ± 2.9**	**1.4 ± 1.9**
Uric acid crystals	3	Acute urate nephropathy/lymphoproliferative disease/ gout	92.7 ± 3.4	4.8 ± 2.7	2.5 ± 3.4
Monohydrated calcium oxalate crystals	3	Crystalluria due to drugs (e.g., vitamin C, naftidrofuryl oxalate)/ethylene glycol intoxication	95.1 ± 3.1	3.7 ± 2.8	1.3 ± 1.2
Bihydrated calcium oxalate crystals	2	Calcium oxalate urolithiasis	93.1 ± 4.7	6.5 ± 5.3	0.5 ± 0.6
Triple-phosphate crystals	2	Bacterial infection caused by urea-splitting microorganisms	96.5 ± 2.3	2.6 ± 1.8	1.0 ± 0.5
Amorphous urates	1	Uric acid urolithiasis associated with increased uricuria	92.7	2.4	4.9
Amorphous phospate + Ca-phosphate crystals	1	Calcium phosphate urolithiasis	96.6	3.4	0.0
Crystals due to drugs (indinavir, amoxicillin)	3	Drug-related crystalluria	98.6 ± 2.4	0.6 ± 1.0	0.8 ± 1.3
Micro-organisms	**5**		**94.6 ± 4.2**	**4.1 ± 4.2**	**1.4 ± 1.5**
Egg of *Schistosama haematobium*	1	Infection of the urinary system due to a parasite	91.0	5.3	3.7
Egg of *Enterobius vermicularis*	3	Faecal contamination	95.5 ± 5.2	3.7 ± 5.9	0.9 ± 1.1
Yeasts	1	Vaginal contamination	95.4	4.1	0.5
Contaminants	**6**		**93.6 ± 7.5**	**5.7 ± 7.6**	**0.7 ± 1.8**
Starch	1	Urine contamination from environment	92.9	2.7	4.4
Vegetables fibres / vegetal fibre with starch	3	Faecal contamination	90.8 ± 10.3	9.2 ± 10.3	0.0
Muscle fibre	1	Faecal contamination	98.2	1.8	0.0
Alternaria	1	Urine contamination from environment	98.1	1.9	4.4

RTECs, renal tubular epithelial cells.

Table 3: Answers supplied by participants for each clinical cases.

n	Clinical case	n of participants with access to diagnosis	Diagnosis			
			n of diagnosis evaluated	Correct	Incorrect	No answer
1	Acute nephritic syndrome	168/325 (51.7%)	168	146 (86.9%)	21 (12.5%)	1 (0.6%)
2	Ureteric stone	125/310 (40.3%)	125	119 (95.2%)	6 (4.8%)	0 (0.0%)
3	Urine contamination from genital secretions	251/326 (76.9%)	251	194 (77.3%)	54 (21.5%)	3 (1.2%)
4	Nephrotic syndrome	275/310 (88.7%)	275	257 (93.4%)	15 (5.4%)	3 (1.1%)
5	AKI with ATN from urate nephropathy	175/284 (61.6%)	175	129 (73.7%)	45 (25.7%)	1 (0.6%)
6	Microscopic isolated haematuria of glomerular origin	113/285 (39.6%)	113	110 (97.3%)	0 (0%)	3 (2.7%)
7	Protozoan contamination of urine	232/274 (84.7%)	232	227 (97.8%)	3 (1.3%)	2 (0.9%)
8	AKI from acute rhabdomyolysis	160/268 (59.7%)	160	157 (98.1%)	3 (1.9%)	0 (0.0%)
9	Acute pyelonephritis	181/281 (64.4%)	181	165 (91.2%)	16 (8.8%)	0 (0.0%)
10	Drug-induced acute interstitial nephritis	197/276 (71.4%)	197	179 (90.9%)	16 (8.1%)	2 (1.0%)
11	Haematuria from bladder catheterization and urinary tract infection	97/242 (40.1%)	97	92 (94.9%)	4 (4.1%)	1 (1.0%)
12	Membranoproliferative glomerulonephritis	82/252 (32.5%)	82	68 (82.9%)	12 (14.6%)	2 (2.5%)
13	Relapsing lupus nephritis	137/248 (55.2%)	137	136 (99.3%)	1 (0.7%)	0 (0.0%)
14	Pyelonephritis in nephrotic syndrome	79/242 (32.6%)	79	70 (88.6%)	9 (11.4%)	0 (0.0%)
15	ATN in a patient with Wegener granulomatosis	100/225 (44.4%)	100	95 (95.0%)	5 (5.0%)	0 (0.0%)
16	Acute pyelonephritis	138/238 (58.0%)	138	131 (94.9%)	7 (5.1%)	0 (0.0%)
17	Nephrotic syndrome in a patient with decompensated diabetes mellitus	112/236 (47.5%)	112	103 (92.0%)	9 (8.0%)	0 (0.0%)
18	Uric acid nephropathy	163/236 (69.1%)	163	156 (95.7%)	6 (3.7%)	0 (0.6%)
19	Membranoproliferative glomerulonephritis	145/226 (64.2%)	145	112 (77.2%)	33 (22.8%)	0 (0.0%)
20	Urine contamination from genital secretions	200/227 (88.1%)	200	129 (64.5%)	70 (35.0%)	1 (0.5%)
21	Schistosomiasis	157/231 (68.0%)	157	154 (98.1%)	2 (1.3%)	0 (0.5%)
22	Pyelonephritis	165/219 (75.3%)	165	133 (80.6%)	32 (19.4%)	0 (0.0%)
23	Nephrotic syndrome	137/219 (62.6%)	137	82 (59.9%)	55 (40.1%)	0 (0.0%)
24	Membranoproliferative glomerulonephritis in nephrotic syndrome	102/221 (46.2%)	102	94 (92.2%)	8 (7.8%)	0 (0.0%)
25	Nephropathy with microhematuria due to bladder stagnation	155/203 (76.4%)	155	127 (81.9%)	27 (17.4%)	1 (0.7%)
26	Hepato-renal syndrome	75/197 (38.1%)	75	74 (98.7%)	0 (0.0%)	1 (1.3%)
27	Protozoan contamination of urine	163/202 (80.7%)	163	159 (97.5%)	4 (2.5%)	0 (0.0%)

Among contaminants, whose correct identification is important because highlights an inaccurate sample collection [30], fibres were quite often misidentified: the types of fibre can at times mislead even experienced microscopists due to the wide morphological spectrum they may have. Even contaminants may be important because some of them may be confused with other particles such as casts (cellulose fibres) or crystals (starch structures) [21].

In the period 2001–2014, when the survey allowed a free-text interpretation of images, the program showed that participants often did not use the correct terminology to name the particles. This aspect was highlighted several times in the comments sent to participants at each survey. For epithelial cells, we strongly recommended to replace obsolete and misleading terms such as “cells from the high, intermediate, or low urinary tract” with the terms of renal

tubular cells, transitional cells (either superficial or deep) and squamous cells respectively [21, 32]. For erythrocytes, we recommended to abandon vague terms such as "degenerated, pale, old, etc." with the clinically relevant distinction between dysmorphic and isomorphic erythrocytes [32, 39]; for calcium oxalate crystals we always suggested to use the complete terminology, which includes the distinction between mono-hydrated and bi-hydrated subtypes, each of which can be found in different clinical conditions [21, 32].

An important target of our EQA program has always been the improvement of the identification skills of the particles. As our results and Figure 4 show, this improvement has been achieved over time, even though in a non-linear way. This can be due to several factors, such as a non-homogeneous distribution of "difficult" particles through the years, a non-ideal quality of some images, and/or a turn-over in the participants, which implies inevitable differences in experience, knowledge, and identification skills.

All these findings stress the importance of EQA programs as well as other interventions such as educational courses on the subject [19], and the publications of guidelines on the analytical and post-analytical phases [31, 32, 40, 41].

The rate of correct answers on clinical meaning of particles is very satisfactory, even if for the evaluation of clinical associations, we know that multiple choice answers, by restricting the number of possible clinical association to four or five, may facilitate participants.

The present study reports on all 27 clinical cases; the results on 10 and seven of which have been described in detail in two previous papers [11, 22].

In our opinion, the results obtained in this part of our EQA program are interesting in two respects.

First of all, they demonstrate a limited capability of participants to correctly identify all four or five urinary sediment particles associated with each case. In fact, several urinary sediment particles are, entirely or partly, misidentified by laboratory personnel, as demonstrated in previous studies [5, 42]. This misidentification can have important clinical implications, for example, erythrocytes subtypes are instrumental in identifying the source, glomerular or non-glomerular, of haematuria [43] and deep transitional epithelial cells indicate a severe damage of the uroepithelium such as that caused by urolithiasis, cancer of the excretory urinary system, and other urological disorders [44].

Second, our results demonstrate a variable rate of correct answers for clinical diagnoses, the worst rate was for case 23 (nephrotic syndrome): 59.9% and the best for case 13 (Lupus nephritis in relapsing course): 99.3%.

For 17 cases the rate of correct answers for clinical diagnoses was >90% showing that, once the correct identification of urinary sediment particles is obtained, most of participants were able to organize the urinary sediment findings into clinical conditions, even when they were complex and uncommon.

However, it cannot be omitted that the presentation to participants, for each case, of a multi-choice diagnostic answer could have favourably influenced the results. In spite of this limitation, there is no doubt that a laboratory able to propose a diagnostic hypothesis based on urinary findings can be of great help to clinicians (especially non nephrologists), who are not always aware of the clinical meaning and relevance of some urinary changes. This encouraging finding demonstrates that laboratory medicine is today able to provide interpretation of the results it produces.

Of course our program has also some limits. For instance, each particle is shown by means of only one image. This, without the possibility of focussing, changing of magnification or searching of other similar particles as can usually be done with true samples under the microscope, may have limited the identification capabilities of participants, especially in surveys with atypical or less usual particles. Future technologies may help to alleviate limitations created by single digital images. Moreover, since the same images are presented to all participants, colleagues from nearby or friendly laboratories could consult with each other and thus give rise to the same type of answers.

In spite of these limitations, our program can be used as a tool: – to focus on a diagnostic tool that is usually scarcely considered, – to improve the identification of urine particles and the knowledge of their clinical meaning and – to encourage specialists of laboratory medicine to correlate urinary findings with other laboratory data and the clinical history, an aspect that improves the value of the day by day work.

Manual microscopy of urine sediment examination is becoming a "lost art" for the new generation of laboratory medicine professionals who mainly use automated instrumentation.

Automated analysers enables the reduction of time, labour and cost analysis and have better inter-observer variability than manual methods; however they have limitations in the recognition of urine elements, especially in highly pathological samples and manual microscopic examination cannot be abandoned.

For this reason a proficient microscopic examination of urine sediment by skilled professionals is even more important. Furthermore, the international accreditation standards as ISO 15189 stressed the importance of the professional competence throughout the entire testing process. Any accredited laboratory should adopt a clear procedure to evaluate the level of competence of the employees and establish a method providing evidence of harmonization among different laboratory morphologists [3, 45, 46].

National and international guidelines [30–32, 40, 41], online access to educational resources, image Atlas of urinary microscopy and sediment analysis [5, 47, 48], textbooks [21, 49] are available tools to train the professionals and EQA programs are a necessary means to evaluate their learning [50–56].

Therefore, EQA programs on urinary sediment should be encouraged and sustained by Scientific Societies of Laboratory Medicine.

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