Micro-percutaneous nephrolithotomy (Microperc) for renal stones, outcomes and learning curve

La micro néphrolithotomie percutanée (Microperc) pour calculs rénaux, résultats et courbe d’apprentissage

Floriane Michel\textsuperscript{a}, Thibaut Negre\textsuperscript{b}, Michael Baboudjian\textsuperscript{a}, Khalid Al-Balushi\textsuperscript{a}, Jauffray Oliva\textsuperscript{a}, Bastien Gondran-Tellier\textsuperscript{a}, Pierre-Clément Sichez\textsuperscript{a}, Veronique Delaporte\textsuperscript{a}, Sarah Gaillet\textsuperscript{a}, Akram Aikiki\textsuperscript{a}, Alice Faure\textsuperscript{c}, Gilles Karsenty\textsuperscript{a}, Eric Lechevallier\textsuperscript{a}, Romain Boissier\textsuperscript{a,∗}

\textsuperscript{a} Department of Urology and Kidney Transplantation, La Conception Academic Hospital, Aix-Marseille University, AP–HM, 13005 Marseille, France
\textsuperscript{b} Urology Department, Parc-Rambot Clinic, Aix-en-Provence, France
\textsuperscript{c} Department of Pediatric Urology, Timone Academic Hospital, Aix-Marseille University, AP–HM, Marseille, France

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KEYWORDS
Renal lithiasis;
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Microperc;
Urinary diversion;
Neurogenic bladder

Summary
Objective. — To report the effectiveness, reliability and learning curve of Microperc, a minimal invasive percutaneous technique using a 4.85-Ch (16-gauge) sheath, in the treatment of nephrolithiasis.

Material and methods. — 31 consecutive Micropers for nephrolithiasis < 2.5 cm were performed by 2 operators in 2 different institutions from the 1st of May 2015 to 31st of December 2017.

Results. — The mean size of stones was 19 mm ± 11 mm, and mean density was 1048 ± 249 UH. Stones were located in lower calyx in 21/31 (68%), medium calyx in 3/31 (10%), pelvis in 4/31 (12%) and were multi-caliceal in 3/31 (10%). Five patients (16%) had urinary diversion (4 ileal

∗ Corresponding author.
E-mail address: romain.boissier@ap-hm.fr (R. Boissier).
conduits, 1 enterocystoplasty with Mitrofanoff + bladder neck closure) all of those having neurological disease (2 multiple sclerosis, 3 spinal cord injury). Mean operating time was 83 ± 35 min and decreased after short period for both operators. 9/31(29%) patients had complication: 8 (26%) had fever (Clavien II) and 1 (3%) had renal colic pain (Clavien III) (required JJ stent). Stone-free was obtained in 13/31(42%) and 11/31(36%) had residual microfragments < 3 mm which did not require further treatment, corresponding to a technical success of 78% (24/31). Success rate was similar in patients with urinary diversion and patients with normal anatomy. 

Conclusions. — This study showed that Microperc was an effective technique for kidney stone treatment with low complication rate, acceptable operating time and short learning curve. Microperc was useful for stones in the lower calyx and/or urinary diversion where retrograde ureteroscopy could reach its limits. 

Level of evidence. — 3. 

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**Introduction**

For lower calyx renal stones < 2 cm, the treatment options can be: External Shock Wave Lithotripsy (ESWL), Percutaneous Nephrolithotomy (PNCL) and Retrograde Intra-Renal Surgery (RIRS) [1]. The drawbacks of ESWL are lower stone clearance rate and the need of repeated sessions especially in hard stones [2].

Because of potential severe complications of conventional PCNL such as bleeding, injury to adjacent organs and septic-shock, the retrograde ureteroscopy considered as the standard for < 2 cm renal stone management. Nowadays, PCNL is mainly indicated in large kidney stones treatment [1].

However, there are certain situations where percutaneous approach can be of more advantage compared to RIRS, like urinary diversion (ileal conduit, enterocystoplasty), stones in lower kidney calyx or stones in caliceal diverticulum. Therefore, studies were carried out in order to reduce the risk of severe complications associated with the PCNL [3]. These studies mainly focused in reducing the caliber of used materials. This led to new invention in the percutaneous approach such as: mini PCNL, ultra mini PCNL and super mini PCNL with diameter of access sheath that ranged from Ch 7 to 18 [3].

Micro-Per-Cutaneous-Nephro-lithotomy (MicroPCNL) or Microperc is a percutaneous technique for kidney stone management using a 4.85-Ch (16-gauge) sheath [4]. Microperc can be an alternative to RIRS in the management of kidney stones < 2 cm, as it was proved to provide less complications compared to conventional PCNL and to be feasible in ambulatory [5].
The aim of this study was to report the results and the learning curves of 2 operators who started Microperc in the treatment of kidney stones as an alternative to RIRS.

Material and method

This was a retrospective study that included all Micropercs performed for the treatment of kidney stone by 2 operators in 2 different institutions from the 1st of May 2015 to the 31st of December 2017. Thirty-one procedures that involved 31 patients were identified. Microperc was proposed initially to patients with nephrolithiasis in the lower calyx then the criteria were widened to involve patients with stones in the urinary pelvis and medial calyx. Stone size was determined preoperatively by CT scan with the largest diameter and was less than 25 mm. All patients signed a written consent for clinical data use. Institutional ethics committee approved the study considering the Microperc as a type of PCNL that followed current guidelines.

The demographic characters including age, gender, BMI, urinary tract anatomy (normal or urinary diversion), stone size, stone density, stone locations and periproductive parameters were recorded. Preoperative evaluation included a clinical examination, urine culture, blood test (control of hemostasis and coagulation) and abdominal non-injected CT-scan. A preoperative positive urine culture was treated with antibiotics accordingly. Any anticoagulant/antiplatelet therapy was discontinued before surgery and restarted postoperatively according to specialized advises. All the data were collected in a dedicated anonymous database. All patients were informed of the innovative nature of the Microperc technique and signed a consent that authorized the anonymous use of clinical, biological and imaging data.

Material of Microperc

Materials used in the technique of Microperc included: a reusable flexible microfiber optics with a diameter of 0.9 mm and a view field of 120° and a single-use kit that contained: an access sheath of 4.85Ch external diameter, its inner needle with stylet and a 3-ways connector for irrigation, laser fiber (230 μm) and endoscope [4]. The endoscope was connected to the light source and the camera of a standard endoscopy column. All connections were supported by a 4-joints arm hooked on the endoscopy column.

Technique of Microperc

All interventions were performed under general anesthesia and patients were installed in a modified supine position (Valdivia). The first step involved the placement of a ureteral catheter (7Ch) in the renal pelvis using a cystoscope and fluoroscopic guidance. The second step was the introduction of the Microperc sheath. After inflating the renal pelvis and calyx with saline solution through the ureteral catheter, a caliceal puncture was performed with the Microperc needle of 4.85Ch under ultrasound and fluoroscopic guidance. For the needle puncture we used both freehand or needle guide fixed to the ultrasound probe. The aim of the puncture was to target the papilla of the preferred calyx. The correct position was verified initially by the emission of clear urine through the sheath when the inner needle was removed and was confirmed visually when the fiber optic was introduced in the access sheath. The 3-ways connector was attached to the outer end of the Microperc sheath. The connector middle channel was used to pass the flexible optic fiber (0.9 mm).

One channel was used to connect the irrigating fluid using an irrigation pumping system (Endoflow, Rocamed, Monaco) set at a constant pressure of 60 mm Hg with possibility of manual flush. The solution used was normal saline heated at 37 °C. The third channel was used to introduce a 230 μm laser fiber.

The third step involved percutaneous lithotripsy under visual and fluoroscopic guidance. The lithotripsy was performed using a 30 Watts Holmium:YAG laser machine (MH01, Rocamed, Monaco) set up in dusting mode (0.2-0.8 J with 10-20Hz frequency, long pulse). We avoided the production of stone fragments as it was not possible to extract the fragments through the narrow Microperc sheath. At the end of procedures, the sheath was removed under visual control.

The ureteral catheter was normally removed in day 1 postoperation, unless significant hematuria or fever. For patients in ambulatory, the ureteral catheter was converted to JJ stent Ch7 under fluoroscopic guidance and removed in day 15 in out-patient clinic under local analgesia.

Data and endpoints

The operating time was the duration from the insertion of the ureteral catheter until the withdrawal of the Microperc sheath at the end of the procedure (min). The postoperative data were: hospital stay, and complications, that were graded according to the Clavien-Dindo classification.

The follow-up consultation was at 1-month post-intervention and involved a clinical examination, blood tests and renal imaging. Renal imaging was either with ultrasound/radiography or CT scan (no contrast injection and low dose).

The treatment outcome was defined using postoperative imaging as:

- “Stone-free” defined as the absence of any residual fragments;
- “Microfragments” defined as one or more asymptomatic and non-obstructive fragments <3 mm, for which the operator did not indicate any other intervention;
- “Incomplete treatment” defined as one or more residual fragments> 5 mm that indicated a second intervention with a technique selected by the operator.

The primary endpoint was technical success that was defined as complete stone-free or the presence of microfragments <3 mm. Secondary endpoints were postoperative morbidity and treatment outcomes in the subgroups of patients with urinary diversion compared to patients with normal anatomy. Cases of urinary diversion and neurogenic disorders were all performed by operator 1. Learning curves were drawn according to consecutive operating times for operator 1 and 2, not taking into account the potential technical difficulties.
Statistics
Quantitative non-continuous data are presented as the median and range [min-max] and were assessed by the Mann-Whitney test. Quantitative continuous data are presented as the mean and standard deviation and were assessed by the Mann-Whitney test. Qualitative data are presented as counts and percentages and were assessed using the Fisher exact test. Two-tailed significance was considered at 0.05 for all statistical tests and XLStat® software version 2018.5 (Addinsoft, Paris, France) was used for all statistical analyses.

Results
The demographical characteristics of patients are reported in Table 1. The mean age was 51 ± 17 years and the mean body mass index (BMI) was 26 ± 2 m²/kg. The average glomerular filtration rate (GFR) was 108 ± 37 mL/min. Six (19%) patients had a history of neurological disease (2 multiple sclerosis and 4 traumatic tetraplegia), and 5 (16%) of them had urinary diversion: 4 (13%) ileal conduit (bricker), 1 (3%) enterocystoplasty with Mitrofanoff and closure of the bladder neck. The stone characteristics are reported in Table 1. The average size was 19 mm ± 11 and the average density was 1048 ± 249 HU. Stone locations: lower calyx in 21/31 (68%), middle calyx in 3/31 (10%), renal pelvis in 4/31 (12%) and multi-caliceal in 3/31 (10%).

The average operating time was 83 ± 35 min (Table 2). The learning curves of both operators are presented in Fig. 1: according to operating time (Fig. 1A), stone-free rate and stone size (Fig. 1B). Stone-free rate were similar between the first 5 cases of each operator and the last (P = 0.49, Fischer’s test). Severe complication rate (>Clavien II) were similar between the first and the last five patients of each operator (P = 0.42, Fischer’s test). We reported 2 technical failures: 1 puncture failure (operator 2) and 1 peroperative breakdown of the endoscope (operator 1). Both cases occurred in patients with history of renal surgery for complex stones with costal incision. Fourteen (45%) interventions were performed in ambulatory. For the 17 (55%) hospitalized patients, the median hospital stay was 3 days [2–7] (Table 2).

The overall complication rate was 9/31 (29%). Clavien II complication (fever) occurred in 8 patients (26%) and all of them got resolved with antibiotic treatment. We reported one (3%) Clavien III complication in a patient who initially refused any postoperative drainage and finally underwent a retrograde JJ stent in day 1 post-intervention for renal colic and fever. No bleeding complications reported neither pneumothorax or digestive complications (Table 2).

On postoperative imaging at 1 month, 13/31 (42%) patients were stone-free and 11/31 (36%) had residual micro-fragments < 3 mm. Overall success rate was 78% (24/31). Seven patients (22%), including the 2 peroperative failures, had residual fragments > 5 mm (Table 2).

We compared the characteristics and results between 5 patients with urinary diversion (derivation group) and 26 patients with normal anatomy. The initial characteristics of patients with urinary diversion versus normal anatomy are reported in Table 1. In the urinary diversion and normal anatomy groups the median number of stones were respectively 2 [1–5] versus 1 [1] (P = 0.04), the mean size of the stones was 13 ± 4 vs 14 ± 6 (mm) (P = 0.96) and the average density was 800 ± 258 vs 1100 ± 224 UH (P = 0.06). In derivation and normal anatomy groups, the mean operative time was 95 ± 25 vs 81 ± 37 min (P = 0.29), hospital stay (days) was 3 [2–7] vs 1 [1–7] (P = 0.02), and technical success was 60% vs 81% (P = 0.99) respectively. The rate of preoperative positive urine culture and antibiotic treatment requirement was higher in patients with urinary diversion 80% vs 4% (P = 0.01). The complication rate was higher in patients with urinary diversion, although the difference was not significant 40% vs 23% (P = 0.56).

Discussion
In this study including 31 consecutive Microperc interventions for kidney stones < 2 cm, we reported technical success rate of 78% with low incidence of severe complications. Our results were concordant with series published in litterature up to date that reported success rates from 80 to 97%. Several studies compared Microperc to miniPCN [6,7] or RIRS [8–10] and concluded to similar success and complication rates. Most of these studies included pediatric patients, in whom the Microperc was easily adapted owing to the minimal diameter of the access sheath [8,11–14].

ESWL is another alternative to the treatment of nephrolithiasis of the lower pole. Recently a systematic review demonstrated that PCNL and RIRS were more effective than ESWL for > 10 mm stones, but that the magnitude of the benefit decreased for stones < 10 mm [15]. A systematic review that focused on lower pole renal stones 10–20 mm confirmed lower Stone-free rate, higher retreatment rate and auxiliary procedure rate with ESWL, but a shorter operative time and hospital stay [16]. A prospective randomized comparative study of Microperc vs RIRS for lower pole nephrolithiasis concluded to similar stone clearance and complication although Microperc was associated to prolonged hospital stay and scopy time [17]. Taken all together, these results suggest that ESWL could be a first-line treatment for lower pole stones especially for renal stones <10 mm but that Microperc/RIRS were 2 minimally invasive technic with higher stone-free rate.

Microperc is a useful and effective technique for the treatment of lower calyx stones, where RIRS reaches its limits. As any percutaneous technique, Microperc preserves the ureter while RIRS could need ureteral dilatation or even re-intervention and could cause ureteral damage [18]. In retrograde ureteroscopy, the fragmentation efficacy is not impacted by the location of the stone, but the management of lower calyx stones can be challenging in RIRS [19]. Since the laser fiber reduces the maximum deflection of the ureteroscope, it may be necessary to relocate the stone to an upper pole calix for easier fragmentation [19–21]. Some urologists consider that relocation of the lower calyx stones is mandatory as prolonged maximal deflection could damage the ureteroscope [22–25]. Furthermore, successive introduction and withdrawal of laser fiber and stone retrieval basket should be done with minimal ureteroscope deflection to reduce the risk of ureteroscope damage. As a consequence, this requires to relocate the ureteroscope in the
renal pelvis before any reentry of the basket probe or laser fiber in the lower calyx [19–21,23]. Single-use ureteroscope could be a solution in interventions with high risk of ureteroscope damage such as lower calyx stones [26]. However single-use ureteroscope doesn’t provide any solution to the RIRS loss of ergonomics in lower calyx and was also proved as less cost effective than reusable conventional RIRS [27].

The Microperc is particularly suitable for the treatment of kidney stones in patients with urinary diversion compared to RIRS. In our series in 5 patients with urinary diversion, we reported similar operating time and technical success to patients with normal anatomy. In our experience, kidney stone management in patients with urinary diversion could be challenging by RIRS because of the difficult anatomical angulations that reduce the maneuverability and increase the risk of damage to the ureteroscope [25]. Given the small caliber of the Microperc sheath, several puncture can be performed in the same procedure. Therefore, patients with multiple stone locations are not expected to have multiple interventions with Microperc. In our series, we reported

Table 1  Baseline characteristics of patients and stones.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All cohort</th>
<th>Urinary diversion (D)</th>
<th>Normal urinary anatomy (N)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>31</td>
<td>5</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>18:13</td>
<td>2:3</td>
<td>16:10</td>
<td>0.90</td>
</tr>
<tr>
<td>Age, years (mean, SD)</td>
<td>51±17</td>
<td>45±12</td>
<td>53±18</td>
<td>0.23</td>
</tr>
<tr>
<td>Body mass index, kg/m² (mean, SD)</td>
<td>26±5</td>
<td>24±7</td>
<td>27±4</td>
<td>0.38</td>
</tr>
<tr>
<td>Charlson comorbidity (median, [min-max])</td>
<td>1[0–6]</td>
<td>2[2–4]</td>
<td>0[0–6]</td>
<td>0.02</td>
</tr>
<tr>
<td>Neurogenic disease (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>2 (6%)</td>
<td>2 (40%)</td>
<td>1 (4%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Traumatic (tetraplegia)</td>
<td>4 (13%)</td>
<td>4 (60%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Urinary Diversion (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bricker</td>
<td>4 (13%)</td>
<td>4 (80%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Enterocystoplasty + mitrofanoff</td>
<td>1 (3%)</td>
<td>1 (20%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min (mean, SD)</td>
<td>109±37</td>
<td>135±45</td>
<td>96±28</td>
<td>0.15</td>
</tr>
<tr>
<td>Stone size, mm (mean, SD)</td>
<td>18±10</td>
<td>20±7</td>
<td>17±9</td>
<td>0.96</td>
</tr>
<tr>
<td>Stone location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower calix</td>
<td>21 (68%)</td>
<td>2 (40%)</td>
<td>19 (72%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Middle calix</td>
<td>3 (10%)</td>
<td>1 (20%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td>Pelvis</td>
<td>4 (12%)</td>
<td>1 (20%)</td>
<td>3 (12%)</td>
<td></td>
</tr>
<tr>
<td>Multi-caliceal</td>
<td>3 (10%)</td>
<td>1 (20%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2  Surgical outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All cohort</th>
<th>Urinary diversion (D)</th>
<th>Normal urinary anatomy (N)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>31</td>
<td>5</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Operating time, min (mean, SD)</td>
<td>83±35</td>
<td>95±25</td>
<td>81±37</td>
<td>0.29</td>
</tr>
<tr>
<td>Type of hospitalisation (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambulatory</td>
<td>14 (45%)</td>
<td>0 (0%)</td>
<td>14 (54%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Standard</td>
<td>17 (55%)</td>
<td>5 (100%)</td>
<td>12 (46%)</td>
<td></td>
</tr>
<tr>
<td>Hospital stay, days (median [min-max])</td>
<td>3 [2–7]</td>
<td>3 [2–7]</td>
<td>1 [1–7]</td>
<td>0.02</td>
</tr>
<tr>
<td>Technical failurea</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td>Success rate (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stone-free</td>
<td>13 (42%)</td>
<td>1 (20%)</td>
<td>12 (46%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Microfragments &lt; 3 mm</td>
<td>11 (36%)</td>
<td>2 (40%)</td>
<td>9 (35%)</td>
<td></td>
</tr>
<tr>
<td>Macrofragments</td>
<td>7 (22%)</td>
<td>2 (40%)</td>
<td>5 (19%)</td>
<td></td>
</tr>
<tr>
<td>Complications (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clavien I–II</td>
<td>8 (26%)</td>
<td>2 (40%)</td>
<td>6 (19%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Clavien III</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Drainage (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JJ</td>
<td>21 (68%)</td>
<td>0 (0%)</td>
<td>21 (81%)</td>
<td>0.01</td>
</tr>
<tr>
<td>MonoJ</td>
<td>10 (32%)</td>
<td>5 (100%)</td>
<td>5 (19%)</td>
<td></td>
</tr>
</tbody>
</table>

a Including day of admission.

b 1 puncture failure and 1 peroperative break of the endoscope in patients with history of flank incision for nephrolithiasis.
that 3 patients with both inferior and middle calyx stones had a successful treatment through several punctures and fragmentation of all stones in a single intervention. Dusting lithotripsy (low energy, high pulse laser frequency) limits the risk of a significant fragment formation which could be flushed in an inaccessible cavity.

Systematic peroperative and postoperative drainage is debatable considering that Microperc could be technically feasible without ureteral catheters. In early experience of Microperc that didn’t use per and postoperative drainage, authors reported cases of fluid extravasation and retroperitoneal collections. This complication occurred in none of our patient [28,29]. The main reason for such a complication is the lack of an outer access sheath, as in conventional PCNL, which may result in intrarenal pelvic pressure that could be high, especially in prolonged operating time [30]. Operator 1 who managed all cases of neurogenic patients and urinary diversion preferred postoperative drainage with MonoJ stent which was removed at D1 before patient was discharged, while operator 2 favored ambulatory and drainage with JJ stent which was removed at D15 in out-patient clinic.

The main limitation of our study is its retrospective design. Moreover, the small number of patients did not allow to assess a multivariate analysis to clearly identify factors associated to technical failure. Despite its small size, this cohort study has demonstrated the feasibility of the Microperc technique in several specific situations: stones of the lower calyx, multiple locations (mid and lower calyx) and urinary diversions. A disadvantage of the Microperc technique is the small caliber of the sheath that does not allow the extraction of fragments for SPIR analysis. In our experience, Microperc was an alternative to RIRS in the treatment of kidney stones and even a first-line treatment in patients with urinary diversion.
**Conclusion**

The results of this study suggested that Micoperc was a minimally invasive and effective technique for kidney stone treatment, with low complication rates. We reported a high success rate in situations where ureteroscopy could be challenging (lower calyx stones and urinary diversions) showing that Micoperc could be complementary to RIRS considering its low morbidity, the feasibility in ambulatory cases and the rapid shortening of operating time even in the beginning of the experience.

**Author contributions**

Romain Boissier had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Protocol/project development: Boissier, Negre, Lechevallier.

Data collection or management: Michel, Boissier.

Data analysis: Boissier, Michel, Lechevallier.

Manuscript writing/editing: Boissier, Al-Balushi, Michel.

Other (please specify briefly using 1 to 5 words): critical revision of the manuscript for important intellectual content: Faure, Al-Balushi, Sichez, Gondran-Tellier, Oliva, Delaporte, Gaillet, Akiki, Baboudjian, Karsenty.

**Financial disclosures**

None.

**Ethical statements.**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

**Disclosure of interest**

The authors declare that they have no competing interest.

**References**


