Bleeding Meckel’s diverticulum in adults

also

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Urinary tract infection in patients after renal transplantation: evaluation of risk factors

Life – threatening bleeding nine years after kidney transplantation with Bricker – type ureterointestinal anastomosis

Kidney donor risk index assessment – analysis of current literature
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Kindest Regards,

Michal Wszola MD, PhD
Artur Kwiatkowski MD, PhD

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Meckel's diverticulum (MD) is the most common malformation of the digestive system, due to the incomplete closure of the omphalomesenteric duct. It is usually asymptomatic and less than 6% of patients develop complications. In adults, the most frequent symptoms are bowel obstruction and inflammation, gastrointestinal bleeding is much more common in the pediatric age group. Although symptomatic MD is an uncommon diagnosis after childhood, when observed, urgent diagnosis and surgical treatment is often required. MD preoperative diagnosis may be challenging.

The study reports two cases of gastrointestinal hemorrhage with diagnostic difficulties in identifying a source of pathology, which turned out to be Meckel's diverticulum containing bleeding ectopic gastric mucosa (with gastrointestinal stromal tumor within one of them).

Staggering improvement of noninvasive diagnostic methods, including capsule endoscopy (CE), double-balloon endoscopy (DBE), CT-angiography, Tc-99m pertechnetate scintigraphy, allow for a visualisation of the small intestine and detection of active bleeding source. Nevertheless, there are still cases when all those methods are not sufficient for making a proper diagnosis. Nowadays, explorative laparoscopy, as minimally
invasive, reduced the applications of laparotomy, and is considered as a method of choice in cases with gastrointestinal hemorrhage with undetermined source. Once the underlying pathology has been determined, an exploratory laparoscopy may be also continued as a therapeutic procedure.

Although infrequent, MD should be considered as a possible source of rectal bleeding in adults as well as children. It should be looked for in all cases of an acute abdomen of uncertain etiology. Surgical resection of symptomatic MD shall be the treatment of choice.

BACKGROUND

Meckel’s diverticulum (MD) is the most frequently occurring congenital anomaly of the gastrointestinal tract with the incidence ranging from 0.3% to 1.7% and a male-female ratio of 3:2 (1, 2, 3). MD is located on the antimesenteric border of the ileum, about 40-130 cm proximal to the ileocecal valve. It ensues from the failure of the omphalomesenteric duct to obliterate. Ectopic gastric mucosa is the most frequent finding MD microscopy. This condition is usually asymptomatic and less than 6% of patients develop complications, such as gastrointestinal bleeding, obstruction, diverticulitis, or umbilical abnormalities (4). The majority of symptomatic diverticula arise in the pediatric age group. Although symptomatic MD is an uncommon diagnosis in adults, when observed, emergency surgery is often required. The usual presentation is that of small bowel obstruction or inflammation. Gastrointestinal hemorrhage after childhood is even more infrequent. MD preoperative diagnosis may be challenging. When digestive tract bleeding is massive and cannot be properly controlled by conservative methods, making a precise diagnosis as soon as possible is extremally important. Staggering improvement of noninvasive diagnostic methods over the last decades, including capsule endoscopy (CE), double-balloon endoscopy (DBE), CT-angiography, Tc-99m pertechnetate scintigraphy, has revolutionized the diagnostic approach to the small intestine. The new methods allow for a visualisation of the entire alimentary tract and detection of the source of bleeding. Exploratory laparoscopy, with conditional MD surgical resection, remains a gold standard in emergency situations, that need to be resolved immediately.

AIM

The aim of this study is to evaluate the role of diagnostic laparoscopy for detection and treatment of bleeding Meckel’s diverticulum, basing on two cases of MD containing ectopic gastric mucosa with difficulties in identifying the source of recurrent gastrointestinal hemorrhage.

CASE PRESENTATION 1

In 1988, a 29-year-old male was admitted to emergency department with a history of weakness and abdominal pain, accompanied by multiple bloody diarrhea. His past medical history revealed similar episodes of upper abdominal pain for 3 years. There was no history of medication or drug abuse. Radiological examination of the stomach and duodenum did not show any pathologies. On admission, the patient’s blood pressure was 130/80 mm Hg, pulse 80 beats per minute, haemoglobin concentration was 5.5 g/dl and hematocrit was 28%. On physical examination, he had a soft, flat abdomen with midline rebound tenderness. Digital rectal examination revealed black stool masses. Gas gastroscopy was performed and revealed no abnormalities in upper gastrointestinal tract.

On the second day, patient manifested fever and persistent, severe pain in the right lower abdomen, with guarding and rigidity of abdominal muscles and positive Blumberg sign. Leukocyte count rose from 6.1 L 10^3/mm³ to 9.4 L 10^3/mm³. The patient was scheduled for urgent laparotomy. Appendicitis with a small perforation and local peritonitis was found at surgery. Patient underwent appendectomy, then MD was found approximately 50 cm from the ileocecal valve and resected. The patient made uncomplicated recovery. Postoperative gastroscopy revealed no abnormality in the upper gastrointestinal tract. Histopathological examination confirmed 3.5 cm-long MD with ulceration in heterotopic gastric mucosa and pancreatic tissue nearby.

CASE PRESENTATION 2

In 2014, a 22-year-old male presented to the surgical department with complaints of recurrent abdominal pain and melena. He denied taking any medications. He had not travelled outside of the country recently or eaten unusual or spoiled food. The review of systems was negative. On physical examination, the vital signs were within normal limits. His abdomen was soft, with mild tenderness in the right iliac fossa and nondistended. Normoactive bowel sounds were heard. Rectal examination revealed melena with traces of fresh blood. The admission hemoglobin concentration was 10.0 g/dL with a decrease from 14.0 g/dL from the previous day.

The patient’s past medical history revealed several similar episodes of gastrointestinal bleeding over last 5 years in his native country of Portugal. At the age of 17, he underwent colonoscopy and no abnormality was identified. Afterwards, a 99m-Tc pertechnetate
gamma camera imaging of the abdomen and pelvis revealed a focus of atypical tracer deposition in the right hypogastric region concomitant with the appearance of gastric activity in left hypochondrium. Based on this, MD with ectopic gastric mucosa was suspected. Capsular endoscopy was performed to confirm the diagnosis, but it failed to identify the source of bleeding. During that time the patient had been repeatedly reporting to Emergency Room with complaints of abdominal pain. Further investigation with the use of ultrasonography and double balloon endoscopy did not reveal any pathologies.

Symptoms of digestive tract bleeding recurred in 2013. There were still no abnormalities observed on ultrasonography of the abdomen. Upper gastrointestinal tract endoscopy, reaching the second portion of the duodenum, was negative. Even angiotomography was performed but it was also unsuccessful in identifying any active bleeding. The patient continued to have bloody diarrhea necessitating blood transfusions. Hemoglobin concentration decreased to 7.0 g/dl currently and he had received 4 units of red blood cells concentrate and 2 units of fresh frozen plasma. The real diagnostic dilemma began.

After admission to the ward, another angiotomography scan and gastroscopy were performed, which still revealed no pathology. On the second hospital day, patient was taken to the operating room for an exploratory laparoscopy. Intraoperatively, a 3.5 cm long, 2.5 cm-wide Meckel’s diverticulum was found, located about 60 cm from the ileocecal valve. It was resected with mechanical staplers (fig.1, fig.2). There was blood both proximal and distal to the lesion. The rest of the bowel was explored and did not reveal any signs of inflammation or bleeding. Histopathological examination of the specimen confirmed the presence of MD with bleeding gastric mucosa and totally excised gastrointestinal stromal tumor (GIST) within (fig.3). It was 4 cm in diameter, CD 117 – positive, mitotically inactive (zero per high-power field), with Ki67 index reaching 3% indicating a low relapse risk after resection according to AFIP-NCCN criteria (tab.1)(5). Accordingly, no further oncological systemic therapy with tyrosine kinase inhibitor (imatinib) was offered. Patient was discharged after 3 days with no recurrent episodes of bleeding and no other complications postoperatively.

**DISCUSSION**

The incidence of Meckel’s diverticulum is reported at about 2% among gastrointestinal anomalies of the general population (male more frequent than female, predominantly in the age range between 11-87 months) (3, 6). Just under half of MD are symptomatic in adults. The most frequent symptoms are bowel obstruction (22-50%) and inflammation (20%), bleeding is much more common in the pediatric age group. Digestive tract hemorrhage is reported to occur in 11.8% of all MD, but accounts for 25% of symptomatic cases (7). The majority of patients will develop bleeding symptoms before the age of 20. Past medical history often reveals recurrent gastrointestinal hemorrhage in up to 40% of them.

As per literature, less than 5% of gastrointestinal bleeding originates from small intestine (3). Dumpre et al. reviewed 1489 patients with lower intestinal hemorrhage from 1989 to 1993 and identified 10 cases of bleeding originating from the small bowel (0.7%). Only 4 of them (0.26%) were caused by MD (9). Due to the rarity of cases in adults, the diagnosis of MD may be extremely difficult to arrive at preoperatively. This is particularly true in patients presenting with symptoms other than bleeding. Kusumoto et al. reported a study of 776 patients with MD in which 88% presenting as bleeding had a correct preoperative diagnosis versus 11% with symptoms other than bleeding (10).

MD is an embryonic defect due to the incomplete closure of the omphalomesenteric duct. Since cells lining the yolk stalk are pluripotent, heterotopic mucosa may be present in MD and is responsible for occurrence of complications like hemorrhage, chronic peptic ulceration and perforation. The incidence of heterotopic mucosa reaches 60% of MD cases. The most commonly found is gastric mucosa (61%), pancreatic mucosa (6%), both gastric and pancreatic (5%), jejunal (2%), Brunner’s glands (2%), gastric and duodenal (2%) (11, 12). Bleeding is associated with ectopic gastric mucosa in 96% of cases. In those rare cases of MD diagnosed in adulthood, bleeding is uncommon and often due to perforation of MD itself (13). Main mechanism of bleeding is the acid secretion from ectopic mucosa, leading to ulceration of adjacent ileal mucosa. The pathogenic role of Helicobacter pylori in the development of gastritis and bleeding in the ectopic tissue is still debatable. Also NSAIDs’ effect on it is yet to be proved (3). Heterotopia makes 99m technetium-pertechnetate taken-up by ectopic gastric mucos secreting cells the most commonly performed functional imaging for localization of MD. Although this scan is 85-90% sensitive in diagnosing symptomatic MD in pediatric population, the diagnosis is not readily established in adults (sensitivity up to 60%), as ectopic gastric mucosa is found much less frequently in the diverticulum in this age group (11, 12).

The incidence of heterotopic cells is a predictive factor for the occurrence of neoplastic changes originating from the gastric tissue (14). The tumors within the MD are observed infrequently and are known to occur only in 0.5–3.2% of cases (15, 16). Most of them are benign tumours like leiomyomas, angiomas and lipomas. Malignant neoplasms include adenocarcinoma, sarcoma, carcinoid tumour and gastrointestinal stromal tumor (GIST). GISTs are rare neoplasms which account for 0.1–1% of gastrointestinal malignancies. The majority of GISTs (60% to
70%) have been reported to arise in the stomach, whereas 20% to 30% originate in the small intestine, and less than 10% in the esophagus, colon and rectum. They also occur in the extra-intestinal abdominopelvic sites such as the omentum, mesentery, or retroperitoneum. GISTs arising from Meckel’s diverticulum are extremely rare. However, 12% of all neoplasms arising within MD turn out to be GIST (14). The most common presentation of a neoplasm of MD is intussusception followed by melaena (17, 6). With regard to GIST molecular markers, detection of Ki-67 and CD117 is routinely performed. The Ki-67 protein exists in actively proliferating cells. Ki-67 index reflects the proportion of cycling cells in a given population. Certain studies have reported that Ki-67-positive expression is closely associated with aggressive biological behaviour of tumor cells. Whereas, CD117 has been found to be located at the tumor cell membrane and cytoplasm and the positive rate recorded was up to 95% in GISTs. CD117-negative expression is believed to be associated with an early postoperative GIST recurrence (19). Other neoplasms arising from the gastrointestinal tract, including lipoma, leiomyoma, leiomyosarcoma are typically CD117 – negative.

Nowadays, progress in diagnostic methods, including DBE and CE, provides the opportunity for improved small intestine visualisation and identification of a source of active bleeding. Nevertheless, there are still cases where those methods are not sufficient for obtaining a diagnosis. Because of the distance between the diverticulum and the ileocecal valve (ranging from an average distance of 34 cm in children (<2 years) to 67 cm in adults), a typical colonoscope cannot usually reach the part of small intestine in which MD is located. It is usually impossible to diagnose bleeding from MD during colonoscopy, except in cases with bleeding seen distally to the ileocecal valve. Capsular endoscopy may be indicated for patients with gastrointestinal blood loss when other diagnostic methods such as upper and lower endoscopy have failed to localize the source of bleeding (18). There were only few cases of detecting MD after capsular endoscopy in adults reported in the literature. The method is especially dedicated to the pediatric age group. CE and DBE can play complementary roles in preoperative diagnosis of bleeding MD. Detection rates of abnormalities in small intestine range from 65% for CE to 53% for DBE (20). As the source of bleeding can not be indentified by endoscopy, angiography with 99mTc-labelled red blood cells can be performed. Traditional CT scans are usually unhelpful in diagnosing MD because of difficulty in distinguishing it from intestinal loops. Angiography can show the bleeding site but it can be negative in patients with intermittent bleeding. Animal studies have demonstrated that a bleeding rate of 0.5 mL/min is necessary in order for angiography to be positive (21).

As in the reported cases, an explorative laparotomy has been preferred for patients with symptoms either of an acute abdomen of uncertain etiology or a digestive tract bleeding of long duration. Despite the passing of time, surgery is still the procedure of choice when the diagnosis is not available via clinical diagnostic methods or when doubts remain. With the increasing availability of sophisticated imaging modalities and other investigative techniques, the indications for and scope of exploratory laparotomy have shrunk over time. The increased availability of laparoscopy as a minimally invasive means of inspecting the abdomen has further reduced the applications of exploratory laparotomy. Once the underlying pathology has been determined, an exploratory laparoscopy may also be continued as a therapeutic procedure. It is worth noting that surgical resection is the only way to unambiguously confirm the diagnosis via histopathological examination.

CONCLUSIONS

Meckel’s diverticulum requires a high level suspicion. Although rare, MD should nevertheless be considered as a possible source of bleeding in adults as well as children. Hemorrhage is generally associated with the presence of ectopic gastric mucosa. The character of heterotopic cells also is a predictive factor for the occurrence of neoplastic changes. MD should be looked for at laparotomy in cases of acute abdomen. Even the use of several up-to-date diagnostic methods does not provide certainty of correct diagnosis in some cases. Then, exploratory laparoscopy with surgical resection remains the method of choice for not only recognition but also treatment at the same time, as minimally invasive, quicker and more efficient in comparison to laparotomy.

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<table>
<thead>
<tr>
<th>mitotic activity</th>
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<th>duodenum</th>
<th>jejunum or ileum</th>
<th>rectum</th>
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<tr>
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<td>&gt;10 cm</td>
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HPF - high power field (× 400)
The impact of kidney weight to recipient weight ratio (Kw/Rw) on kidney graft function after transplantation

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ABBREVIATIONS Kw/Rw-kidney weight to recipient weight, eGFR-estimated glomerular filtration rate, DGF-delayed graft function, AR-acute rejection, BMI-body mass index, ICU-intensive care unit, ECD-expanded criteria donors, HLA-human leukocyte antigen, CIT-cold ischemia time, KTx-kidney transplantation, CsA-cyclosporin A, BSA-body surface area.

ABSTRACT

Background: Kidney transplantation is the best method of renal replacement therapy. Recent studies assess the suitability of kidney selection for a recipient based on kidney weight to the recipient weight ratio (Kw/Rw). Low ratio can indicate insufficient nephron mass for the recipient. The aim of this study was to calculate Kw/Rw ratio useful to evaluate kidney function until one year post surgery. Materials and Methods: In the years 2010 – 2011 at the Department of General and Transplantation Surgery in Warsaw 262 kidney transplantations were performed. We retrospectively analyzed a group of 103 patients who underwent the transplant procedure from a deceased donor. Collected data considered delayed graft function, acute rejection episodes, creatinine, recipient survival and one year graft survival. Kw/Rw ratio was calculated for all of them. Recipients were divided into two groups: group low-ratio (n=36; Kw/Rw ratio<4,29 g/kg), group high-ratio (n=67; Kw/Rw ratio...
Progressive kidney failure leads to end-stage renal disease (ESRD). The number of patients suffering from ESRD is increasing worldwide reaching almost 600 million. In Poland, 4 million people suffer from various stages of renal failure [1]. The best renal replacement therapy (RRT), resulting in lower morbidity and mortality rates and improved quality of life for patients with ESRD is kidney transplantation (KT). Moreover, renal transplantation therapy (RTT) is a more cost-effective therapy in comparison to hemodialysis or peritoneal dialysis for patients with chronic kidney disease [2,3]. In 2011, according to Poltransplant’s statistics, there were 2623 people on the National Waiting List for Kidney Transplantation; transplantation was performed in 1074 patients, 998 of whom received a kidney from a deceased donor [4]. Worldwide, there are still not enough donors as compared to the number of recipients. Kidney retrieval from Expanded Criteria Donors [5] or living donors [6] is a possible route to overcome this organ shortage. On the other hand, better graft matching to the recipient is an important aim of contemporary transplantation. The aim is to prolong organ survival time and satisfactory kidney function. Graft function and its survival depend on many immune and non-immune factors. Recent studies, based on kidney weight and recipient weight ratio (Kw/Rw), have assessed the suitability of kidney-recipient matching. This ratio in an adult healthy person has a value of 7g/kg. Low Kw/Rw ratio can indicate insufficient nephron mass for recipient weight, which may lead to hyperfiltration, hypertension and proteinuria [7, 8, 9]. As a result, glomerulosclerosis can develop and the risk of graft rejection is increased [7,8,9]. The aim of the study was to assess, how the ratio kidney/recipient and transplanted nephron mass affect one year graft survival.

MATERIAL AND METHODS

Between January 2010 and December 2011, 262 kidney transplantations were performed in our center. Kidneys were procured from living related donors – LRD (22/262; 8.4%) and deceased donors – DD (240/262; 91.6%). Two hundred twenty DD kidneys were kept in LifePort (Organ Recovery, Itasca, IL, USA) or MOX-100 (Waters Instruments, Rochester, MN, USA) machine perfusion prior to transplantation. The remaining 20 DD kidneys were kept in cold storage.

Demographic, clinical, and laboratory parameters of donors (age, sex, BMI, number of days on ICU, cardiac arrest, hypertension, number of ECD, creatinine level, cause of death) kidney grafts (CIT, weight, preservation methods) and recipients (weight, age, sex, dialysis before transplantation-time and method, HLA matching, immunosuppression) were recorded. Patients were assessed in terms of delayed graft function and acute rejection episodes, creatinine level on 7th, 28th, 180th, 360th day after KTx, eGFR, proteinuria, also hospitalization time and recipient and kidney survival, until one year after transplantation. Data were collected retrospectively. Kidney weight prior to transplantation and recipient’s weight were obtained for 103 kidneys and recipients.

Kw/Rw Ratio

For every recipient Kw/Rw ratio was calculated ([kidney weight (g)/recipient weight (kg)]). Recipients were retrospectively divided into two groups: group low-ratio (n=36; ratio<4,29 g/kg) and group high-ratio (n=67; ratio >4,29 g/kg).

Expanded Criteria Donor

was defined accordingly to the Organ Procurement and Transplantation Network (OPTN) / United Network for Organ Sharing (UNOS) definition. Donors aged 60 years old or older, or 50 years old or older with at least two out of three following conditions: history of arterial hypertension, serum creatinine levels >1.5 mg/dL, cause of death from a cerebrovascular incident were considered ECD. All others donors were SCD. Delayed graft function (DGF) was recognized as a need for dialysis in the short term (7 days) following kidney transplantation regardless of reason (hyperkalemia, high serum urea concentration, hyperhydration). Primary Non-Function (PNF) was defined as permanent loss of graft function immediately after transplantation. Acute rejection (AR) was biopsy proven and diagnosed according to Banff 2009 criteria. Cold Ischemia Time (CIT) was recorded as the period between in situ perfusion and vascular anastomosis.

Imunosuppression treatment

Triple drug immunosuppression is standard therapy in our center. Cyclosporine or tacrolimus, myco- phenolate mofetil, and steroids were the primary immunosuppressive agents. All recipients were administrated 500 mg of intravenous steroids just before restoration of blood flow to the allograft, and intake of steroid was maintained at a dose of 20 mg per day gradually decreasing to 5 mg at 3 weeks following KTx. Cyclosporine or tacrolimus therapy was also started immediately just before surgery,
with dosage subsequently adjusted to maintain a trough concentration of 200–300 nanograms (ng) per mL or 10–12 ng per mL, respectively. Induction immunosuppression (basiliximab or thymoglobulin) was administered in cases of second transplantation, panel reactive antibodies (PRA) above 20%, 4 or more mismatches.

**Kidney storage and preparation**

All kidneys in the study groups (n=103) were kept in LifePort (Organ Recovery, Itasca, IL, USA) or MOX-100 (Waters Instruments, Rochester, MN, USA) machine perfusion prior to transplantation. Following pre-operative bench surgery, all kidneys were weighed on an electronic scale.

**Statistical Analysis**

Short and long-term outcomes of transplantation were compared using Student t-test (statistically significant p<0.05). Creatinine values were represented by linear regression. Continuous variables were expressed by the mean value and standard deviation. The correlation between the kidney and donor weight was verified by the Pearson's correlation coefficient.

**RESULTS**

**Kw/Rw Ratio**

Mean Kw/Rw Ratio in low-ratio group was 3.5 g/kg vs. 6.06 g/kg in high-ratio group (p<0.00001). Recipients’ characteristics of both groups are presented in table 1. The recipient with low-ratio group had mean weight about 77 kg, compared to mean 67 kg of body weight in high-ratio group (p=0.00062). Kidney mass in the low-ratio group was about 266.4 g compared to 398.7 g in the high-ratio group: 398.7 g (p<0.001). There were no differences in HLA matching, immunosuppression treatment, duration and type of RRT prior to transplantation (tab.1).

**Donors’ characteristics**

The most common cause of donor’s death was cerebrovascular accident (53% donors). Characteristics of donors in both groups are presented in table 2. Except BMI, there were no differences in donors’ data between the groups.

**Post-transplant results**

Mean surgery time did not differ between the groups and was 170±48 min vs. 178±48 min in high-ratio and low-ratio groups, respectively (p=0.4). Mean Cold Ischemia Time was 29,2±6.5 h vs.27.5±6.9 h in high-ratio and low-ratio groups (p=0.24). Delayed Graft Function occurred more often in low-ratio group (Fig.1). Mean serum creatinine concentration was significantly lower for high-ratio group during almost the whole first year following transplantation (Fig.2), although one year graft survival was similar in both groups: 98% vs 97% in high-ratio and low-ratio respectively (p=0.68). One-year patients’ survival was identical in both groups and was 100% vs 100% in high-ratio and low-ratio group respectively. Interestingly, acute rejection rate within the first year was higher in the low-ratio group – 30% (11/36) vs. 15% (10/67) in the high-ratio group (p=0.075), although it did not reach a significant value.

**DISCUSSION**

Numerous authors have found an impact of Kw/Rw ratio on early and late graft outcomes (creatinine, DGF, AR and proteinuria). [10 – 20]. In our analysis we have found a significant impact of Kw/Rw ratio on creatinine level up to one year and DGF. AR episodes were more frequent in the group of patients with low-ratio although this did not reach statistical value. Nevertheless it did not have an influence on one-year graft and patients’ survival. In our study, donor’s and recipient’s BMI significantly differed between the groups. In view of this data it can be noticed that in the group with low-ratio a small kidney, from small donor was received by heavier and taller recipient, whereas in the high-ratio group, larger kidney from heavier donor, went to a smaller recipient. Patients who received smaller kidneys and had an inadequate number of nephrons, also had a higher incidence of DGF and higher level of creatinine up to one year. The risk of hyperfiltration development is high in such patients. It may bring hypertension (although not observed in our patients). Nevertheless it may potentially influence patient and graft survival [21]. Luyckx and Brenner found a strong correlation between congenital deficit in nephron number and hypertension and kidney diseases in adults [22]. Hyperfiltration may result in glomerulosclerosis and in further insufficiency of transplanted organ. Generally, most of the publications have found association between low Kw / Rw ratio and long-term kidney function - kidney parenchyma deficiency results in slow graft damage (hyperfiltration->inflammation->glomerulosclerosis) [13,19,23,].

As mentioned above, Kw/Rw ratio in a healthy adult person is 7g/kg approximately. Values of the ratio appearing in the literature ranged from about 2.3 g/kg to 4.5 g/kg[13, 18]. In our study, the limit value was 4.29 g/kg. Mean ratio in a group of patients with better functioning grafts was 6.06 g/kg and mean ratio in a group with worse functioning grafts was 3.5 g/kg.

With reference to the conclusion based on better functioning of larger kidney in the recipient, there are also studies denying this relationship. After receiving large kidneys, small patients needed time to adapt the blood flow to the size of the kidney, that may
result in worse graft functioning and, eventually, rejection [24]. Similar results were obtained in the study on kidney transplantation from adults to children. The large kidney transplanted into the small recipient was associated with graft ischemic injury [25]. Such results could be associated with a large disparity between the kidney size and the recipient weight. It should also be mentioned that there are studies with no evidence proving that the size of the graft influences the outcome of kidney transplantation. In another study on kidney transplantation from adult to children, it was shown that much larger kidneys can be successfully transplanted into children. The results of these transplantations were comparable to those where the donor had been selected by size to the recipient [26].

In our study, Kw/Rw ratio impacts graft function, with no effect on graft and patient survival up to one year post transplantation. It is an independent predictor of renal function, therefore may be considered an additional differentiating factor in donor-recipient matching. The most reliable surrogate for nephron mass is kidney weight [19, 27]. However, weighing kidneys is not very useful in practice due to the fact that it is performed during the transplantation. That is the reason why using the kidney size as a one of matching parameters is inconvenient. Therefore, the other surrogates for the number of nephrons, such as Body Surface Area, BMI, renal volume [17, 28, 29], assessment of renal size by ultrasound [14, 30] should be taken under consideration. These methods are much more useful in practice because of the possibility of using the obtained data for donor-recipient matching.

Discrepancies in study results, showing the influence of Kw/Rw ratio on graft function, should stimulate studies of larger populations. Such differences occur probably due to the insufficient number of examined patients and the variety of groups, also due to the usage of various nephron mass surrogates. Taking kidney’s size in kidney-recipient matching into consideration can be the next step to improve results in kidney transplantation.

CONCLUSIONS

Patients who have received insufficient nephron mass at transplantation are more likely to experience delayed graft function, acute rejection and worse kidney function. Kidney mass is an important non-immunological determinant of renal transplant function.

ACKNOWLEDGEMENTS

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MEDtube Science Sep, 2014; Vol.II (3); 13-17.

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Tab. 1. Recipient factors related to kw/rw ratio
Tab. 2. Deceased donors’ analysis

TABLE 1. RECIPIENT FACTORS RELATED TO KW/RW RATIO

<table>
<thead>
<tr>
<th>Recipient factors</th>
<th>Low-ratio (n=36)</th>
<th>High-ratio (n=67)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51 ± 13,74</td>
<td>48 ± 14,07</td>
<td>0.23</td>
</tr>
<tr>
<td>% male</td>
<td>77,8%</td>
<td>58,2%</td>
<td>0.038</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>25,56 ± 3,39</td>
<td>23,78 ± 3,67</td>
<td>0.01</td>
</tr>
<tr>
<td>Time on dialysis prior to KT (months)</td>
<td>40 ± 28</td>
<td>47,4 ± 42</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>80%</td>
<td>90%</td>
<td>0.3</td>
</tr>
<tr>
<td>HLA mismatch</td>
<td>3,66 ± 1,12</td>
<td>3,41 ± 1,01</td>
<td>0.27</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>11,1%</td>
<td>10,4%</td>
<td>0.91</td>
</tr>
<tr>
<td>Induction therapy (%)</td>
<td>25%</td>
<td>26,8</td>
<td>0.83</td>
</tr>
<tr>
<td>Triple-drug immunosuppression</td>
<td>100%</td>
<td>100%</td>
<td>1.0</td>
</tr>
</tbody>
</table>

TABLE 2. DECEASED DONORS’ ANALYSIS

<table>
<thead>
<tr>
<th>Deceased donor factors</th>
<th>Low-ratio (n=36)</th>
<th>High-ratio (n=67)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44,4 ± 17,9</td>
<td>45,9± 14,1</td>
<td>0.67</td>
</tr>
<tr>
<td>% ECDs</td>
<td>30,5%</td>
<td>28,3%</td>
<td>0.81</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>5,08 ± 3,2</td>
<td>4,7 ± 2,57</td>
<td>0.17</td>
</tr>
<tr>
<td>Creatinine level (mg/dl)</td>
<td>1,56 ± 1,16</td>
<td>1,98 ± 1,63</td>
<td>0.13</td>
</tr>
<tr>
<td>% Hypertension</td>
<td>17%</td>
<td>28%</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean BMI (kg/m2)</td>
<td>23,8 ± 2,91</td>
<td>25,6 ± 4,1</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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Fig. 1. Incidence of DGF between the groups
Fig. 2. Mean creatinine concentration

FIGURE 1. INCIDENCE OF DGF BETWEEN THE GROUPS
FIGURE 2. MEAN CREATININE CONCENTRATION

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Occult breast cancer: a challenging diagnostic and therapeutic problem

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\textbf{RUNNING TITLE} Occult breast cancer

\textbf{KEYWORDS} Occult breast cancer, axillary lymph node metastasis, T0N+ breast cancer, prognostic factors, overall survival

\textbf{WORD COUNT} 1 721

\textbf{CONFLICT OF INTERESTS} no conflicts of interest

\section*{INTRODUCTION}

Breast cancer (BC) is a major oncological problem in developed countries and also an increasing problem in developing countries. In European Union countries, BC was diagnosed in over 330 000 women in 2008 and 89 000 women died due to BC. In Poland, approximately 16 000 women were diagnosed with breast cancer and over 5000 women died due to breast cancer in 2010. The incidence of breast cancer increases with age reaching its peak at 50-59 years. Eighty per cent of breast cancer occurs after the age of 50. The increase in mortality persisted in Poland until the mid-80s, followed by a stabilization of mortality rate at 15-16/105. Since the mid-90s of the last century there is a continuing decrease in mortality from breast cancer [1].

The recent decades have seen a rapid increase in the rate of diagnosed early breast cancer [2]. Despite improvement in BC diagnosis and treatment methods, occult breast cancer still remains a clinical problem. Occult breast cancer (OBC) is defined as isolated metastatic axillary lymphadenopathy with no palpable mass in the breast and no signs of primary breast cancer on mammography and no detected primary tumor outside the breast [3, 4]. It is classified by the American Joint Committee on Cancer as T0N1-3M0 stage II-III [5]. Breast cancer presenting as axillary adenopathy with clinically occult breast tumor was first described by Halsted in 1907 [6]. It is a rare presentation of the disease, accounting for 0.3-1\% of all breast cancers [7]. On the other hand, less than 3\% of metastases to the axilla originate from non-mammary sites [8]. The most common solid tumor is carcinoma (58\%), followed by melanoma (22\%) and sarcoma (20\%). Among carcinomas, the most frequently encountered are lung, skin, stomach and ovary [9]. However, these metastases are rarely the first signs of disease [10]. The natural history of occult primary breast cancer remains unclear [11]. Prospective randomized trials have not been performed because of the scarcity of the patients [4]. National Comprehensive Cancer Network (NCCN) guidelines recommend magnetic resonance imaging (MRI) for...
these patients to identify neoplasms that are not identified on clinical examination or mammography. The current treatment options for T0N+ breast cancer conform to NCCN guidelines and include mastectomy with axillary lymph node dissections (ALND) with or without post-mastectomy radiation (BR) or ALND with whole-breast irradiation with or without lymph node irradiation [12].

With regard to non-occult breast cancer, the most important prognostic factors are: tumor size, histological type and grading, number of metastatic axillary lymph nodes, estrogen and progesterone receptor expression, infiltration of peritumoral lymphatic vessels and veins, HER2 status and assessment of the degree of proliferation based on Ki67 index [13]. However, there is no consensus regarding the prognostic factors of occult breast cancer [14].

**DISCUSSION**

Despite the improvement in investigative techniques, such as mammography, ultrasound and magnetic resonance imaging (MRI), occult breast cancer still poses a diagnostic and therapeutic challenge. Additionally, there is no consensus regarding the prognostic factors of OBC [14].

National Comprehensive Cancer Network guidelines recommend magnetic resonance imaging for identification of occult breast lesions that are not identified on clinical examination or mammography. MRI has high sensitivity for detection of cancer (range 94-100%) [15]. However, specificity has generally been lower and more variable and ranges from 37% to 97% [16]. In addition, magnetic resonance imaging is able to detect lesions that are not visible by conventional techniques, including mammography, ultrasonography, and physical examination, in 10-39% of cases [17]. Suspicious lesions detected by MRI must be confirmed histologically due to its low specificity [18].

NCCN guidelines recommend that women with T0N+ breast cancer receive the same treatment as patients with similarly staged cancer and an identified (T+) primary breast tumor [12]. Prospective randomized trials have not been performed because of the scarcity of the patients. Based on a retrospective study, overall survival (OS), disease-free survival (DFS) and cause-specific survival (CSS) among groups of patients who were treated with different methods has been compared. There have been reports that any treatment of the ipsilateral breast, including breast conserving therapy (BCT), mastectomy, or axillary lymph node dissection (ALND), can improve survival rates compared with nontreatment [4, 19, 20]. It was found that patients who underwent mastectomy had better OS and DFS compared with patients who had no local treatment [19]. However, mastectomy did not improve CSS compared with BCT [4].

Ping at al. [21] have compared the clinical characteristics between occult and non-occult breast cancer and observed that patients with OBC were significantly older than patients with non-OBC and estrogen receptors (ER) positive rate of OBC was lower. Furthermore, no significant difference was noticed in 5- and 10-year survival rate between OBC and stage III non-OBC patients.

Wang et al. [19] analyzed retrospectively 51 patients with OBC from 1990 to 2003 at a single institution. Among 51 patients, 38 patients received mastectomy and 13 patients had no local treatment of the breast. Disease-free survival was significantly increased in patients who had mastectomy compared with patients who had no local treatment of the breast (76 vs. 23 months, p<0.001). It was also found that patients who underwent mastectomy had better overall survival compared with patients who had no local treatment (p<0.001). The recurrence rate for breast cancer patients who had undergone a mastectomy and who had been only observed was 26% and 77%, respectively.

Montagna et al. [22] reviewed information on 15 490 consecutive primary breast cancer patients, who underwent surgery at the European Institute of Oncology between 1997 and 2008. In this study, patients with OBC were compared with an equal number of patients with small invasive breast carcinomas (pT1) observed at the same institution during the same period, matched for year of surgery, age, nodal status and biological features. There was no significant difference in the disease-free survival (5-years DFS 66 vs. 68% p=0.91) and the overall survival (5-years OS 80 vs. 86% P = 0.99) between the OBC and control groups. A statistically significant worse outcome was observed within the group of OBC for patients with more than four involved lymph nodes (T0N2, T0N3) and with triple negative tumors. High risk of relapse and death was observed in OBC patients with triple negative tumors and extensive nodal involvement. Walker et al. [4] suggest that treatment with radiation and axillary lymph node dissection (ALND) may be an appropriate alternative to mastectomy for T0N+ breast cancer. The cause-specific survival (CSS) and overall survival (OS) of women with T0N+M0 ductal, lobular, or mixed breast cancer, who were treated between 1983 and 2006, were analyzed. The retrospective study included 750 out of 770 030 patients (incidence, 0.1%) with T0N+M0 disease. Of 750 patients, 276 patients underwent mastectomy (36.8%), 336 patients received radiation therapy (RT), and 220 patients received neither of these treatments (29.3%). In total, 596 patients underwent ALND (79.5%). In this group, 126 patients underwent ALND only (21.1%), 188 patients underwent mastectomy (31.5%), 202 patients received RT (33.9%), and 80 patients both underwent mastectomy and received RT (13.4%). Patients who received less than optimal locoregional therapy according to NCCN guidelines had worse outcomes. Specifically, the patients who
underwent breast conserving therapy or mastectomy had 10-year OS rate of 64.9% compared with 58.5% for patients who underwent ALND only (p=0.02) and 47.5% for patients who underwent observation (p=0.04). The 10-year CSS rate for patients who underwent breast conserving therapy or mastectomy was 74.6% compared with 71.2% for patients who underwent ALND only (p=0.09) and 71.9% for patients who underwent observation (p=0.69). In multivariate analysis of CSS for patients who underwent mastectomy or breast conserving therapy, the following factors were correlated with an unfavorable outcome: positive estrogen receptor status, ≥10 positive lymph nodes, and <10 resected lymph nodes. Mastectomy did not improve CSS when compared to breast conserving therapy (p=0.79).

He et al. [14] evaluated the treatment outcomes and prognostic factors in patients with occult breast cancer. The investigators retrospectively analyzed 95 patients with OBC who were treated between 1998 and 2010. Of the 95 patients, 64 underwent mastectomy plus ALND with or without post-mastectomy radiation (Mast + ALND group), 13 underwent ALND followed by ipsilateral breast radiotherapy (BR + ALND group) and the remaining 18 were treated with ALND (ALND group). The median follow-up was 38.2 months (range: 4-160 months). Patients who underwent Mast + ALND or BR + ALND had significantly improved rates of locoregional recurrence-free survival (LRFS), recurrence/metastasis-free survival (RFS) than patients who only underwent ALND (p<0.05). There were no significant differences in the LRFS (p=0.718), RFS (p=0.935) and breast cancer-specific survival (BCSS) (p=0.991) rates between the patients who underwent Mast + ALND compared with those who received BR + ALND. Multivariate analysis revealed that patients with four or more involved lymph nodes had significantly worse outcomes (p=0.042 for BCSS and p=0.038 for RFS).

The overall survival (OS) and prognostic factors associated with OBC were evaluated in a study in Korea [23]. The retrospective study included 142 out of 85,733 patients (incidence, 0.17%) with T0/TxN-1-N3M0 disease, who were treated between 1990 and 2009. Authors claim that it is the largest series published comparing the prognosis of OBC patients to that of patients with T1N1-N3 disease. The median follow-up was 78 months (range, 15-198 moths). Overall, 32 patients (22.5%) underwent ALND only (ALND only group), 56 patients (39.4%) had breast conserving surgery (BCS) with ALND (BCS + ALND group) and 54 patients (38.0%) received mastectomy with ALND (Mast + ALND group). Of the 56 patients who underwent BCS with ALND, 83.9% received subsequent radiotherapy, and among 54 patients who underwent mastectomy with ALND, 38.9% received radiotherapy. No significant differences in OS were observed between patients undergoing ALND only (80.8%), BCS with ALND (98.0%), and mastectomy with ALND (92.5%). Nodal status was a significant prognostic factor (p=0.004) on univariate analysis. When compared with T1 patients group, T0/TxN1 patients showed better survival than T1N1 patients (HR-0.253; p=0.003), but T0/TxN2, T0/TxN3 patients showed similar survival to T1N2, T1N3 patients (HR-0.557 and HR-1.104, respectively; p=0.186 and p=0.822, respectively). In this series, the 10-year OS of OBC patients was 88.03%.

CONCLUSIONS
Occult breast cancer still remains a clinical problem. Patients who receive less than optimal locoregional therapy according to NCCN guidelines have worse outcomes. Definitive locoregional treatment with either mastectomy or breast conserving therapy improved outcome of patients with T0N+ breast cancer. Nodal status is a significant prognostic factor with regard to occult breast cancer.

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Urinary tract infection in patients after renal transplantation: evaluation of risk factors

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Standard Antibiotic Prophylaxis, which appears to be over-aggressive, can lead to colonization by microorganisms resistant to treatment, so identifying relevant perioperative UTI risk factors is crucial for optimizing prevention strategies in individual patients.

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Urinary tract infection in patients after renal transplantation: evaluation of risk factors

KEYWORDS
kidney transplantation, urinary tract infections, standard antibiotic prophylaxis, risk factors

WORD COUNT
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CONFLICT OF INTERESTS
no conflicts of interest

ABBREVIATIONS
CFU – colony-forming units
DDs – deceased donors
DGF – delayed graft function
ECDs – extended criteria donors
eGFR – estimated glomerular filtration rate
ESBL - extended spectrum β-lactamase producer
ESBL (+), extended spectrum β-lactamase positive;
ESBL (-), extended spectrum β-lactamase negative;
HLA – human leukocyte antigen
HLAR – high-level aminoglycoside-resistant strains of enterococci
IGF – immediate graft function
KTx – kidney transplantation
MBL (+), metallo-β-lactamase - positive,
MBL (-), metallo-β-lactamase - negative;
MDR – multi-drug resistant
MVL – metallo-β-lactamases
NODAT – new-onset diabetes after transplantation
PRA - Panel Reactive Antibody
SAP – standard antibiotic prophylaxis
UTI – urinary tract infection
VRE – vancomycin-resistant enterococci
ABSTRACT

Background: Kidney transplantation is currently the best method of renal replacement therapy in patients with chronic renal failure. A common complication in renal transplantation patients is urinary tract infection (UTI). We assessed UTI risk factors in kidney recipients from deceased donors and its impact on graft function and survival.

Material and Methods: Retrospective analysis was applied to a group of 220 patients who underwent the transplant procedure in 2010 and 2011. Patients were divided into two groups: patients diagnosed with UTI in the first month post-transplant (n=55) and patients without UTI (n=165).

Results: Statistically significant risk factors for increased UTI included receiving a kidney from a donor with expanded criteria, lower flow in the fourth hour of mechanical perfusion (<120 ml/min), lower HLA compatibility (>4 mismatches), operation time (<200 min), the occurrence of delayed graft function, post-transplantation diabetes mellitus, and urological complications after transplantation. Patients with UTI experienced a significantly prolonged hospital stay (28 days vs. 15 days, p=0.01). Factors such as gender, age, body mass index, duration of dialysis in the recipient, length of surgery, type of immunosuppression used, and one-year graft survival rates did not differ between the two groups.

Conclusions: ECD donor, 4 and more mismatches in HLA compatibility, long surgery time and lack of IGF are the predicting pre-transplant factors of UTI. Analyzing known risk factors before transplantation, (with reference to factors possible to occur after Tx) could determine how UTI prophylaxis is to be administered.

BACKGROUND

Kidney transplantation (KTx) is currently the best method for treating patients with end-stage renal disease (1,2), although burdened by possible complications such as hemorrhage, urinary fistula, lymphocele (3), infections, including urinary tract infections (UTI) as the most common (4,5), accounting for approximately 40-65% of all infectious complications and often leading to morbidity and allograft failure (6,7,8). Incidence of UTI in patients in the first year after KTx ranges from 20% to 76%, depending on the transplant center (9,10,11,12). Variation in reported incidence may be due to differences in follow-up time, population studied and in definitions in UTI detection (13,14). UTI which occurs in the first month after transplantation is evaluated to vary from 2,3% – 56,7% (5,14,15,22-27). Because each clinical center applies its own prophylactic regimen to KTx patients, it is unclear if established standard antibiotic prophylaxis (SAP) and empirical testing methods are universal to all patient populations (15). SAP, which appears to be over-aggressive, can lead to colonization by microorganisms resistant to treatment (5), so identifying relevant perioperative UTI risk factors is crucial for optimizing prevention strategies in individual patients. Although the duration of SAP in KTx patients has not been standardized, there is a current trend toward a decreased use of antibiotic prophylaxis for renal transplantation. In this study, we defined the incidence of UTI in patients after renal transplantation, assessed the prevalence and nature of UTI by identifying its risk factors, and identified a group of recipients who could avoid extensive SAP based on the presence or absence of these risk factors.

MATERIAL AND METHODS

Kidney transplant data collection

262 KTx were performed at the Department of General and Transplantation Surgery, Warsaw Medical University, between January 2010 and December 2011. Kidneys procured from living related donors were excluded from further analysis and accounted for 8.4% (22/262). Deceased donors (DDs) represented 91.6% of the total (240/262). From DDs, 220 kidneys were maintained in LifePort (Organ Recovery, Itasca, IL, USA) or MOX-100 (Waters Instruments, Rochester, MN, USA) machine perfusion prior to the transplantation. The other 20 kidneys from DDs, stored in simple hypothermia, were excluded from the observation. Records from the 220 allograft recipients were analyzed, and we determined the incidence of UTI in these patients during the first month after transplantation (early UTI).

We retrospectively, collected demographic and clinical data for the 220 patients, including age, gender, cause(s) and duration of end-stage renal disease, comorbidities, and intraoperative plus post-transplantation parameters. We also considered donor sources (extended criteria donor (ECD) or standard criteria donor), body mass index, the donor’s cause of death, length of stay in the intensive care unit, positive microbiological cultures from the donors, perfusion parameters, and surgical procedure information, such as total duration and cold ischemic time. Additionally, all UTIs detected at our center were nosocomial, as it is required for the kidney recipients to be free from any urinary infection before transplantation. All recipients, prior to being placed on the waiting list for Tx must have three sterile urine cultures.

Immunosuppression protocol

Immunosupresion therapy was based on three-drug protocol, during one-year follow up period - calcineurin inhibitors (tacrolimus or cyclosporine) combined with prednisolone and mycophenolate mofetil or mycophenolate sodium. Tacrolimus or cyclosporine was administered at 0.2 mg/kg or 10 mg/kg per day, respectively, starting with a half-dose on the day
of transplantation with individually-adjusted doses based on tested blood levels. Mycophenolate mofetil or mycophenolate sodium were administered twice a day in 1.0g or 720mg doses. Intravenous prednisolone was given on the day of surgery: 250 mg during anastomoses and 125 mg over 12-24 h. Twenty milligrams prednisolone was given orally on the third post-operative day, followed by a decrease to 10-15 mg by the end of the month and 5 mg by the end of the year. Induction immunosuppression (basiliximab or thymoglobulin) was administered in cases of second transplantation, PRA (Panel Reactive Antibody) above 20%, 4 or more mismatches.

**Surgical methods**

Transplantation procedures were performed using standardized techniques. All recipients had their hair removed from the surgical field with a razor. Before placing a Foley catheter into the bladder, the recipient’s skin was prepared using an Octenisept solution (Octenidine dihydrochlorid 0.1g, 2-Phenoxyethanol 2.0g). The kidney graft was placed retroperitoneally in the iliac fossa and the ureter was anastomosed to the recipient’s bladder using the Lish-Gregoir or MacKinnon techniques, depending on the surgeon’s preference. A double-J catheter was not routinely placed.

**Standard antibiotic prophylaxis (SAP)**

Depending on their daily diuresis (<1 L/day or >1 L/day), patients received a dose of 1.0g or 2.0g ceftriaxone prophylactic antibiotic, respectively, within 30 min prior to transplantation. This therapy was continued for another 72 h, but then discontinued if decreasing white blood cell and C-reactive protein levels were observed and no signs of inflammation present, as well as no other complications such as hematoma, lymphocele, or urinary leakage. Increasing the dosage or duration of antibiotic therapy was considered post-operatively when signs of infection were detected. To prevent Pneumocystis iiroveci infection, trimethoprim-sulfamethoxazole was administrated (480mg/day) beginning on the fourth post-operative day, continued for 3 months post-transplantation. No sulfa-allergies occurred among the studied group.

Diagnosis and treatment of post-operative UTIs

The development of UTI as a primary outcome was defined. For the transplantation procedure patients with sterile urine culture (data obtained from the national register of patients for organ-transplantation – Statutory Transplant Registers). A positive UTI in a kidney recipient was defined as the presence of 10-16 white blood cells/high power field and more than 100,000 colony-forming units (CFU) of pathogenic microorganisms per milliliter of urine. Clinical signs of urinary infection, such as fever, urinary urgency and frequency, dysuria, and suprapubic tenderness were also used to diagnose UTIs. Asymptomatic cases were diagnosed only using a positive urine culture (more than 100,000 CFU of pathogenic microorganisms per milliliter of urine). Diagnosis was provided in accordance to standardized CDC/NHSN definition of UTI (13). To isolate and identify the microorganisms responsible for the UTI, we obtained samples from urine mid-stream or from newly-established catheters. Diagnosed UTIs were treated with fluoroquinolone (ciprofloxacin) in doses of 200 mg or 400 mg twice daily, depending on the patient’s kidney function (eGFR). If necessary, the antibiotic therapy was adjusted based on microbiological data.

**Sample collection for microbiological analysis**

Microbiological analyses were performed by the Department of Medical Microbiology at Warsaw Medical University. Isolated strains were identified and characterized by standard microbiological methods. Specifically, the specimens were cultured under aerobic conditions at 35-37°C for 24-48 h using commercially available blood agar (Difco, Detroit, MI, USA) and MacConkey agar media (bioMérieux, Marcy l’Etoile, France). Moreover, Sabouraud’s agar (Difco) was used for fungal cultivation. The biochemical characteristics of cultured strains were investigated using VitekII (bioMérieux) according to the manufacturer’s instructions. Antimicrobial susceptibility testing of pathogenic strains was performed using the VitekII system (bioMérieux), and disc-diffusion method, according to recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (10). Additional tests were performed to identify the specific mechanisms of resistance in the case of multi-drug resistant (MDR) strains. The additional tests included checking the capability of production of ESBLs (extended spectrum beta-lactamases) and/or EMBLs (metallo-beta lactamas) by Gram-negative bacteria and, in the case of enterococci, the susceptibility to high concentrations of gentamicin and streptomycin were examined. All tests were performed and interpreted according to EUCAST recommendations (10).

**Statistical Analysis**

Chi-square or Fisher’s exact tests were used to compare categorical variables of the two patient groups. For testing differences between means or medians, student’s t-tests or Wilcoxon tests were applied, respectively. A critical level for hypothesis testing was set at 0.05. The statistical software, used for analysis was Statistica 10.0 (Statsoft, Tulsa, OK, USA).

**RESULTS**

Data from 220 KTx procedures performed at our institution between January 2010 and December 2011 were collected. For all kidneys, mean cold ischemic time accounted for 29.5 ± 8.1 h. Sixty-nine patients (31.3%) were observed to have delayed graft function (DGF) and primary non-function occurred in three patients (1.3%). Approximately 62% of the recipients...
were male and the average age of the recipients was 47.6 ± 14.5. UTIs were detected in 55 patients (25%). The remaining patients (n=165) were defined as the control group. Demographic and clinical data are presented in Table 1.

Recipient-related factor analysis

Patients in the UTI group did not differ from the control group with respect to age, immunosuppression protocol (as all recipients received treatment according to one regimen), or cardiovascular co-morbidities (Table 1). The occurrence of new-onset diabetes after transplant (NODAT) was significantly higher in the UTI cohort (8/55, 14.5%) than in the control group (7/165, 4.2%; p<0.05). The development of urological complications resulting in instrumental manipulation or surgical intervention in the urinary tract was significantly more frequent (p<0.05) in the UTI group (5/55, 9%) than in the control group (2/165, 1.2%). Mean recipient body mass index (BMI) was higher in the UTI group (24.7 ± 5.6 kg/m2) than in the control group (23.2 ± 4.7 kg/m2), but the difference was not statistically significant (p=0.41). BMI was not a risk factor for UTI. Human leukocyte antigen (HLA) compatibility was an independent risk factor for the development of UTIs, as recipients with more than four HLA mismatches were more likely to develop a UTI (18/55, 32.7%, in the UTI group vs. 29/165, 17.5%, in the control group; p<0.05). There was no statistical difference in immunosuppression therapy between the groups. Induction therapy was given in 29.6% (49/165) of patients in control group and 29% (16/55) in UTI Group (p=0.71).

The occurrence of DGF strongly correlated with the UTI incidence. DGF was observed in 34 of 55 patients (61.8%) with UTIs, in comparison to 35 of 165 control patients (21%; p<0.05). In this study DGF was estimated as a risk factor for UTI. As a factor which can not be taken under consideration in perioperative assessment, we can assume that lack of IGF can be detected early postoperatively and identified as DGF. According to this data, lack of immediate graft function may be considered a perioperative risk factor for UTI.

Microbiological analyses

From all recipients, urine samples were taken if any symptom of UTI presented. Isolation of at least one pathogenic microorganism was confirmed in 32 of 55 UTI episodes and 16 strains of nine bacterial species were identified (four Gram-positive and 12 Gram-negative; Table 2). Most of the identified pathogens (13/16, 81.25%) were resistant to at least one antibiotic and considered to be an alert strain (Table 2). Escherichia coli and Klebsiella pneumoniae were the most common clinical isolates in the patients with UTI as they were identified in nine (28.1%) and five (15.6%) cases, respectively. More than 95% of those strains (92% of E. coli and 100% of K. pneumoniae) were extended spectrum β-lactamase producers (ESBL+), moreover ESBL+ strains from all Gram-negative bacteria were diagnosed in 18 of the 24 (75%) cases. None of the obtained strains produced KPC (Klebsiella pneumoniae carbapenemase) or MBL (metallo-beta-lactamase).

Enterococci were identified in 8 (25%) cases and five (62.5%) of them were resistant to glycopeptides (vancomycin-resistant enterococci, VRE). Also 5 strains were identified as a high-level resistance to aminoglycosides (HLAR).

Donor-related factor analysis

The study collected 125 DD transplants, of which 115 involved both kidneys from DDs. Five kidneys were transferred to other centers and excluded from research. In two cases, kidneys as transplanted together with the pancreas, were not taken into account and further analysis. In other two cases, due to histopathological irregularities and poor perfusion parameters, the kidneys were discarded. In one case, only one kidney was available for transplantation. Kidneys from 109 DDs were received by recipients in the control group while in the UTI group recipients received kidneys from 47 DDs. The ECDs percentage was significantly higher (p<0.05) in the UTI group (21/147, 47.4%) than in the control group (32/109, 27.8%). The analysis of donor-related factors shows that there are no statistically significant differences with relation to donor’s creatinine levels, occurrence of hypertension, age or length of stay in the intensive care unit between the UTI and control groups (Table 3).

Surgical procedure and perfusion analysis

Mean transplantation time was significantly higher in the UTI group (192 ± 62 min) than in the control group (172 ± 46 min; p<0.05). Time of transplantation was ≥ 200 min in 21 of 55 UTI patients (38.1%), but only in 33 of 165 control patients (20.0%; p<0.01). Flow differences during the fourth hour of machine perfusion (greater than or less than 120 ml/min) in both groups were also statistically significant. Mean flow was higher in the control group (128 ± 40.67 ml/min) than in the UTI group (111 ± 31.06 ml/min). Mean flow was less than 120 ml/min in 38 of 55 recipients with UTI (69%) compared to 84 of 165 control recipients (51%; p<0.05).

Analysis of perioperative independent risk factors for UTI

Independent perioperative risk factors for UTI included ECD-related transplants, lower flow in the fourth hour of machine perfusion (<120 ml/min), HLA compatibility (>4 mismatches), time of surgical procedure (>200 min), and the occurrence of DGF (which we can be interpreted as lack of IGF). Forty-eight of 220 patients (20.1%) did not have any of the
risk factors (Group 1); 118 (53.6%) had one or two risk factors (Group 2); and 60 (26.3%) of patients had three or more risk factors (Group 3). UTI occurred in 4% (2/48), 24% (28/118) and 45% (24/54) of patients in Group 1, 2, and 3, respectively (Fig. 1).

Hospital Stay

Also a correlation (p=0.01) between UTI occurrence and length of hospital stay was observed. Patients who had an early infection (within the first month after transplantation) experienced a longer hospital stay (28 days) compared to patients without infection (15 days).

One year graft and patient survival

We analyzed the impact of UTI on renal function during the following periods: 7, 14, 30, 90,180, and 360 days after transplantation. We evaluated annual graft and patient survival, as well as renal function based on serum creatinine at certain intervals (Table 4). Annually, all (UTI + nonUTI) patients’ survival rate was 98%, with 90% graft survival. Patients survival in the group where UTI was not detected was more than 99% (± 8), and 95% (± 2) in recipients with UTI during the first month post transplant (p=0.2). During the first six months post-transplantation, we observed a statistically significant difference in the rate of decrease in serum creatinine between patients with or without UTIs. However, after 360 days post-transplant, this statistical significance no longer existed. The one-year graft survival rates in the UTI group vs. the control group were not statistically different (p=0.2) and were respectively 87% ± 34 vs. 94% ± 24. (Fig.2)

DISCUSSION

After cardiovascular events (28), infections, are one of the leading causes of mortality after kidney transplantation (13,17). Optimizing immunosuppression, introduction of new drugs with principles of prevention treatment and surgical techniques reduces the number of infection-related complications. Nevertheless, infection still remains a serious threat. According to many sources, incidence of UTI after KTx decreases time-dependently and most of episodes occur in the early posttransplantation period, with a high incidence of recurrence. Vidal et al. observed UTI in 36.55% of recipients (5), in Verox’s 1-month-observation, 20% of kidney recipients suffered from UTI (14). Downward trend in the number of UTI complications with time can also be found in Ariza-Heredia’s study (6). It is clear that UTIs prophylaxis and optimal prevention is essential from the very beginning of kidney transplantation procedure. Numerous papers describe a variety of risk factors for urinary tract infection. Several can be definitely associated with donor, recipient (DGF, age) or connected with individual center regimens in treatment (duration of bladder catheterization, especially when >7 days, presence of ureteric stent, immunosuppression regimen) (5,10,22). Ariza – Heredia also included presence of urological abnormalities, namely: comorbidity- benign prostatic hypertrophy, ureteral obstruction, bladder dysfunction, urinary incontinence or vesicoureteral reflux, and also female gender, which for some is one of the strongest risk factors (10,23-25). Other studies did not confirm those conclusions (29).

Identification of a group of recipients in which SAP could be safely avoided is very problematic. However, we observed a significant correlation between UTI incidence and longer procedure time, possibly due to the patients’ increased exposure during surgery to microbes involved in post-operative infections. Donor status also played a significant role in the occurrence of UTIs. Due to wider acceptance of organs from ECD (30), patients more frequently developed UTIs, which likely leads to DGF (and lack of IGF) in these kidneys. Our findings confirm previous results that show a significant relationship between DGF and the development of UTI (7-11). Patients who developed NODAT were more likely to develop a UTI than non-diabetic patients, possibly due to all problems and “challenges” in glycemic control that appear after renal transplantation (9). But that factor, as well as the possible urological complications can be assessed only in the posttransplantation period. Correlation with the type of immunosuppression treatment and occurrence of UTIs was not present. This is probably because in most patients immunosuppression procedures are very consistent, and proliferative signal inhibitors - drugs reported to promote UTI, are not used during the initial post-operative period (11,15). These drugs are only introduced after one month post-transplantation, if necessary. Also two recent observations in a large group of recipients investigated particular types of immunosuppression protocols used in particular centers. Both brought the authors to the conclusion, that neither immunosuppression therapy, the maintenance of corticosteroid therapy versus early cessation, nor type of induction of immunosuppression therapy (ATG vs. Basiliximab) are independent risk factors for UTI (5,10). Also hypertension and ischemic heart disease, as recipient co-morbidities, did not influence UTI occurrence.

In our patients, the rate of urinary tract infection during the first month post-transplantation was only 25%, while rates reported from other centers vary from 20% to 47% (5,6,10,17-20). All that leads us to the conclusion of correctness in the pursuit of procedures implemented at our institution to protect patients from UTI. The differences in these UTI incidence rates may be explained by the use of different SAP protocols, the specific antibiotic susceptibility profiles of UTI-associated pathogens in our patients, and discrepancies in the criteria adopted for UTI diagnosis.

Over 50% of the pathogens identified in our pa-
tients were classified as MDR, and these pathogens negatively impact the course of treatment, what leads to the conclusion that minimal SAP is evidently essential. According to previous reports, SAP which is provided shorter than 48 h seems to be safe and does not lead to higher UTI occurrence (9). In this study we would like to encourage to minimize SAP in patients with no perioperative UTI risk factors identified in our research, as we also know that complete cessation of prophylactic treatment and current medical practice can be too revolutionary. Although our procedures in antibiotic prophylaxis were identical, the presence of UTI must have been associated with particular risk factor/s. And this is our proposition and hope for the future, to provide “gentler” SAP for those recipients where probability of UTI is lower and adjust more “alert” procedures for those with higher possibility of UTI. If there is lower possibility of UTI occurrence, we may assume that prolonged SAP could be easily avoided. Closer surveillance for those with more potential risk factors could be introduced. Low risk factor patients may benefit from a single dose of prophylactic antibiotics that could provide them with post-operative protection, but also discourage MDR pathogen colonization. Each center should adjust the type of SAP to target pathogens, which are most frequently isolated locally. In some cases, if there are no additional signs of infection, such as fever, inflammation, or elevation of C-reactive protein, antibiotic treatment may be suspended until a positive urine culture is detected.

Another the tendency we observed in our study seems crucial. Recipients without UTIs during the first post-operative month initially experienced a faster decrease in serum creatinine levels (<0.05), but by the end of the first post-operative year, this difference was no longer statistically significant. Although the occurrence of UTIs did not appear to significantly affect graft function or survival after one year post-transplantation, patients with UTIs did experience significantly longer hospital stays compared to recipients without UTIs. This extended stay generates excessive cost and exposes patients to further infections or complications that could be avoided if UTI risk factors were identified pre-transplantation and the SAP regimen adjusted appropriately.

CONCLUSIONS

In summary, we decided to focus on the risk factors that were independently associated with perioperative UTI development. These included: ECD-related donation, lower flow in the fourth hour of machine perfusion (<120 ml/min), donor-recipient HLA compatibility (>4 mismatches), surgical procedure time (>200 min), and the occurrence of DGF (construed as failure in obtaining IGF), NODAT, and urological complications after transplantation also turned out to be risk factor for UTI in the post-transplantation period. As a result, hospital stay was significantly longer in patients with UTIs compared to patients with no diagnosed UTI.

Additional multi-center research is essential to assess if prophylactic antibiotic treatment may be unnecessary and even devastating in specific cohorts of kidney transplant patients by promoting MDR infections.

ACKNOWLEDGEMENTS

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LIST OF THE FIGURES

Fig. 1. Risk factors for occurrence of UTI
Fig. 2. The one-year graft survival rates

FIG. 1. RISK FACTORS FOR OCCURRENCE OF UTI

Figure shows relation between UTI, dependent on number of risk factors of the individual patient. UTI occurred in 4% (2/48), 24% (28/118) and 45% (24/54) of patients in group 1 (0 risk factors), 2 (1-2 risk factors) and 3 (3 and more risk factors) respectively.

FIG. 2. THE ONE-YEAR GRAFT SURVIVAL RATES

UTI group vs. the control group were not statistically different (p=0.2)

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Tab. 2. Pathogens identified from UTIs
Tab. 3. Deceased donor analysis
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TAB. 1. RECIPIENT FACTORS RELATED TO THE DEVELOPMENT OF UTI

<table>
<thead>
<tr>
<th>Recipient factors</th>
<th>Control group (n=165)</th>
<th>UTI group (n=55)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47 ± 14.3</td>
<td>49.5 ± 15.5</td>
<td>0.28</td>
</tr>
<tr>
<td>% male</td>
<td>61.8% (102/165)</td>
<td>61.8% (34/55)</td>
<td>0.68</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>24.29 ± 3.7</td>
<td>24.8 ± 3.4</td>
<td>0.41</td>
</tr>
<tr>
<td>HLA mismatches &gt; 4</td>
<td>17.5% (29/165)</td>
<td>32.7% (18/55)</td>
<td>0.03</td>
</tr>
<tr>
<td>Flow in fourth hour of mechanical perfusion (ml/min)</td>
<td>128 ± 40.67</td>
<td>111 ± 31.06</td>
<td>0.002</td>
</tr>
<tr>
<td>% DGF</td>
<td>21% (35/165)</td>
<td>61.8% (34/55)</td>
<td>0.0005</td>
</tr>
<tr>
<td>% type of dialysis (HD)</td>
<td>92% (152/165)</td>
<td>93% (51/55)</td>
<td>0.72</td>
</tr>
<tr>
<td>% NODAT</td>
<td>4.2% (7/165)</td>
<td>14.5% (8/55)</td>
<td>0.046</td>
</tr>
<tr>
<td>% hypertension</td>
<td>86% (142/165)</td>
<td>80% (44/55)</td>
<td>0.3</td>
</tr>
<tr>
<td>% ischemic heart disease</td>
<td>14% (23/165)</td>
<td>9% (5/55)</td>
<td>0.32</td>
</tr>
<tr>
<td>Urologic complications</td>
<td>1.2% (2/165)</td>
<td>9% (5/55)</td>
<td>0.04</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>172 ± 46</td>
<td>192 ± 62</td>
<td>0.045</td>
</tr>
<tr>
<td>Operation time &gt;200 min</td>
<td>20% (33/165)</td>
<td>38.19% (21/55)</td>
<td>0.019</td>
</tr>
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TAB. 2. PATHOGENS IDENTIFIED FROM UTIS

<table>
<thead>
<tr>
<th>Pathogens identified</th>
<th>Frequency (Number of strains)</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Enterococcus faecium HLA R VRE</td>
<td>4</td>
</tr>
<tr>
<td>Enterococcus faecium HLA R</td>
<td>4</td>
</tr>
<tr>
<td>Escherichia coli ESBL (+)</td>
<td>8</td>
</tr>
<tr>
<td>Escherichia coli ESBL (-)**</td>
<td>1</td>
</tr>
<tr>
<td>Enterobacter cloacae complex Amp C (+)</td>
<td>1</td>
</tr>
<tr>
<td>Enterobacter cloacae ESBL (+), Amp C (+)</td>
<td>1</td>
</tr>
<tr>
<td>Enterobacter cloacae complex ESBL (+)</td>
<td>1</td>
</tr>
<tr>
<td>Enterobacter gergoviae</td>
<td>1</td>
</tr>
<tr>
<td>Klebsiella pneumoniae ESBL (+)</td>
<td>5</td>
</tr>
<tr>
<td>Proteus mirabilis ESBL (+)</td>
<td>1</td>
</tr>
<tr>
<td>Serratia marcescens ESBL (-)*</td>
<td>1</td>
</tr>
<tr>
<td>Serratia marcescens ESBL (+), MBL (-)**</td>
<td>2</td>
</tr>
<tr>
<td>Acinetobacter Iwoffii MBL (-)**</td>
<td>1</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus faecium HLAR VRE</td>
<td>4</td>
</tr>
<tr>
<td>Enterococcus faecium HLAR</td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus faecium VRE</td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>2</td>
</tr>
</tbody>
</table>

** Concerns Gram-negative bacilli vancomycin-resistant enterococcus (VRE)
* Concerns Gram-negative bacilli by Gram-negative rods AmpC (+), chromosomal β-lactamase of Ambler class C overexpression

TAB. 3. DECEASED DONOR ANALYSIS

<table>
<thead>
<tr>
<th>Deceased donor factors</th>
<th>Control group (n=165)</th>
<th>UTI group (n=55)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.4 ± 154</td>
<td>50.6 ± 153</td>
<td>0.01</td>
</tr>
<tr>
<td>% ECDs</td>
<td>27.8% (32/165)</td>
<td>47.4% (24/55)</td>
<td>0.01</td>
</tr>
<tr>
<td>Intensive care unit stay (days)</td>
<td>4.55 ± 2.6</td>
<td>4.7 ± 2.92</td>
<td>0.75</td>
</tr>
<tr>
<td>Creatinine level (mg/dl)</td>
<td>1.89 ± 1.46</td>
<td>1.65 ± 1.38</td>
<td>0.27</td>
</tr>
<tr>
<td>% Hypertension</td>
<td>22% (24/109)</td>
<td>31% (15/47)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

TAB. 4. SERUM CREATININE (MG/DL) OF RECIPIENTS AFTER TRANSPLANT (TX)

<table>
<thead>
<tr>
<th>Days after Tx</th>
<th>Control group (n=165)</th>
<th>UTI group (n=55)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>7</td>
<td>3.38 ± 2.29</td>
<td>5.83 ± 3.41</td>
<td>0.01</td>
</tr>
<tr>
<td>14</td>
<td>2.28 ± 1.63</td>
<td>3.49 ± 1.92</td>
<td>0.015</td>
</tr>
<tr>
<td>30</td>
<td>1.89 ± 1.23</td>
<td>2.29 ± 1.05</td>
<td>0.019</td>
</tr>
<tr>
<td>90</td>
<td>1.66 ± 0.81</td>
<td>2.04 ± 1.03</td>
<td>0.024</td>
</tr>
<tr>
<td>180</td>
<td>1.62 ± 0.94</td>
<td>2.00 ± 1.00</td>
<td>0.033</td>
</tr>
<tr>
<td>360</td>
<td>1.67 ± 0.93</td>
<td>1.93 ± 0.93</td>
<td>0.144</td>
</tr>
</tbody>
</table>

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Life–threatening bleeding nine years after kidney transplantation with Bricker–type ureterointestinal anastomosis

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ABSTRACT
Bricker–type ureterointestinal anastomosis is a widely used technique for performing ureteroenteric anastomosis. In some cases it is the only possible urinary drainage after kidney transplantation for patients with lower urinary tract abnormalities.

A 58–year–old female patient, nine years after kidney transplantation with Bricker–type ureterointestinal anastomosis, with recurrent urinary tract infections, was admitted to the hospital because of severe bleeding through the urostomy. Hemoglobin level was 3.4 g/dl. Patient had also impaired cloth formatin and coagulopathy with prolonged protrombine time due to chronic hepatitis C. Ultrasound and lifesaving laparotomy showed no source of bleeding. During operation bleeding stopped spontaneously and didn’t return again. After surgery also endoscopy through stoma was undertaken. This procedure showed no source of bleeding in intestine and made more probably graft hemorrhage. Graft biopsy showed no signs of rejection. Due to progressive loss in renal function patient needed dialysis again.

The Bricker ileal conduit is a great surgical solution in some patients but like most surgical procedures has both positive and negative implications.
INTRODUCTION

Kidney transplantation is the best method of renal replacement therapy. In patients with lower urinary tract dysfunction it is usually impossible to perform transplantation with uretero-bladder anastomosis. There are several methods of urinary diversion which can be used in that cases e.g. ureterocutaneostomy, ileal conduit, colonic conduit, continent urinary reservoir, uretersigmoidostomy, ureterocolostomy and many others [1]. In most cases surgeons choose Bricker – type ureterointestinal anastomosis as the best solution. Like most surgical procedures this type of operations has both positive and negative implications. The most common complications after kidney transplantation with Bricker – type ureterointestinal anastomosis are recurrent urinary tract infections [2] or urosepsis [3], renal stone disease [3] and ileus [4].

CASE REPORT

58 y.o. female patient, after kidney transplantation with Bricker – type ureterointestinal anastomosis, admitted to the hospital because of severe bleeding through the urostomy.

Cause of the end stage renal disease was chronic interstitial nephritis. Transplantation was performed nine years ago and because of low capacity of the bladder (50ml) standard urinary drainage was impossible to perform and Bricker – type ureterointestinal anastomosis was made. Patient received daclizumab for induction and was maintained on mycophenolate mofetil, tacrolimus and steroids. Early and long-term post-transplants results were satisfactory (creatinine between 1 to 3 mg/dl). 6 months prior to hospital admission continuous rise of serum creatinine level was observed.

On admission to the hospital patient’s hemoglobin level was 3.4 g/dl. Patient had also impaired cloth formatins and coagulopathy with prolonged protrombin time (INR 2.0) due to chronic hepatitis C. Patient got immediate blood transfusion and received fresh frozen plasma. Ultrasound was made and showed large volume of free liquid in the abdominal cavity but no source of bleeding. The lifesaving laparotomy was performed. There was no blood in peritoneum and the fluid was ascites, probably due to chronic cirrhosis.

During laparotomy bleeding stopped spontaneously. Foley catheter was placed in the Bricker loop to irrigate intestine with saline.

After surgery hemoglobin level was 6.5 g/dl so patient got another blood transfusion. Next day endoscopy through stoma was undertaken. This procedure showed no source of bleeding in intestine and made more probably graft hemorrhage.

Although diuresis was sufficient (about 2000 ml per day) but serum creatinine level rise was observed – before operation was 4.3 mg/dl and was increasing every day. Graft biopsy showed no signs of rejection. Due to progressive loss in renal function patient needed dialysis. The bleeding didn’t return again.

DISCUSSION

Kidney transplantation is surgical procedure with high probability of complications. Most common complications are renal artery or vein thrombosis, urine leak [5], infections (urinary tract infections, viral infections, pneumonia, wound infections) [6] and lymphocele [7]. When the transplantation is performed with Bricker – type ureterointestinal anastomosis there is also risk of additional complications. This complications are result of procedures performing on intestine and non-physiological drainage of urine and sometimes are unpredictable. However, in some cases of patients with lower urinary tract abnormality, this procedure is the only possible urinary drainage after kidney transplantation. Those patients often decided to undergo that surgery to release them from hemodialysis and improve their quality of life.

CONCLUSIONS

The Bricker ileal conduit is a great surgical solution in some patients but like most surgical procedures has both positive and negative implications.

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Kidney donor risk index assessment – analysis of current literature

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ABSTRACT

With the ongoing shortage of standard criteria donors (SCD) efforts to expand the organ pool such as use of expanded criteria donors (ECD) have intensified. Various kidney donor risk indexes have been developed to predict graft survival with various combinations of donor and recipient characteristics. Continuous kidney donor risk index (KDRI) was proposed by Rao at al. The graded impact on kidney allograft survival seems to make it more useful tool at the time of the deceased donor kidney offer than expanded and nonexpanded criteria donor classification.

Kidney transplantation is the optimal form of kidney replacement therapy. Most importantly it is beneficial to the patient by prolonging expected lifespan, improving quality of life, decreasing morbidity and limiting complications of uremia. It is also advantageous to the medical care system, being less expensive than chronic dialysis.

The increase in waiting lists for a cadaver transplant is a worldwide trend. According to a report issued in 2011 the population of patients with end stage renal disease increases by 7% annually (1).

In the USS the median time to transplant for wait-listed adult patients increased from 2.7 years in 1998 to 4.2 years in 2008. (2)

Transplantations from a live donor cover only a fraction of demand for kidneys. In an attempt to shorten the waiting lists and improve recipients’ prognosis, transplantation centers implement optimized rules for organ allocation and often collect organs from donors fulfilling expanded criteria (ECD – expanded criteria donor).

The ubiquitous acceptance of ECD kidneys does have a price, however. The disadvantages include a greater incidence of delayed graft function (DGF) and
acute rejection, prolonged hospitalization, higher cost of treatment and unsatisfactory long-term kidney function. (3, 4, 27) The relationship between DGF and a decreased kidney-graft life is also well established. Early function of the transplanted kidney is a predictor of long-term function, while serum creatinine levels at 6 and 12 months after transplantation are an independent prognostic factor (5). The risk of losing the organ is proportional to the time of dialysis. Transplantation increases the expected lifespan twofold. (6, 7, 8, 13)

One of the key issues in modern transplantology is an objective assessment of a kidney donor to be performed before accepting the organ for transplantation. There have been various attempts at creating a numerical scale to evaluate the quality of kidneys harvested from cadaver donors (9). An adequate analysis of the donor would aid in selecting the optimal recipient. It would also be helpful in assessing the risk of potential early and late complications, choosing the immunosuppressive regimen and appropriate surveillance (such as timing of protocol biopsies).

Nyberg et al. have attempted to establish a donor risk index, taking into consideration parameters that influence the early function of a kidney-graft. They performed a retrospective analysis of 12 donor-related and 6 recipient-related risk factors, assessed during organ harvest in 250 cases. The study identified 7 factors that affected the primary end-point, eGFR (estimated glomerular filtration rate) at 30 days after transplantation. The factors regarding the donor were: cause of death, history of arterial hypertension, eGFR, age, history of diabetes, total ischaemia time and atherosclerosis of the renal arteries. Each risk factor contributed points to the scale – up to 32 in total. The influence of human leukocyte antigen (HLA) compatibility and glomerular sclerosis in time-zero biopsy were not proven to be of statistical significance. 70% of recipients with a summary risk index of 0-15 (groups A–C) had an eGFR of over 40 ml/min within a month. The risk of DGF in this group was found to be less than 25%. Transplanting a kidney from a donor with a risk index of over 15 points (group D) is, in comparison, associated with a 60% chance of DGF, longer hospitalization and higher cost of treatment (10).

It has been proven that an integrated evaluation of all 7 mentioned risk factors is a better indicator of early kidney-graft function than any single one. Consequently, the next step was to identify risk factors that would allow for a prognosis regarding long-term kidney-graft function. An analysis was performed of 34,324 patients, who received a kidney transplant between 1994 and 1999. Seven aforementioned donor-related risk factors were considered, along with 4 recipient-related ones – CMV serological status, HLA compatibility, creatinine clearance, graft survival at 6 and 12 years. The key risk factors were (in order of importance): age of donor, eGFR, duration of hypertension, HLA compatibility and cerebrovascular incident as donor’s cause of death. A single and multivariate analysis of the influence of the 5 mentioned parameters on kidney function at 6 months was performed, yielding an improved deceased-donor score (DDS). In order to simplify the index a number of risk factor were excluded. These included CMV serological status, history of diabetes and nationality (as having low prognostic importance) and time of ischaemia (as being undetermined at the time of donor qualification). More index points were indicative of a worse prognosis regarding eGFR at 6 and 12 months after transplantation, as well as 6-year kidney-graft survival. A donor index of over 20 points (a so-called marginal donor) corresponds to a donor fulfilling ECD criteria (UNOS) in regard to prognosis. Donors evaluated at 21-30 points have been labeled a moderate risk group (C). In this population a short ischaemia time has been reported to improve prognosis. For the high risk group (D) the time of ischaemia is irrelevant. Increasing the time of follow-up to 6 years has shown an statistically significant relationship for HLA compatibility between the donor and recipient and long-term kidney-graft function. The key conclusion of the improved donor index is that 40 years is the critical age of the donor. Regardless of other prognostic factors, any donor aged 40 years or less is considered to be a non-marginal one (11). A retrospective analysis of a cohort of 7209 kidney recipients in France (transplanted between 1996 and 2000) performed by Pessionne et al. (12) has led to the development of a new index – the Pessionne score. This tool is based solely on 3 independent donor-related risk factors: cardiovascular cause of death, history of hypertension and a serum creatinine concentration of over 150 mmol/l.

Concurrently, a German team under Schold introduced a donor risk score (DRS) – an indicator of graft survival at 1 and 5 years after transplantation. This scale included risk factors such as age, race, cause of death, history of hypertension, diabetes, CMV status, time of ischaemia and HLA mismatching. The cited assessments of the transplanted organ do not, however, take into account the influence of early surgical complications or chronic microscopic damage on graft survival (14).

Due to an increase in demand, towards the end of the XX century procedures were developed for harvesting organs from non-heart-beating and elderly donors. The share of cadavers with a history of cardiovascular disease and advanced age increased. In the beginning of the XXI century, one in four donors in Spain was aged over 60. Because function and survival of kidney-grafts from such donors was notably worse than was usual, transplantologists were faced with a dilemma. Should they offer their patients a kidney from a marginal donor or continue dialysis, a form of kidney-replacement therapy inferior in regard to morbidity and mortality? Consequently, in 2001
the Organ Procurement and Transplantation Network (OPTN) and United for Organ Sharing (UNOS) developed criteria for expanded criteria donors (ECD). These were introduced to aid physicians and patients in deciding whether to accept kidney-grafts from marginal donors. ECDs were defined by Port et al. as donors of an organ with a risk of dysfunction greater than 1.7 compared to a donor aged 10-39, with a serum creatinine concentration <1.5 mg/dl, a negative history of hypertension and a non-cardiovascular cause of death. The risk varies between 1.74 (for a donor aged 50-59, with a history of hypertension and an elevated creatinine level) to 2.69 (for a donor aged over 60, with a history of hypertension and a cardiovascular cause of death). It is standard practice that the recipient must consent to being transplanted an organ from an extended criteria donor. Studies reveal that the mortality of ECD kidney recipients aged over 40 is lower than those, who continue dialysis. According to reports by the Scientific Registry of Transplant Recipients (SRTR) the annual mortality of patients waiting for a kidney transplantation is 7%, while ECD kidney recipients have a survival 5 (4-11) years longer than those on the waiting list. In recent years the share of ECD kidneys increased to 17-31% of all reported donors (18, 19). Meanwhile the survival rates of recipients continue to improve. The average graft survival of ECD kidneys is 6.3 years, compared to 10.2 years for standard criteria donors (SCD). (14-17)

Extended criteria and the scoring systems developed by Nyberg and Schold are based on an arbitrary categorization of risk, hence potentially decreasing the accuracy of evaluation. In an attempt to improve the previous tools, Rao et al. have developed a continuous risk scales by eliminating categorized variables. The indexes introduced by Rao’s team, the Kidney Donor Risk Index (KDRI) and Kidney Donor Profile Index (KDPI) include the analysis of factors previously not considered. Donor-related risk factors are: age, height, weight, ethnicity, history of hypertension, diabetes, smoking, cause of death, serum creatinine concentration, HCV status, donation after circulatory death (DCD) status and incompatibility in major histocompatibility complexes (MHC). KDPI also considers nine factors to ECD’s four. Finally they provide a more specific characteristic of the donor along with ECD’s labeling of “better or worse” quality of donor. This is crucial in establishing the threshold for accepting an ECD donor for recipient from a particular transplantation center.

Rao’s KDRI estimates the risk of function loss of a kidney-graft transplanted to a “reference” donor. This is defined as a person 40 year old, non-afroamerican, 170cm tall, weighing 80kg, with a creatinine level of 1 mg/dl, 2 HLA-B mismatches, 1 HLA-DR mismatches, negative history of hypertension, diabetes and hepatitis C, a cold ischaemia time of <20h and deceased by brain death. The formula for calculating KDRI is as follows:

\[
\text{KDRI RAO} = \exp \{-0.0194 \times (I(\text{Age} < 18 \text{ years})) + 0.0128 \times (\text{Age} - 40 \text{ years}) + 0.0107 \times (I(\text{Age} > 50 \text{ years})) + 0.179 \times (I(\text{Race} = \text{African American})) + 0.126 \times (I(\text{Hypertensive})) + 0.130 \times (I(\text{Diabetic})) + 0.220 \times (\text{SCR} - 1 \text{ mg/dl}) - 0.209 \times (\text{SCR} > 1.5 \text{ mg/dl}) + 0.126 \times (\text{SCR} - 1.5 \text{ mg/dl}) + 0.0881 \times (I(\text{COD} = \text{CVA})) - 0.0464 \times (\text{Height} - 170 \text{ cm})/10) - 0.0199 \times (I(\text{Weight} < 80 \text{ kg}) \times ([\text{Weight} - 80 \text{ kg})/5]) + 0.133 \times (I(\text{DCD})) + 0.240 \times (I(\text{HCV})) - 0.0766)\]

where I is equal to 1 if the condition is true and I is equal to 0 if the condition is false.

The Rao KDRI result is then normalized by a scaling factor using the following formula:

\[
\text{KDRI MEDIAN} = \frac{\text{KDRI RAO}}{\text{scaling factor}}
\]

The scaling factor is a median value for all donors from the previous calendar year. Its value is listed in a KDRI to KDPI conversion mapping table. For example, in 2010 this was 1.24. The KDRI MEDIAN is interpreted as a relative risk of graft function loss in an average adult recipient for this donor as compared to a median donor in the previous calendar year. When assessing long term trends or performing retrospective analyses of KDRI, the scaling factor should be omitted (taking into account only KDRI RAO) or a single scaling
factor value should be used.

The KDRI is usually between 0.5 and 3.5. Higher values are associated with relatively worse graft survival rates. The mean predictive value of KDRI is 0.6 (c=0.62). It increases notably in the extreme ranges (c=0.78), while it is lower in average ranges (c=0.58). The greater the difference between two compared values of KDRI the more plausible the estimated difference in kidney-graft survival. Utilizing the KDRI index can potentially limit the number of rejected organs, especially in cases of kidneys with a high KDRI value interpreted along with ECD criteria.

The KDPI is a derivative of KDRI determined by the KDRI to KDPI conversion mapping table. KDPI is a value ranging from 0 to 100%. A donor with a KDPI of >90% has a KDRI higher than 90% of the reference donor population for the previous calendar year in the USA. Data obtained from the reference group of donors allow for computing the scaling factor for a given year. It also allows for developing the KDRI to KDPI conversion mapping table, that shows the relationship between KDPI and any KDRI value. A donor with a KDPI of 0% has a KDRI lower than all the donors from the reference population. A donor with a KDPI of X% has a KDRI of more than (X-1)% but no more than X% of all the reference population donors. For example, a donor with a KDPI of 30% has a KDRI between 29 and 30% of all the reference population donors.

Aside from calculating the KDRI by the formula described above, that involves a donor-only version of the KDRI, Rao’s group has suggested a „full KDRI”. This value would also include the cold ischaemia time, HLA mismatches and the type of transplantation (single, double or en-bloc). These factors influence the survival rates of the kidney-graft but are unknown when the decision to accept the organ is made by the transplantation team. Because of this the full KDRI is of lesser practical importance. In theory the predictive value of the donor-only version of the KDRI (c=0.596) is very similar to that of the full KDRI (c=0.601). The survival of the kidney-graft is also determined by a number of factors related to the recipient (such as age and comorbidities), that are not taken into account by the KDRI. The strength of the relationship between the KDRI/KDPI and the estimated survival rate of the kidney-graft is influenced by these recipient-related parameters in a minor way. KDPI is, however, limited by the lack of information regarding the microscopic image of the kidney-graft, as well as any damage or visible abnormalities. Furthermore, the KDRI does not include the risk of transmitting an infectious disease or malignancy. The described indexes are not constant values. During the last 10 years the values of KDRI and KDPI have increased by 7% and 6% respectively.

A teams from Richmond and Cleveland underlines the difference in KDPI when taking the initial or final creatinine level into account. In 10% of donors the difference is over 11 points. The more stable the creatinine levels, the better the KDPI reflects the true quality of the donor. The Kidney Transplantation Committee (KTC) gathers data regarding the influence of variable creatinine levels during donor evaluation on the final KDPI value. It has not yet been determined whether this will influence the kidney-graft allocation system (24).

As was mentioned earlier the KDPI allows for estimating the survival rate of a kidney-graft. It thus helps in deciding whether to accept a kidney harvested from an ECD or wait for a possible SCD donor. KDPI has been part of DonorNet® since 2012 and it is an integral part of the new kidney allocation system (KAS) developed by the OPTN KTC, that is expected to be implemented in the US by the end of 2014. Introducing the KDPI is intended to help with “longevity matching” - a new kidney-graft allocation algorithm, that involves an estimated post-transplant score (EPTS). KDPI, as a measurement of donor quality, is supposed to help transplantologists match a particular organ and a recipient with a suitable prognosis, while taking into account the ischaemia time related to his transplantation center. A recipient with a EPTS of less than 20% should be matched with a kidney-graft from a donor with a KDPI of less than 20%. Utilizing the KDPI can help decide to transplant 2 kidney-grafts to a recipient in a case where a single organ might provide insufficient eGFR. The formula for calculating the EPTS was developed using a multivariate analysis by Cox proportional hazard model, that included 4 factors associated with patient survival after kidney transplantation: age, time of dialysis, previous transplantations and current diabetes. The calculated EPTS in a value between 0 and 100% and signifies the percentage of the recipient population with a longer expected survival rate after kidney transplantation. Every patient on the waiting list is assigned an EPTS, that is updated after every year of chronic dialysis or when the patient is diagnosed with diabetes. The new allocation system, involving the KDPI and EPTS is meant to optimize the matching of <20% KDPI donors and <20% EPTS recipients. An organ with a good estimated long-term function should be transplanted to a recipient with a suitably long expected survival rate. Matching a kidney with a good estimated long-term function and a recipient with a poor EPTS is an example of suboptimal organ use. Similarly, a young patient with a EPTS of less than 20% given a kidney-graft with a high KDPI is a bad match, as he would soon be in need of a re-transplantation. The mean kidney-graft survival for a donor with a KDPI <20% is 11,5 years, compared to 12 years for a living donor (30). Ramanathan et al, interpreting a retrospective analysis of 528 recipients, has shown that best kidney-graft survival rates are attained when the donor is 15 years younger than the recipient (28). A study of recipients in Washington has shown a statistically significant influence of KDPI on serum creatinine concentrations at 6 an 12 mon-
ths after transplantation. It has confirmed better kidney-graft function for donors of a KDPI <20% compared to >20%, irrespective of ECD status (35). A retrospective analysis by Yang et al. has demonstrated a correlation between KDRI and recipient eGFR at 12 months after transplantation (37). Meanwhile, Halloran et al. have shown that evaluating KDRI along with molecular markers of acute kidney injury, such as ITGB6, KIM1 or LCN2, is advantageous compared to an assessment of a single of these factors (36).

The new kidney allocation system, based on the donor index allows for maximal use of harvested organs and optimal recipient matching. The EPTS is only taken into account when allocating kidneys from donors with a KDPI <20%. The EPTS only sets priority in 20% cases of transplantation. A simulation performed last year by Kasiske et al. has shown that the new allocation system will improve the half-life of kidney-grafts from 8.82 to 9.07 years and increase the chance of transplantation for recipients aged 18-49, while slightly lowering the chances of transplantation for patients aged 50-64 years (29). A retrospective, single-center analysis of over 500 recipients suggests a similar one-year survival for kidney-grafts from donors with a KDPI >85% and 20-84%. The difference in prognosis are noticeable after 3 years.

The share of ECD kidneys among transplanted organs is increasing, as is the average age of patients on the waiting lists. The influence of donor-related risk factors on the recipient differs depending on the age, race, history of diabetes and ESRD cause of the recipient. The quality of the donor has a significant clinical interaction with the recipient characteristic. ECD kidneys are an appropriate option for recipients that are aged or suffer from comorbidities such as diabetes. In these cases the risk of losing the kidney-graft is lower than for younger, healthier recipients. It has been demonstrated that greater KDRI values have a lesser impact on older recipients with a history of diabetes. Conversely, the donor-related risk factors have a stronger influences on younger patients with fewer comorbidities. By definition the organ quality measured by KDPI should be constant, so additional analyses regarding other factors (such as time of ischaemia) on the survival rates of both graft and recipient are easier to perform and more predictable.

Reports show that organs fulfilling extended criteria are disqualified more often. A team from Boston has performed a retrospective analysis of the survival rates of 138 717 kidney-graft recipients, transplanted between 1995 and 2010. The analysis has demonstrated that survival of recipients is superior to those on the waiting list, regardless of the KDPI value of the transplanted organ. A common index measuring the risk of death for both recipient and a candidate for transplantation was established. It included 15 traits, with age, race and cause of ESRD being the most important. Next, groups of recipients and candidates with a similar index were compared. The study showed a significantly longer five-year survival for kidney-graft recipients of all risk groups compared to patients waiting for a transplantation. Sub-analyses show superior survival rates even for recipients of a kidney with a KDPI of 81-100% (31).

A team from the Johns Hopkins University School of Medicine has reached similar conclusions. Transplanting a kidney with a high KDPI value, compared to waiting for a “better” organ, is associated with an increased short-term and long-term mortality. The benefit is visible after 2 years. After 5 years the survival rates for recipients are superior to candidates for all KDPI values. A single-center retrospective analysis of over 500 recipients shows a similar one-years survival for kidneys with a KDPI >85% and 20-84%. The differences in survival between these groups are significant after 3 years (25). Accepting an organ with a KDPI >71% is an especially appropriate option for patients who are over 50 years old or come from a center with an average waiting time of over 33 months (32).

Kidneys with a high KDPI value (>80%) are not accepted by more than half cases in the US. The histological evaluation of a time-zero biopsy can be helpful in making a choice. Gandolfini has shown that a kidney with a greater KDPI value has better survival rates if it is also assigned a better Remmuzzi score. He concludes that a histological evaluation of an ECD kidney with a high KDPI value might be crucial in qualifying the graft for transplantation. A Remmuzzi score of over 4 points can be an indication for transplanting 2 kidney to one recipient (33, 34). The KDRI and KDPI include the donor-related factors that independently influence the overall survival of the kidney-graft harvested from a particular donor. The KDPI arranges the harvested organs according to their quality, reflecting relative risk in the population. The index should not be used as a singular tool to decide whether or not to accept a given organ. The curve of relative risk of kidney-graft survival for KDPI values between 20 and 80% is almost flat. Hence, particular KDPI values in this range do not reflect important differences in the quality of organs. The curve of kidney-graft survival increases steeply for KDPI values of over 80%. Taking into account the cited data regarding longer survival of recipients, regardless of the quality of the transplant, compared to patients on the waiting list, it is difficult to define a KDPI value of 80% as a cut-off point. The decision rests with the patients and the transplantologist. If the organ is accepted, pulsatile perfusion should be applied and ischaemia time should be shortened. The plan for monitoring the graft by biopsies and the immunosuppressive regimen should take the expected delayed graft function into account.

Woodside et al. performed a study of transplantations from SCD and ECD donors with the same KDRI score from 2002 to 2012. They focused on donors with a KDRI between 1,4 and 2,1. This population was split into 3 groups covering the following ranges:
1.4-1.6; 1.6-1.8 and 1.8-2.0. An analysis of these groups has shown a similar number of ECD and SCD kidneys qualified for transplantation. Despite the opinion that ECD kidneys are associated with a worse prognosis, no difference in graft survival was noted within each KDRI range. That is, for organs harvested from donor with a KDRI from 1.6 to 1.8 the survival rates were not influenced by their ECD/SCD status (20).

Utilizing the KDPI/KDRI indexes for stratification of risk in organs harvested outside the US remains controversial. Bradley et al have developed a British donor risk index, based on an analysis of 7620 first-time kidney-graft recipients from years 2000-2007. The most important donor-related factors influencing graft survival were found to be: age, history of hypertension, weight, time of hospital stay and vasopressor use. The number of donors suffering from diabetes is relatively smaller in the UK, as is the percentage of ethnic minorities. The UUKKDRI (United Kingdom Kidney Donor Risk Index) is equal 1 for a donor aged 40-59 years, 75kg, with no history of hypertension, a hospital stay of under 24 hours and no vasopressor use. The difference in kidney-graft survival for extreme values of the index is 40%. The formula for calculating UUKKDRI includes only 5 donor traits. Since the predictive value of both indexes is similar (statistical compatibility for UUKKDRI is 0.62 versus 0.63 for the USKDRI), the simplicity of the UK index is a significant advantage (26).

A kidney harvested from a particular donor should be assigned a risk index and be allocated to a recipient most likely to benefit. The kidney allocation system cannot be based solely on choosing the recipient with the longest waiting time and smallest number of HLA mismatches. It should, most importantly, take into account how the quality of a particular organ will influence a specific candidate’s survival. Such an approach may lead to an increase of kidneys accepted for transplantation. In consequence, the survival times of graft recipients should improve and the number of patients waiting for a retransplantation decrease. Estimating the donor-related risk correctly allows for decreasing the time required to accept the organ, reducing the duration of ischaemia. In the last 2 decades several risk indexes have been proposed to predict graft survival, dealing with factors related to the donor, recipient and other parameters of the transplantation procedure. Some of these were based on large populations of donor-recipient pairs and have been accepted by local organ allocation systems. As of yet none has been endorsed by international institutions a universal predictive model of graft function. The new kidney allocation system implemented in the US rates the harvested organs, based on the risk index, from 1 (worst) to 100 (best). Doubt exists as to whether KDPI, as a single parameter, is sufficient information to accept or reject an organ (38). UNOS suggests utilizing all organs with a KDPI under 85%. Who should decide if and when to accept organs rated at over 85%? Does the choice lie with the doctor, the patient or both? Questions such as these remain unanswered.

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