Executive summary

Management of urinary tract infection in solid organ transplant recipients: Consensus statement of the Group for the Study of Infection in Transplant Recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Network for Research in Infectious Diseases (REIPI)

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Executive summary. Abordaje de la infección urinaria en receptores de trasplante de órgano sólido: documento de consenso del Grupo de Estudio de la Infección en Receptores de Trasplante (GESITRA) de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC) y la Red Española para el Estudio de Patología Infecciosa (REIPI)

Las infecciones del tracto urinario (ITU) son muy frecuentes en los receptores de un trasplante de órgano sólido (TOS). Hemos realizado una revisión sistemática para determinar el abordaje de la ITU en receptores de TOS.
Se realizan recomendaciones sobre el abordaje de la bacteriuria asintomática y sobre la profilaxis y tratamiento de las UTI en receptores de TOS. Se han revisado el abordaje diagnóstico-terapéutico de las ITU recurrentes y el papel de la ITU en el rechazo o disfunción del injerto renal. Finalmente, se incluyen recomendaciones sobre las interacciones entre antimicrobianos e immunosupresores.

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Introduction

The use of solid organ transplantation (SOT) has been established as accepted therapy for end-stage disease of the kidneys, liver, heart, and lungs for nearly 30 years. Intestinal and pancreas transplantation are also generally available but are provided on a more limited basis.

Infections remain a major cause of morbidity and mortality in transplant recipients. Urinary tract infections (UTI) are one of the most common infections in SOT, with a high prevalence, reaching 75% in some series involving kidney recipients. Experienced SOT researchers and clinicians have developed and implemented this consensus document in support of the optimal management of these patients.

The target population of this document are adults receiving SOT. The intended guideline audience is physicians involved in the care of SOT recipients (including primary care physicians). Here we report a consensus with the objective of assessing the overall available evidence and to propose recommendations on the following key issues:

1. Definitions.
2. Epidemiology and risk factors for UTI in SOT recipients.
3. Should SOT recipients receive primary prophylaxis for UTI?
4. What should be the management of asymptomatic bacteriuria in SOT recipients?
5. What is the best empirical treatment of UTI in SOT recipients?
6. What is the best definitive treatment of UTI in SOT recipients?
7. How long should SOT recipients receive antibiotics for a UTI?
8. What should be the management of UTI caused by Candida spp. in SOT recipients?
9. What should be the diagnostic-therapeutic management of recurrent UTI in SOT recipients?
10. What role does UTI play in kidney graft rejection or dysfunc-
11. Antimicrobial and immunosuppressant interactions.

Methods

We conducted a systematic review to assess the management of UTI in SOT recipients. Data for this document were identified through a search of PubMed and references from relevant articles using the search terms “transplant” and “urinary tract infection”. The search criteria included articles in English that involved human participants. We selected and revised a total of 3043 articles from 1968 to June 2014.

The evidence level based on the available literature is given for each recommendation to assess the strength of the evidence for risk and benefits of the procedure. This article was written in accordance with international recommendations on consensus statements (Table 1) and the recommendations of the Appraisal of Guidelines for Research and Evaluation II (AGREE II). The authors met twice to discuss the consensus and establish formal recommendations. The coordinators and authors agree on the content and conclusions. The consensus statement was sent to the 96 members of GESITRA for external revision of the manuscript. The board of directors of GESITRA will designate the coordinators to update the statements within 5 years. The full version of the consensus document of this executive summary is available at Ref. 1.

Definitions

Bacteriuria

Bacteriuria is defined according to the criteria proposed by the Infectious Diseases Society of America guidelines. For asymptomatic women, bacteriuria is defined as 2 consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts ≥10^5 colony-forming units (cfu)/ml. A single, clean-catch voided urine specimen with 1 bacterial species isolated in a quantitative count ≥10^2 cfu/ml identifies bacteriuria in men. A single catheterized urine specimen with 1 bacterial species isolated in a quantitative count ≥10^5 cfu/ml identifies bacteriuria in women or men. Asymptomatic bacteriuria (AB) is defined by the presence of bacteriuria in the absence of any symptoms of lower or upper UTI.

Cystitis

Cystitis is defined by the presence of bacteriuria and clinical manifestations such as dysuria, frequency, or urinary urgency in the absence of pyelonephritis criteria.

Pyelonephritis

Pyelonephritis is defined by the simultaneous presence of a urine bacteria count ≥10^5 cfu/ml and/or bacteremia and fever with

Table 1

<table>
<thead>
<tr>
<th>Category, grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength of recommendation</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Solid evidence of efficacy and clinical benefit</td>
</tr>
<tr>
<td>B</td>
<td>Solid or moderately solid evidence of efficacy, but clinical benefit is limited</td>
</tr>
<tr>
<td>C</td>
<td>Insufficient evidence of efficacy or possible benefits in terms of efficacy do not outweigh the cost or risks (toxicity and drug interactions), valid alternatives are available</td>
</tr>
<tr>
<td>D</td>
<td>Moderately solid evidence of a lack of efficacy or poor outcome</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence of a lack of efficacy or poor outcome</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Evidence from at least 1 well-designed and performed trial</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from at least 1 well-designed non-randomized clinical trial, cohort study, or a non-controlled experimental study with non-conclusive results</td>
</tr>
<tr>
<td>III</td>
<td>Expert opinion based on clinical experience, descriptive studies, or reports from expert panels</td>
</tr>
</tbody>
</table>
Epidemiology
urine
urethritis,
urogenital
Complicated
episodes
Reinfection
the
urgency).
prolonged
risk
that
episodes
in
sensitivity
infection,
urinary
frequency,
Recurrent
Prostatitis
Should
a
160–800
the
post-transplant
kidney
imperceptible.
symptoms
of
prostatitis
that
more
failing
a
bacteremia.
The
symptoms
for
prostatic
usually
a
symptoms
of
inflammation.
The
classification
of
patients
with
prostatitis
depends
on
the
bacteriological
study
of
lower
urinary tract
considering
sequential
urine
(B-III).

Reinfection

Reinfection
is
defined
by
a
new
episode
of
infection
with
the
isolation
of
bacterium
other
than
the
one
that
caused
the
previous
infection
or
the
same
bacteria
with
a
different
antibiotic
sensitivity
pattern.
Relapse

Relapse
is
defined
as
the
isolation
of
the
same
microorganism
that
caused
the
preceding
infection,
with
the
same
antibiotic
sensitivity
pattern,
in
a
urine
culture
obtained
≥2
weeks
after
finishing
the
previous
treatment.

Recurrent
infection

Recurrent
infection
is
classically
defined
as
three
or
more
episodes
of
symptomatic
UTIs
over
a
12-month
period
or
two
episodes
in
the
previous
six
months.
Complicated
urinary
tract
infection

A
complicated
UTI
is
defined
as
an
infection
that
is
associated
with
structural
or
functional
abnormalities
of
the
gitourinary
tract,
or
the
presence
of
an
underlying
disease
that
increases
the
risk
of
acquiring
an
infection
or
failing
therapy.

Prostatitis

Prostatitis
is
characterized
by
discomfort
referred
to
the
lower
urogenital
and
perineal
and/or
ejaculatory
discomfort
or
sexual
dysfunction.
Acute
bacterial
prostatitis
is
presented
as
fever
and
chills
accompanied
by
urinary
symptoms
such
as
dysuria,
frequency,
and
perineal
pain.
Chronic
bacterial
prostatitis
has
a
more
prolonged
course,
usually
of
at
least
3
months.
This
is
usually
related
to
or
the
result
of
recurrent
urinary
infection,
or
may
be
a
complication
of
acute
prostatitis
that
is
not
properly
cured,
urethritis,
or
epididymitis.
The
disease
can
occur
continuously
or
episodically.
The
symptoms
are
milder
than
in
acute
prostatitis
and
sometimes
imperceptible.
The
most
common
symptoms
are
perineal
or
pelvic
pain,
low
back
pain,
testicular
difficult,
and
discomfort
when
urinating
or
ejaculating.

The
classification
of
patients
with
prostatitis
depends
on
the
bacteriological
study
of
lower
urinary
tract
considering
sequential
urine
cultures
(Table
2).

Epidemiology
and
risk
factors
for
UTI
in
SOT
recipients

Some
risk
factors
have
been
described
for
the
development
of
UTI
in
SOT
recipients
(Table
3).

Recommendations

Should
SOT
recipients
receive
primary
prophylaxis
for
UTI?

1. Trimethoprim/sulfamethoxazole
(TMP/SMX,
cotrimoxazole
160–800
mg)
antibiotic
prophylaxis
is
recommended
during
the
first
3–6
months
post-transplant
because
it
significantly
decreases
AB
and
symptomatic
UTI,
and
bacteremia
in
renal
transplant
recipients
(A-I).

2. Antibiotic
prophylaxis
is
not
specifically
recommended
for
UTI
in
non-kidney
SOT
recipients.

What
should
be
the
management
of
asymptomatic
bacteriuria
in
SOT
recipients?

3. Screening
for
and
treatment
of
AB
in
kidney
transplant
recipients
(KTR)
is
recommended
in
the
early
postoperative
period
and
up
to
one
month
after
transplantation
(B-III).

4. There
is
not
enough
evidence
to
recommend
continued
screening
for
and
treatment
of
AB
in
a
clinically
stable
KTR
beyond
one
month
after
transplantation
(C-III).

5. Screening
for
and
treatment
of
AB
is
not
currently
recommended
for
other
SOT
recipients
(D-III).

6. Treatment
of
asymptomatic
candiduria
is
not
currently
recommended
for
SOT
recipients.
Among
patients
with
a
urinary
catheter,
removal
of
the
catheter
may
be
sufficient
to
eliminate
candiduria
without
specific
antifungal
therapy
(D-III).

7. Urine
culture
screening
of
patients
awaiting
transplantation
is
not
routinely
recommended
(D-III).

8. Live
donors
should
be
screened
and
treated
for
bacteriuria
before
the
organ
is
harvested
(A-III).

What
is
the
best
empirical
management
of
UTI
in
SOT
recipients?
(Table
4)

Table
2
Sequential
urine
cultures
for
anatomical
location
within
the
lower
urinary
tract.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder emptying 1</td>
<td>BE₁</td>
<td>Initial 5–10 mL of urine stream</td>
</tr>
<tr>
<td>Bladder emptying 2</td>
<td>BE₂</td>
<td>Sample midstream urinary</td>
</tr>
<tr>
<td>Expressed prostatic</td>
<td>EPS</td>
<td>Secretions obtained from transrectal prostate by digital massage</td>
</tr>
<tr>
<td>secretions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder emptying 3</td>
<td>BE₁</td>
<td>First 5–10 mL of urine stream</td>
</tr>
<tr>
<td></td>
<td></td>
<td>immediately after prostatic massage</td>
</tr>
</tbody>
</table>

Stamey
T.
Pathogenesis
and
Treatment
of
Urinary
Tract
Infections.
Baltimore:
Williams;
Wilkins;
1980.

* Definitive
diagnosis
of
bacterial
prostatitis
requires
that
the
number
of
colonies
in
the
BE₁
sample
exceeds
those
in
the
BE₂
sample,
preferably
by
more
than
10	imes.
However,
the
prostate
of
many
patients
with
chronic
prostatitis
contains
only
small
amounts
of
bacteria.
In
these
patients,
a
prostatic
secretions
culture
is
particularly
useful.
Microscopic
examination
of
the
EPS
is
useful
to
identify
leukocytes
and
“oval
fat
bodies” –
large
lipid-laden
macrophages
characteristic
of
prostatic
inflammatory
response.

Table
3
Risk
factors
for
urinary
tract
infections
in
solid
organ
transplantation.

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>MycopHENolate mofetil</td>
</tr>
<tr>
<td>Antithymocyte globulin</td>
</tr>
<tr>
<td>Need for immediate post-transplant dialysis</td>
</tr>
<tr>
<td>Ureteral stent placement &gt; 30 days</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Deceased-donor kidneys</td>
</tr>
<tr>
<td>Number of episodes of acute rejection</td>
</tr>
<tr>
<td>Reflux kidney disease prior to transplantation</td>
</tr>
<tr>
<td>Length of hospitalization</td>
</tr>
<tr>
<td>Length of urinary catheterization</td>
</tr>
<tr>
<td>Number of episodes of acute rejection</td>
</tr>
<tr>
<td>Post-transplant urinary obstructions</td>
</tr>
<tr>
<td>Increase in immunosuppression</td>
</tr>
</tbody>
</table>
Table 4

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Absence of risk factors for multidrug-resistant (MDR) organisms</th>
<th>Presence of risk factors for MDR organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystitis*</td>
<td>Fosfomycin or amoxicillin/clavulunate or second/third-generation oral cephalosporins</td>
<td>Fosfomycin</td>
</tr>
<tr>
<td>Acute uncomplicated pyelonephritis*</td>
<td>Alternative therapy: TMP/SMX or ciprofloxacin Ceftriaxone</td>
<td>Ertapenem or piperacillin-tazobactam</td>
</tr>
<tr>
<td>Severe sepsis/septic shock</td>
<td>Meropenem ± vancomycin (if risk factors for enterococcal infection) ± amikacin (if risk factors for P. aeruginosa)</td>
<td>If potential infection by extensively-drug resistant (XDR) P. aeruginosa or carbapenem-resistant Enterobacteriaceae or MDR A. baumannii, consider expert consultation</td>
</tr>
</tbody>
</table>

In all cases, once culture susceptibility results are available, complete therapy with the most narrow-spectrum antibiotic available.

* Dysuria, urgency, frequency, suprapubic pain without fever, and presence of a urine bacteria count >10^6 cfu/mL.
* Fever, chills, flank/allograft pain, and presence of a urine bacteria count >10^5 cfu/mL.
* Prior hospitalization (within 3 months), previous antibiotic therapy (within 1 month), previous colonization by MDR organisms, reoperation, nosocomial infection, post-transplant hemodialysis, and nephrostomy.

9. The treatment strategy depends on the time elapsed since transplantation and the severity of the illness (B-III).
10. The choice of empirical antimicrobial agents should be based on local epidemiological data and the patient’s history of previous resistant organisms (A-II).
11. Antibiotic therapies prescribed in the previous months should be taken into account (B-III).
12. Review if the patient has recurrent episodes of UTI. The incidence of resistant organisms can rise progressively with the number of episodes (C-III).
13. Especially if resistant organisms are found, expanded antimicrobial testing should be requested from the microbiology lab to identify treatment options for completion of therapy (B-III).
14. Consider removal or replacement of urinary tract instruments such as urethral catheters or urologic stents (B-III).
15. Progression of upper urinary tract disease to a renal or perinephric abscess or emphysematous pyelonephritis usually requires a multidisciplinary approach to treatment, including urologist and/or interventional radiology consultation for percutaneous or surgical drainage of abscesses (A-I).
16. Once culture susceptibility results are available, switch to the narrowest spectrum antibiotic available to complete course of therapy (B-III).
17. Adjust the antibiotic dosage according to the patient’s renal function (A-I).
18. In the event of severe infection with sepsis, consider the option of reducing/discontinuing the immunosuppression therapy (B-III).

What is the best definitive treatment of UTI in SOT recipients?

19. To choose an appropriate antibiotic for the treatment of cystitis caused by Enterobacteriaceae, the recommendations for the general population are adapted to organ transplant patients. For hospitalized patients, we recommend using ceftriaxone or second- or third-generation oral cephalosporin or amoxicillin-clavulanate or fosfomycin troleandom for susceptible strains (B-I). For outpatients, we recommend ciprofloxacin or fosfomycin troleandom (B-I). For the treatment of cystitis caused by extended-spectrum beta-lactamase (ESBL)-producing E. coli, we recommend fosfomycin trometamol (B-I). For cystitis caused by carbapenem-resistant Enterobacteriaceae, we recommend using either fosfomycin troleandom or amoxicillin-clavulanate (B-I). After discharge or in outpatients, we recommend the use of fluoroquinolones (B-I). For pyelonephritis caused by ESBL-producing Enterobacteriaceae, we recommend ertapenem (B-I). Monotherapy with a carbapenem is not recommended for patients with invasive infections caused by carbapenemase-producing Enterobacteriaceae but may be considered in cases of mild invasive infections if adequate source control is readily achieved and the isolate is susceptible (C-III). For patients in which combination therapy is indicated, a regimen with a carbapenem plus one or two fully active drugs (including colistin, an aminoglycoside, or fosfomycin) is recommended if the carbapenem minimum inhibitory concentration (MIC) is ≤8 mg/L; this applies mainly to patients with severe infections caused by KPC-producing Klebsiella pneumoniae (B-II). There are not enough data to recommend including a carbapenem in combination regimens if MIC is >8 mg/L. If this is the case, carbapenems are probably useless. Particularly if MIC is >16 mg/L, we recommend including at least two fully active drugs in the combination regimen according to susceptibility testing results (drugs to be considered: colistin, aminoglycosides, and fosfomycin) (C-III).

20. For the treatment of hospitalized patients with acute pyelonephritis caused by Enterobacteriaceae, we recommend the use of a beta-lactam, either third-generation cephalosporins or amoxicillin-clavulanate (B-I). After discharge or in outpatients, we recommend the use of fluoroquinolones (B-I). For pyelonephritis caused by ESBL-producing Enterobacteriaceae, we recommend ertapenem (B-I). Monotherapy with a carbapenem is not recommended for patients with invasive infections caused by carbapenemase-producing Enterobacteriaceae but may be considered in cases of mild invasive infections if adequate source control is readily achieved and the isolate is susceptible (C-III). For patients in which combination therapy is indicated, a regimen with a carbapenem plus one or two fully active drugs (including colistin, an aminoglycoside, or fosfomycin) is recommended if the carbapenem minimum inhibitory concentration (MIC) is ≤8 mg/L; this applies mainly to patients with severe infections caused by KPC-producing Klebsiella pneumoniae (B-II). There are not enough data to recommend including a carbapenem in combination regimens if MIC is >8 mg/L. If this is the case, carbapenems are probably useless. Particularly if MIC is >16 mg/L, we recommend including at least two fully active drugs in the combination regimen according to susceptibility testing results (drugs to be considered: colistin, aminoglycosides, and fosfomycin) (C-III).

21. For the treatment of cystitis caused by Pseudomonas aeruginosa, we recommend ciprofloxacin for susceptible strains (B-III). For pyelonephritis by P. aeruginosa we recommend the use, when possible, of beta-lactams active against P. aeruginosa in hospitalized patients and quinolones in outpatients (B-III). For the
treatment of pyelonephritis by multidrug-resistant *P. aeruginosa*, we recommend colistin or amikacin with monitoring of renal function when no other options are available (C-III).

22. For ampicillin-susceptible enterococci strains, we recommend oral amoxicillin for the treatment of cystitis (B-III) and intravenous ampicillin for the treatment of pyelonephritis (C-III). For ampicillin-resistant *Enterococcus faecium*, we recommend glycopeptides (C-III). For vancomycin-resistant Enterococcus strains, the treatment should be guided by antibiogram and we recommend the use of quinolones, cotrimoxazole, fosfomycin, nitrofurantoin, and linezolid in order of preference (B-III).

23. For the treatment of infected cysts in patients with renal polycystic disease, we recommend the use of fluoroquinolones or TMP/SMX when possible and percutaneous drainage if necessary (B-III).

24. For the treatment of acute prostatitis we recommend intravenous beta-lactams until apyrexia and consolidation treatment with fluoroquinolones or TMP/SMX when possible (B-I).

   How long should SOT recipients receive antibiotics for a UTI?

25. Kidney recipients presenting AB within the first month of transplantation should receive an oral antibiotic selected according to the susceptibility of the isolated microorganism for a period of 5–7 days (BII). In other SOT recipients, guidelines for the general population should be applied (AII).

26. Cystitis in SOT recipients should be treated for 5–7 days with an oral antibiotic. Early post-transplant cystitis in renal transplant recipients may require longer treatment, especially if a ureteral stent is present (BIIL). Short courses of therapy (single dose or three days) have not been studied in SOT recipients (CIII).

27. KTR with allograft pyelonephritis should undergo a 14-day course of antibiotics. However, patients with allograft pyelonephritis in the early post-transplant period presenting with sepsis should be treated for at least 14–21 days (BIIL). Late uncomplicated allograft pyelonephritis occurring more than six months after kidney transplantation may be treated with antibiotic therapy for 10–14 days (BIIL). At least initially, intravenous antibiotic therapy is recommended in kidney recipients with allograft pyelonephritis (AIII).

28. In non-kidney SOT recipients with uncomplicated pyelonephritis, a 10–14-day course of antibiotics is recommended (BIIL). At least initially, these patients should be treated with intravenous antibiotics (AII).

29. No data are available on short courses (7 days) of antibiotic therapy for pyelonephritis or UTI in SOT recipients. Therefore, short-term treatment is not recommended in SOT (CIII).

30. For SOT recipients with complicated pyelonephritis, an antibiotic course of at least two weeks is recommended and should be extended until abscesses are adequately drained and patient improvement has been achieved (BIIL).

31. For SOT recipients with acute bacterial prostatitis, a 2- to 4-week course of antibiotics is recommended. However, antibiotic therapy can be continued for up to four weeks in patients with severe illness, concomitant bacteremia, and undrained abscesses (BIIL).

32. In SOT recipients with polycystic kidney disease and infected cysts, treatment of not less than 14 days is recommended and may be extended depending on patient evolution, cyst diameter, and possibility of drainage (BIIL).

   What should be the management of UTI caused by Candida spp. in SOT recipients?

   What should be the initial diagnostic approach to a SOT recipient with candiduria?

33. SOT recipients with candiduria should be classified according to the presence of risk factors for disseminated candidiasis, indications for obtaining a urine culture (surveillance or infection suspicion), and according to their clinical situation (asymptomatic, with urinary tract symptoms or with general manifestations of sepsis) (A-III).

34. Predisposing risk factors should be eliminated or controlled (antibiotic use, malnutrition, hyperglycemia) and urinary catheters should be removed or at least changed if possible. The presence of candiduria should be verified with a second, clean-voided urine culture (A-II).

35. Disseminated candidiasis should be considered in all hospitalized SOT with candiduria. If clinical manifestations are compatible, blood cultures, a second urine culture after removal or replacement of the urinary catheter, fundoscopy, cultures from any other significant site (vascular accesses, peritoneal fluid, etc.), and a kidney imaging study should be obtained (AII).

36. Patients with persistent candiduria and no indwelling bladder catheter should undergo imaging of the kidneys and collecting system to exclude renal abscess, fungus balls, or other urologic abnormalities (A-II).

37. SOT recipients in whom *Candida* contamination of the preservation fluid is demonstrated or suspected (donors with ruptured abdominal viscus at the time of multiorgan recovery) should undergo urgent diagnostic evaluation including Doppler ultrasound, blood and urine cultures, and cultures from any other significant site (B-III).

   Which patients should receive antifungal drugs?

38. Asymptomatic candiduria in SOT patients that are not neutropenic or undergoing a urologic procedure should not be treated with antifungal therapy (D-II).

39. Candiduria in an unstable SOT should be initially considered as a potential marker of disseminated candidiasis. Prompt effective antifungal therapy has to be provided until an alternative diagnosis is obtained (A-II).

40. Candida cystitis or pyelonephritis should be treated with systemic antifungals for 2–4 weeks (B-II).

41. Fungus balls or casts in the pelvis or urinary bladder need surgery and systemic and/or local antifungal therapy (A-II).

42. KTR with contamination of the preservation fluid or with a donor with digestive tract rupture should receive early effective antifungal therapy (B-II).

   Which drug should be prescribed and for how long? (Table 5)

43. Fluconazole is the agent of choice for most patients with *Candida* UTI due to the high concentration achieved in urine (>100 μg/ml, which is 10-fold the simultaneous plasma level) (A-II).

44. Other antifungal agents should only be considered for patients in unstable clinical condition, allergic to fluconazole, or in whom therapy has clearly failed despite maximum fluconazole doses and optimal management of urologic abnormalities or other predisposing conditions (B-II).

45. A single dose of parenteral amphotericin B (AMB) deoxycholate, with or without oral 5-flucytosine, reach high concentrations in urine, and may be used to treat *Candida* cystitis in patients not responding to or not treatable with fluconazole. *Candida* pyelonephritis can also be treated with AMB. However, potential kidney toxicity limits its use in the transplant population (B-I).

46. Liposomal AMB, with or without 5-flucytosine, may be used to treat *Candida* pyelonephritis in patients not responding to or not treatable with fluconazole. However, due to the low concentration reached in urine, a relapse may occur if the collecting system is infected (C-III).

47. AMB deoxycholate bladder irrigation may be used in patients with symptomatic cystitis that cannot be treated with other drugs (C-II).
Table 5
Antifungal drugs.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indications</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>Drug of choice for <em>Candida</em> cystitis and pyelonephritis</td>
<td>Loading dose 12 mg/kg, followed by 6 mg/kg/d IV or PO (≥400 mg/d for symptomatic candiduria)</td>
<td>Hepatotoxicity in patients with liver insufficiency</td>
</tr>
<tr>
<td></td>
<td>Anti fungal prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preemptive therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Targeted therapy for systemic candidiasis caused by susceptible strains in stable patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d-AMB</td>
<td>Very rarely needed</td>
<td>Parenteral 0.3–1 mg/kg/d</td>
<td>Bladder irritation. Cumbersome</td>
</tr>
<tr>
<td></td>
<td>Symptomatic cystitis or pyelonephritis in patients not responding to or not treatable with fluconazole</td>
<td>Continuous or intermittent bladder irrigation: 50 mg in 1 L (50 μg/ml) 1-7d</td>
<td>Drug interactions: cisplatin, pentamidine, aminoglycosides, cyclosporine, corticoids and others.</td>
</tr>
<tr>
<td>Candins</td>
<td>Initial drugs of choice for systemic candidiasis in unstable patients, in patients who have been exposed to azoles in the previous 3 months and in patients with renal insufficiency requiring external replacement therapy <em>Candida</em> pyelonephritis in patients not responding to or not treatable with fluconazole</td>
<td>Anidulafungin 200 mg/d loading dose, followed by 100 mg/d</td>
<td>Preferred if recent azole exposure, patients in septic shock or with external renal devices</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mecafungin 100 mg/d IV</td>
<td>Low urine concentration. Relapse may occur if the collecting system is the source of the candidemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caspofungin 70 mg loading dose, followed by 50 mg/d IV</td>
<td>Drug interactions: Anidulafungin (none), Mecafungin (sirolimus, nifedipine, itraconazole), Caspofungin (cyclosporine, tacrolimus, efavirenz, nevirapine, ritampicin, desamethasone, phenytoin, carbamazepine)</td>
</tr>
<tr>
<td>L-AMB</td>
<td><em>Candida</em> pyelonephritis in patients not responding to or not treatable with fluconazole</td>
<td>3 mg/kg/d IV</td>
<td>Low urine and kidney concentration. Relapse may occur</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug interactions: digoxin, aminoglycosides, cyclosporine and others.</td>
</tr>
<tr>
<td>Voriconazole</td>
<td><em>Candida</em> pyelonephritis in patients not responding to or not treatable with fluconazole</td>
<td>6 mg/kg/d two loading doses, followed by 3 mg/kg/12 h IV or PO</td>
<td>Low urine concentration. Relapse may occur</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug interactions: rifabutin, rifampicin, methadone, ritonavir, efavirenz, carbamazepine, ranitidine, macrolides, sirolimus, cyclosporine, tacrolimus, warfarin, coumadin, statins, benzodiazepines, omeprazole, oral contraceptives and others.</td>
</tr>
<tr>
<td>5-flucytosine</td>
<td>Symptomatic cystitis in patients not responding to or not treatable with fluconazole</td>
<td>25 mg/kg every 6 h 7–10 d</td>
<td>Emergence of resistance if given alone or for prolonged periods. Adjust dose if renal insufficiency. Gastrointestinal, liver and bone marrow toxicity</td>
</tr>
</tbody>
</table>

48. Echinocandins are the preferred initial agents for systemic candidiasis in unstable patients, in patients who have been exposed to azoles in the previous 3 months, and in patients with renal insufficiency requiring external replacement therapy (A-I).
49. Echinocandins achieve low concentrations in the urinary tract but may be used in patients not responding to or not treatable with fluconazole. If the collecting system is infected, relapse may occur (C-III).
50. All symptomatic UTIs due to *Candida* species in KTR should be considered complicated and treated for at least 14 days (B-II).

What should be the diagnostic-therapeutic management of recurrent UTI in KTR recipients?
51. The diagnostic approach in transplant patients with recurrent UTI must be meticulous in order to rule out the existence of anatomical or functional changes (A-III).
52. If possible, treatment aimed at the sensitivity of the isolated microorganisms must be used in patients with recurrent UTI. TMP/SMX is a good option (B-III). Quinolones must be avoided as empirical therapy (D-II).
53. Duration of antibiotic treatment for recurrent UTIs in transplant patients is not well-defined. At least a 6-week treatment period may be recommendable (B-III), although other authors suggest prolonging treatment more than three months. Indefinite treatment may be evaluated in diabetic patients, patients with a history of UTIs before or soon after transplantation and those receiving high-dose immunosuppressive treatment (equivalent to secondary prophylaxis) (B-II).
54. Anatomical changes related with recurrent UTI must be corrected if possible (A-II).
55. The use of non-antibiotic therapies, such as cranberry extract, L-methionine, topical estrogens, or topical application of Lactobacillus, could be provided to transplant patients with recurrent UTI (C-II). What role does UTI play in kidney graft rejection or dysfunction?
56. Kidney transplant patients are particularly vulnerable to infections, and this is one of the reasons for which primary
Table 6
Interactions between aminoglycosides and immunosuppressants. *

<table>
<thead>
<tr>
<th>Immunosuppressants</th>
<th>AMK</th>
<th>GEN</th>
<th>ETM</th>
<th>EPT</th>
<th>KAN</th>
<th>TOB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
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<td>B</td>
<td>B</td>
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<td>b</td>
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<td>b</td>
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<td>b</td>
<td>b</td>
<td>b</td>
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<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Basiliximab</td>
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<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

AMK: amikacin; GEN: gentamicin; ETM: streptomycin; EPT: spectinomycin; KAN: kanamycin; TOB: tobramycin.

* A/a: these drugs should not be co-administered; B/b: potential interaction – may require monitoring of plasma levels and graft function and/or change in dose; C/c: no clinically relevant interactions; A, B, C: indicate that interaction has been described; a, b, c: indicate that interaction is based on a prediction guided by the pharmacokinetic characteristics of the product.

Prophylaxis has been established (A-I) and early aggressive treatment of symptomatic UTI is recommended (A-II).

57. Although UTI has been associated with induction of acute rejection in kidney transplant patients (A-II), there is controversy about the final impact on the graft in terms of chronic rejection or dysfunction (B-II).

58. Late-onset UTIs, which were traditionally associated with a good prognosis, have also been recently related with a risk of rejection or dysfunction of the kidney graft (B-II).

Table 7
Interactions between beta-lactams and immunosuppressants. *

<table>
<thead>
<tr>
<th>Immunosuppressants</th>
<th>AMP</th>
<th>AMC</th>
<th>CLO</th>
<th>NAF</th>
<th>CFU</th>
<th>CFZ</th>
<th>CFX</th>
<th>AZT</th>
<th>IMI</th>
<th>TIC</th>
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<td>b</td>
<td>b</td>
<td>C</td>
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<td>C</td>
</tr>
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<td>C</td>
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</tr>
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<td>C</td>
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<td>C</td>
<td>C</td>
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</tr>
</tbody>
</table>

AMP: ampicillin; AMC: amoxicillin-clavulanate; CLO: clavulanic acid; NAF: naftidrofuryl; CFU: cefuroxime; CFZ: cefazidime; CFX: ceftiraxone; AZT: aztreonam; IMI: imipenem; TIC: ticarcillin.

* A/a: these drugs should not be co-administered; B/b: potential interaction – may require monitoring of plasma levels and graft function and/or change in dose; C/c: no clinically relevant interactions; A, B, C: indicate that interaction has been described; a, b, c: indicate that interaction is based on a prediction guided by the pharmacokinetic characteristics of the product.

Table 8
Interactions between quinolones and immunosuppressants. *

<table>
<thead>
<tr>
<th>Immunosuppressants</th>
<th>CIP</th>
<th>LEV</th>
<th>MOX</th>
<th>NAL</th>
<th>NOR</th>
<th>OFL</th>
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<tr>
<td>Cyclosporine</td>
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</tr>
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<td>b</td>
<td>b</td>
<td>B</td>
</tr>
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<td>Mycophenolate</td>
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<td>C</td>
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</tr>
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<td>Sirolimus</td>
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</tr>
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<td>C</td>
</tr>
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<td>B</td>
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<td>C</td>
<td>C</td>
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<td>C</td>
</tr>
</tbody>
</table>

CIP: ciprofloxacin; LEV: levofloxacin; MOX: moxifloxacin; NAL: nalidixic acid; NOR: norfloxacin; OFL: ofloxacin.

* A/a: these drugs should not be co-administered; B/b: potential interaction – may require monitoring of plasma levels and graft function and/or change in dose; C/c: no clinically relevant interactions; NA: data not available; A, B, C: indicate that interaction has been described; a, b, c: indicate that interaction is based on a prediction guided by the pharmacokinetic characteristics of the product.

59. The association between AB and graft loss is unclear. *Antimicrobial and immunosuppressant interactions (Tables 6–11)*

60. The treatment of UTIs in SOT recipients is more complex due to interactions between antimicrobials and immunosuppressants.

61. The interactions may jeopardize the transplanted organ and also increase the specific adverse effects of each drug.

Table 9
Interactions between other antibiotics and immunosuppressants. *

<table>
<thead>
<tr>
<th>Immunosuppressants</th>
<th>TIG</th>
<th>VAN</th>
<th>DAP</th>
<th>LIN</th>
<th>COT</th>
<th>DOX</th>
<th>FOS</th>
<th>CLI</th>
<th>MET</th>
<th>FID</th>
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</tbody>
</table>

TIG: tigecycline; VAN: vancomycin; DAP: daptomycin; LIN: linezolid; COT: cotrimoxazole; DOX: doxycycline; FOS: fosfomycin; CLI: clindamycin; MET: metronidazole; FID: fidaxomycin.

* A/a: these drugs should not be co-administered; B/b: potential interaction – may require monitoring of plasma levels and graft function and/or change in dose; C/c: no clinically relevant interactions; NA: data not available; A, B, C: indicate that interaction has been described; a, b, c: indicate that interaction is based on a prediction guided by the pharmacokinetic characteristics of the product.

Comparing the effects of prophylaxis and treatment, it is clear that antibacterial agents pose a significant threat to kidney transplant recipients. A detailed analysis of these interactions will be provided in a future publication.
Table 10

Interactions between azoles, echinocandins and immunosuppressants.a

<table>
<thead>
<tr>
<th>Immunosuppressants</th>
<th>KET</th>
<th>ITR</th>
<th>FLU</th>
<th>VOR</th>
<th>POS</th>
<th>CAS</th>
<th>MIC</th>
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</table>

KET: ketoconazole; ITR: itraconazole; FLU: fluconazole; VOR: voriconazole; POS: posaconazole; CAS: caspofungin; MIC: micafungin; ANI: anidulafungin.

* A/a: these drugs should not be co-administered; B/b: potential interaction – may require monitoring of plasma levels and graft function and/or change in dose; C/c: no clinically relevant interactions; NA: data not available; A, B, C: indicate that interaction has been described; a, b, c: indicate that interaction is based on a prediction guided by the pharmacokinetic characteristics of the product.

* It is recommended to reduce the dose of cyclosporine = 50%.

* It is recommended to reduce the dose of tacrolimus = 25%.

* It is recommended to reduce the dose of sirolimus = 33%.

* It is recommended to reduce the dose of sirolimus = 50%.

Table 11

Interactions between flucytosine, polyenes and immunosuppressants.a

<table>
<thead>
<tr>
<th>Immunosuppressants</th>
<th>FUC</th>
<th>ABD</th>
<th>ABL</th>
<th>ABC</th>
</tr>
</thead>
<tbody>
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<td>B</td>
<td>B</td>
</tr>
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<td>B</td>
</tr>
<tr>
<td>Mycophenolate</td>
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<tr>
<td>Sirolimus</td>
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<td>b</td>
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<td>Everolimus</td>
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<td>B</td>
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<td>B</td>
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</tr>
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<td>Basiliximab</td>
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<tr>
<td>Muromonab</td>
<td>NA</td>
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</table>

FUC: flucytosine; ABD: amphotericin B deoxycholate; ABL: liposomal amphotericin B; ABC: amphotericin lipid complex.

* A/a: these drugs should not be co-administered; B/b: potential interaction – may require monitoring of plasma levels and graft function and/or change in dose; C/c: no clinically relevant interactions; NA: data not available; A, B, C: indicate that interaction has been described; a, b, c: indicate that interaction is based on a prediction guided by the pharmacokinetic characteristics of the product.

Conflict of interest

JMC has received a conference grant from Astellas, Astra-Zeneca, MSD, Novartis, and Pfizer. All other authors have no conflict of interest to declare.

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Reference


62. Key measures to avoid the consequences of these interactions are to know and to prevent them by monitoring the plasma levels of these drugs, monitoring graft function and characteristic adverse effects, and avoiding contraindicated combinations (All).