Tropical and parasitic infections in solid organ transplantation

6th International Congress Infections & Transplantation
Varese Italy 18-20 May 2017.

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Belo Horizonte, Minas Gerais, Brazil
Nothing to disclosure
Highlights

• The Scenario
• Main Challenges
• Specific Diseases
• Take Home Message
**The Scenario**

*Rare complication even in tropical settings, however they are growing in importance ...*

<table>
<thead>
<tr>
<th>Transplantation</th>
<th>Geographical exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing numbers of transplants in the tropics</td>
<td>Travelling to endemic areas</td>
</tr>
<tr>
<td>Expanded organ acceptance</td>
<td>Immigration</td>
</tr>
<tr>
<td></td>
<td>“Transplant tourism”</td>
</tr>
<tr>
<td></td>
<td>Climate changes</td>
</tr>
</tbody>
</table>

- **"True"** incidence is unknown
  - Information based on case reports
  - Frequently misdiagnosed

- Associated with high mortality
DDI, reactivation and community acquired

The Paradigm Shift: Timetable

Tropic and parasitic diseases are expected to occur in any period after transplantation

Fishman J AJT, 2017
Which to choose?

• Protozoa
  – Chagas
  – Leishmaniasis

• Virus
  – Dengue fever
  – Yellow fever
  – Zika
  – Chikungunya

Most relevant diseases: impact or prevalence
Main Questions

- What are the risks for donors and recipients?
  - Endemic x Non-endemic
- How to screen?
- Organ acceptance criteria
- How do you manage?
CHAGAS DISEASE
Chagas Disease

Estimated prevalence *T. cruzi*

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>0.7%</td>
</tr>
<tr>
<td>Brazil</td>
<td>1.3%</td>
</tr>
<tr>
<td>Colombia</td>
<td>3.9%</td>
</tr>
<tr>
<td>Argentina</td>
<td>8.2%</td>
</tr>
<tr>
<td>Bolivia</td>
<td>15.4%</td>
</tr>
</tbody>
</table>

Estimated prevalence *T. cruzi*-infected immigrants

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>2.0%</td>
</tr>
<tr>
<td>Europe</td>
<td>2.9%</td>
</tr>
<tr>
<td>Canada</td>
<td>3.5%</td>
</tr>
<tr>
<td>Australia</td>
<td>3.8%</td>
</tr>
<tr>
<td>Spain</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

Protozoan *Trypanosoma cruzi*
7 - 8 M infected people worldwide, mostly in Latin America countries
Illustrative Case

• 22 yo female admitted 3 mo after KT with intermittent fever and lack of appetite during the last 3 days
  • Pancytopenia (Hb 5.9 g/dL, WBC 1,600 cels/mm³ and platelets 90,000)
  • No respiratory symptoms, no visceromegaly, no skin lesions

  – Direct microscopy: parasites in peripheral blood and bone marrow

  – Negative ChD serology

Surprise!!
C shape trypomastigote with a proeminent kinetoplast

Courtesy of Dr Ligia Pierrotti
Hospital das Clínicas - USP São Paulo. Renal Transplant Service
The Follow-up

The patient

- BZD 300 mg/day, 60 days (acute ChD) with response (PCR and parasitemia negative).

The donor

- Negative ChD ELISA

Further investigation:

- POSITIVE ChD IHA (Hospital where the organs were retrieved)

66 yo female, died due to hemorrhagic stroke (Born in endemic area: Pernambuco, Brazil).

5 mo later and 1 mo after rejection treatment (ATG plus IVIG)

- Readmitted: fever + cytopenia + parasitemia = same symptoms
- ChD relapse (PCR 868,000 parasites/ml blood)

Retreated with BZD 300 mg/day

Monitoring:

- Negative parasitemia after 2 weeks: PCR and parasitological tests
- Serology (ELISA and TESA-blot): persisted negative (no seroconversion)

ChD DDI and reactivation after rejection treatment
What are the risks for recipients?

- **Epidemiological situation:** Endemic x Non-endemic
- **DDI risk:** ~ 10-20% LT and KT.
- **Reactivation:**
  - Higher for heart > kidney: HT (27 to 90%) and KT (8 to 22%)
  - Mostly in the 1st y after transplant.
  - Outcomes are usually similar to those without ChD.
- **Organ acceptance:**
  - Yes: Kidneys and livers chronically infected donors
  - No: Donors with acute infection + Hearts (DDI>75%) and Intestines.
## How to screen and manage?

### Donor Screening:
- **Endemic:** All donors
- **Non-endemic:** If + epidemiology
  - **TARGET SCREENING**
  - At least one single **high-sensitivity and specificity test.**

### For ChD diagnosis:
- **At least 2 serological methods (ELISA, IMF and IHA).**
- **PCR no use as screening test (S: 40 – 95%)** Intermittent parasitemia

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### Studies on prophylaxis for D+/R- or R+ are lacking.
Consider treatment of the **Living donor**

### Recipients should be monitored for 6 to 24 mo (even if prophylaxis is provided).
Routine tests may detect subclinical infection before symptoms.
**No study to validate a specific monitoring program.**

- **Options:** Benznidazole* and Nifurtimox. Cure rate ~ 80%.
- If transmission occurs, test weekly until 2 negative results.

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*Pierrotti et al. Transplantation 2017 in press*
*Pinazo et al PLoS Negl Trop Dis 2013*
*Lattes R & Lasala M CMI 2014*
LEISHMANIASIS
Leishmaniasis

Protozoan disease transmitted through the bite of infected female sandflies.

Broad range of clinical presentation that depends on the species and host.

### Mucocutaneous Leishmaniasis

**INCIDENCE:** 18 cases/100,000 hab
- Few cases in SOT

### Visceral Leishmaniasis

**INCIDENCE:** 2 cases/100,000 hab
- Less frequent GP x More prevalent SOT
- L. infantum chagasi and L. donovani
- Several cases in SOT

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**Region** | **Complex** | **Species** | **Clinical Manifestation**
---|---|---|---
Old World | Leishmania donovani | L donovani | CL, VL, PKLD, ML (rare)
 | L infantum | CL, VL (children), PKLD, ML (rare)
 | L chagasi | CL, VL (children), PKLD, ML (rare)
 | L tropica | CL, ML (rare), VL (rare)
 | L major | CL, ML (rare)
 | L aethiopica | CL, DCL

tropica

New World | Leishmania mexicana | L mexicana | CL, DCL (rare)
 | L amazonensis | CL, DCL, ML, VL (rare), PKLD (rare)
 | L venezuelensis | CL, DCL (rare)
 | L braziliensis | CL, ML, VL
 | L guyanensis | CL, ML
 | L panamensis | CL, ML
 | L peruviana | CL

Leishmania (Viannia) braziliensis

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Illustrative Case

17 yo male, Underwent LT 3 y before. IS regimen: Steroid + FK.

At admission 3 months: weight loss (3kg) + bloody diarrhea.
Visceromegaly + Pancytopenia, but no fever
Negative Anti-Leishmania serology IFAT

COlonic Leishmaniasis: Atypical presentation

Treatment: LamB 3 mg for 7 days with total resolution of clinical and laboratory findings
Relapse 5 mo after treatment.
Mantained with secondary prophylaxis: 3 mg/kg/monthly (18 months)

Clemente et al Transplantation 2011
The role of asymptomatic carrier in the transmission of *Leishmania*

What is the evidence?

- Up to 70% of blood donors were seropositive for *Leishmania* (serological method and endemic area).
- Few cases of transmission by blood.
- No proved SOT DDI reported

Besides the great number of asymptomatic infections VL remains infrequent

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>LT Recipients (N = 50)</th>
<th>Matched-Liver Donors (N = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive IFA (≥ 1:80)</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Anti-Leish rK39 rapid test</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any PCR detection</td>
<td>4 (8%)</td>
<td>4 (23.5%)</td>
</tr>
<tr>
<td>Blood</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Liver</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Spleen</td>
<td>NA</td>
<td>1</td>
</tr>
</tbody>
</table>

None of the LT recipients developed VL over 24 mo follow-up. 3 VL cases ~ 830 LT; 2% asymptomatic infection

*Michel, Acta Tropica 2011*

*Elmahallawy, TID 2015*

*Fukutani, BMC Infectious Diseases 2015*

Organs should not be discarded!

*Clemente et al, AJT 2014*
How to screen the donors?

<table>
<thead>
<tr>
<th>Which tests should be performed?</th>
<th>Donor screening is not recommended!</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor acceptance criteria</td>
<td>Positive serology or previous exposure</td>
</tr>
<tr>
<td></td>
<td>• Does not CI donation</td>
</tr>
<tr>
<td></td>
<td>• Is not recommendation for treatment</td>
</tr>
<tr>
<td></td>
<td><strong>Active disease</strong> (Living donor) <strong>should be treated</strong> before donation.</td>
</tr>
<tr>
<td>If you accept the organ donor, how to manage?</td>
<td>Monitor the recipient</td>
</tr>
<tr>
<td></td>
<td>• Signs and symptoms</td>
</tr>
<tr>
<td></td>
<td>• Sequential PCR could be useful</td>
</tr>
</tbody>
</table>

*Clemente et al. Transplantation 2017 in press*
### Visceral Leishmaniasis after SOT

**Multicenter survey, 1995 - 2012**

*Clemente et al 2014 REIPI Network. CMI 2015*

#### 36 VL cases (mostly KT: ~ 70%)

<table>
<thead>
<tr>
<th>Median time post-transplant</th>
<th>11 months (30% &lt; 6mo)</th>
</tr>
</thead>
</table>

#### Clinical manifestations

- Temperature > 38°C: 86%
- Visceromegaly: 81%
- Cytopenia: 47%

*Only 1/3 exhibited the triad*

#### Diagnostic methods: Microscopy + Serology

- Bone marrow microscopy: 81%
- PCR: 75%
- Culture: 59%
- Serology (IFA + rK39): 76%

#### Treatment option

- Amphotericin B (~ 10 days): 83%
- Miltefosine: Treated twice

#### Relapse after cure

- With NO secondary prophylaxis: 35%
- With secondary prophylaxis: 8%

#### Outcome: Mortality at 30 days 2.8%

#### Miltefosine

Relapse rate of 20% (6 mo follow-up). Increase dose, duration of treatment and prolonged observation period.

*Good option for prophylaxis (?)*

What is the role PCR?

PCR allow species identification  
→ treatment

It can be of use
• pre-emptive approach?
• early detection of relapse?

Case report: Lung Tx recipient: Positive PCR on PB: months before the development of symptoms

Persistence of parasite in tissue after treatment does not necessarily represent relapse.

Moreno EC et al. PloS Negl Trop Dis 2009

Usefulness of highly sensitive real-time PCR for pre-emptive diagnosis

Opota et al TID, 2016
# Leishmaniasis - Recipients

<table>
<thead>
<tr>
<th>What are the risks?</th>
<th>The higher prevalence of latent infection in GP is related to an increased risk active disease after SOT.</th>
</tr>
</thead>
</table>
| Which tests should be performed? | The combination of multiple methods is recommended for diagnosis.  
PCR which may allow species identification and may be positive months before the development of symptoms. |
| How to manage? | Immunosuppressant dose reduction is recommended  
**Treatment depends on patient characteristics, Leishmania species, disease extent, drug availability, concomitant infections and previous treatments**  
Amphotericin B, pentavalent antimonials, miltefosine, among others. |

ARBOVIRUSES
Arboviruses: “arthropod-borne-viruses”

Diseases x Geographical vector distribution

<table>
<thead>
<tr>
<th>Dengue</th>
<th>Chikungunya</th>
<th>Zika</th>
<th>Ae. aegypti</th>
<th>Ae. albopictus</th>
<th>Mostly urban cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aedes spp</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Yellow Fever</th>
<th>Haemagogus</th>
<th>Sabethes</th>
<th>Mostly sylvatic cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aedes spp</td>
<td></td>
<td>Some urban cycle</td>
</tr>
</tbody>
</table>

**Ae. aegypti**

![Map of Ae. aegypti distribution](www.who.int)

**Ae. albopictus**

![Map of Ae. albopictus distribution](www.who.int)
### Urban Arboviruses: Clinical features

#### Similar early clinical signs and symptoms

<table>
<thead>
<tr>
<th></th>
<th>Dengue</th>
<th>Chikungunya</th>
<th>Zika</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incubation period</strong></td>
<td>3 – 15 days (median 6 days)</td>
<td>1 – 12 days (median 5 days)</td>
<td>3 – 12 days</td>
</tr>
<tr>
<td><strong>Period of fever</strong></td>
<td>3 – 7 days</td>
<td>7 – 10 days</td>
<td>3 – 7 days</td>
</tr>
<tr>
<td><strong>Typical clinical picture</strong></td>
<td>High fever start abruptly, myalgia, headache</td>
<td>Fever and arthralgia</td>
<td>Low-grade fever, intense itching, rash and conjunctivitis</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>30 – 50% cases</td>
<td>50% cases</td>
<td>~100% cases</td>
</tr>
<tr>
<td><strong>Leukopenia/Thrombocytopenia</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Hemorrhage</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Asymptomatic cases</strong></td>
<td>Up to 75%</td>
<td>Up to 25%</td>
<td>Up to 80%</td>
</tr>
</tbody>
</table>

Adapted from Ioos S et al. Medecine et maladies infectieuses, 2014
Urban arboviruses in transplant settings

Seldomly described + similar outcomes + death rates

### Dengue
- Several cases among SOT recipients
- Clinical picture and outcome similar to the general population
  - Low risk of DHF due to decreased T-cell responses?

### Chikungunya
- Few cases among SOT recipients
- Apparently with less complications and chronic arthralgia

### Zika
- Very few cases
- Clinical picture and outcome apparently similar to the general population

What we still don’t know: The impact of immunosuppression and the need of adjustments? The influence of overlapping diseases? Viruses shedding pattern?


Vectorial and Non-vectorial Transmission

Vector

Animal bites

Blood + Organ

Sexual (ZIKV)

Accidental Laboratory Exposure

Vertical

Besides vector transmission, other routes...

With and without related birth defects.
Maroun-Ortiz Ginecol Obstet Mex 2014

Thus the presence of virus RNA mean transmission?
Risk assessment

There is not enough knowledge to forecast...

- The viruses are present in blood up to 2-3 weeks after a infected-mosquito bite
- The viruses persist in tissue after clearance from the blood
- Asymptomatic infection allows the donor to pass through the filter of clinical selection
- High viremic titers are seen in asymptomatic patients
- Some samples containing virus RNA can be cultured

The persistence of ZKV in body fluids have been reported to last longer in urine and semen (Kidney transplantation ?)  


Estimated Prevalence of Asymptomatic Viremia in Blood Donors for DENV/ CHIKV/ ZIKV

Positive rate (max):
- DENV up to 0.4%
- CHIKV up to 1.9%
- ZIKV up to 2.8%

Prevalence (%)

- By blood RT-PCR
- By mathematical modeling*

- DENV
- CHIKV
- ZIKV

Data sources:
- Mohammed et al., 2008 (Puerto Rico, 2005)
- Linnen et al., 2008 (Honduras 2004 - 2005)
- Stramer et al., 2012 (Puerto Rico, 2007)
- Diás et al., 2012 (Brazil, 2003)
- Galian et al., 2012 (French West Indies, 2014)
- Chiu et al., 2015 (Puerto Rico, 2014-2015)
- Simmons et al., 2015 (Puerto Rico, 2014)
- Appassakij et al., 2016 (French Polynesia before...)
- Aubry et al., 2015 (French Polynesia 2013-2014)
- Musso et al., 2014 (French Polynesia 2013-2014)
- Kuehnert et al., 2016 (Puerto Rico, 2016)
### Illustrative Case

#### Blood DDI Transmission (ZIKV)

<table>
<thead>
<tr>
<th>The Recipient:</th>
<th>The Blood Donor:</th>
</tr>
</thead>
<tbody>
<tr>
<td>– 55-yo male</td>
<td>– 54-yo male who was a <strong>repeat</strong> blood donor</td>
</tr>
<tr>
<td>– Hepatocellular carcinoma</td>
<td>– <strong>3 days after donation</strong>: contacted the center reporting <strong>fever, malaise and headache</strong> since 2 days after donation</td>
</tr>
<tr>
<td>– Underwent to LT from a DD</td>
<td>– On physical exam: <strong>no rash and no conjunctivitis</strong></td>
</tr>
<tr>
<td>– Received pool platelet concentrate one day after LT</td>
<td></td>
</tr>
</tbody>
</table>

*ZIKV RT-PCR detected in blood: donor and LT recipient*

*LT recipient: develop no symptoms related to ZIKV infection*
## Organ DDI Transmission

### What do we really have?

<table>
<thead>
<tr>
<th>Virus</th>
<th>Source of Transmission</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZKV</td>
<td>Blood products</td>
<td>N: 3 Good outcome</td>
<td>Brazilian Health Regulatory Agency - ANVISA</td>
</tr>
<tr>
<td>CHKV</td>
<td>Positive CHIKV RNA in corneoscleral rims</td>
<td>N: 4/12 Potential risk</td>
<td>Couderc T JID 2012. SP donors with + IgG apparently do not transmit CHKV.</td>
</tr>
</tbody>
</table>

There are only a few cases of proven DDI transmission, usually with favorable outcome.
Yellow Fever

Recent and ongoing outbreak in numbers...

<table>
<thead>
<tr>
<th>Brazilian Outbreak</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec 2016 to Apr 2017</td>
<td></td>
</tr>
<tr>
<td>Suspected cases</td>
<td>2900</td>
</tr>
<tr>
<td>Confirmed cases</td>
<td>681</td>
</tr>
<tr>
<td>Discarded</td>
<td>1451</td>
</tr>
<tr>
<td>Under investigation</td>
<td>768</td>
</tr>
<tr>
<td>Case fatality rate</td>
<td>34%</td>
</tr>
</tbody>
</table>

Flavivirus (like Zika, Dengue, and WN)
500 M people at risk in Africa and ~ 400 M in LA
High case-fatality rate


Brazil: Sylvester transmission
(no urban described cases since 1942).

Mining Disaster (Samarco company) November 2015

Concidently nearly one year ago the rupture of a dam caused the contamination of a major river (Rio Doce river) in MG, in the same area that the outbreak started.

Ecosystem Imbalance: Rio Doce basin

Cause effect relationship is under investigation!
YF in Transplant Setting

- No reported cases in transplant recipients
- YF vaccine: live attenuate strain
  - Not recommended to immunocompromised
  - Recommended before transplantation

- Transmission related to transfusion after YFV (CDC MMWR, 2010) → Temporary defer donation after live virus vaccine (at least 2 weeks)

Brazilian recommendations (ANVISA/MS no.001/2017): 4 weeks after vaccination for blood and organ donation; 6 months for cells and tissues.
Illustrative Case
YF patient as a potential candidate for LT?

41 yo woman from a rural area of Caratinga-MG, admitted to emergency room presenting gastrointestinal bleeding after one week of febrile illness.

History of abuse of alcohol in the past.

YF Vaccination status: unknown

At 3rd day of febrile illness: YF IgM serology: negative.

In the hospital:

24h after admission: YF IgM serology: positive/ YF PCR in house: positive

Should LT be indicated in fulminant hepatitis secondary to YF?

**Phase 1:** Viremic
- **Remission**

**Phase 2:** Toxic
- **Recovery or Death**

**Fulminant hepatitis:** occur during the toxic phase
- Is there a risk of persistent viremia after transplantation?
  - **Not known!!**

**Diagram:**
- **Death**
  - Severe cases: Jaundice, bleeding (10 - 20%)
  - **Mild symptoms:** Flu-like (20 - 30%)
  - **Asymptomatic infection:** (40 - 65%)

Monath TLID, 2001
Safety donation strategies and management are defined by epidemiological situation and need continuous adaptation

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Endemic</th>
<th>Non-endemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are the risks?</td>
<td>Need to be alert to any symptoms pre and after donation (for living donors).</td>
<td>Travellers returning from endemic regions.</td>
</tr>
<tr>
<td>Which tests should be performed?</td>
<td>Clinical screening</td>
<td>Epidemiological screening</td>
</tr>
<tr>
<td></td>
<td>Viremia screening using NAT</td>
<td>• exclude if recent travel</td>
</tr>
<tr>
<td></td>
<td>• does not replace clinical screening for recent infection: arbovirus can persist in tissue after clearance from blood!</td>
<td>Living donors should be educated to avoid infection prior to donation</td>
</tr>
<tr>
<td>Donor acceptance criteria</td>
<td>Discard donors with suggestive of recent arbovirus infection.</td>
<td></td>
</tr>
<tr>
<td>Temporary defer (living donors)</td>
<td>Usually shorter period Ex: 30 d if medical diagnosis of ZIKV</td>
<td>Usually longer period Ex: 6 mo if medical diagnosis of ZIKV</td>
</tr>
<tr>
<td>How do you manage?</td>
<td>Serology and/or molecular testing. <strong>RT-PCR is considered the gold standard</strong> (due to serological cross-reactions between the same family)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vaccine: <strong>DENV and YV vaccines</strong> uses live attenuated strains and are <strong>CI for SOT recipients</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Morris M et al. Transplantation, 2017 in press*
Take Home Message

• Tropical diseases in SOT are still a big challenge!
• There are gaps of knowledge in infectivity and disease development
• Vector-borne diseases depends on very complex eco-social conditions for emergence and spread.
• Endemic and non-endemic areas should be assessed in different ways, but only with mutual cooperation of experience and tools, we will be prepared to recognize and manage these diseases.

We are living in a globalized world: people and diseases have no boundaries.
Thank you for your attention

Spero che oggi non sia un addio ma un arrivederci!

Hospital das Clínicas, Faculty of Medicine
Federal University of Minas Gerais (UFMG)

Transplant Infection Commission of the Brazilian Organ Transplant Association (ABTO)

Transplant Infection Commission of the Transplant National System

ESGCIH ESCMID Study group
**Acknowledgments: > 50 authors**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Endemic Fungal infections</td>
<td>8. Tuberculosis</td>
<td>11. MAPS</td>
<td></td>
</tr>
</tbody>
</table>
C’mon guys, we’ll find someone with the answers. Just keep looking.