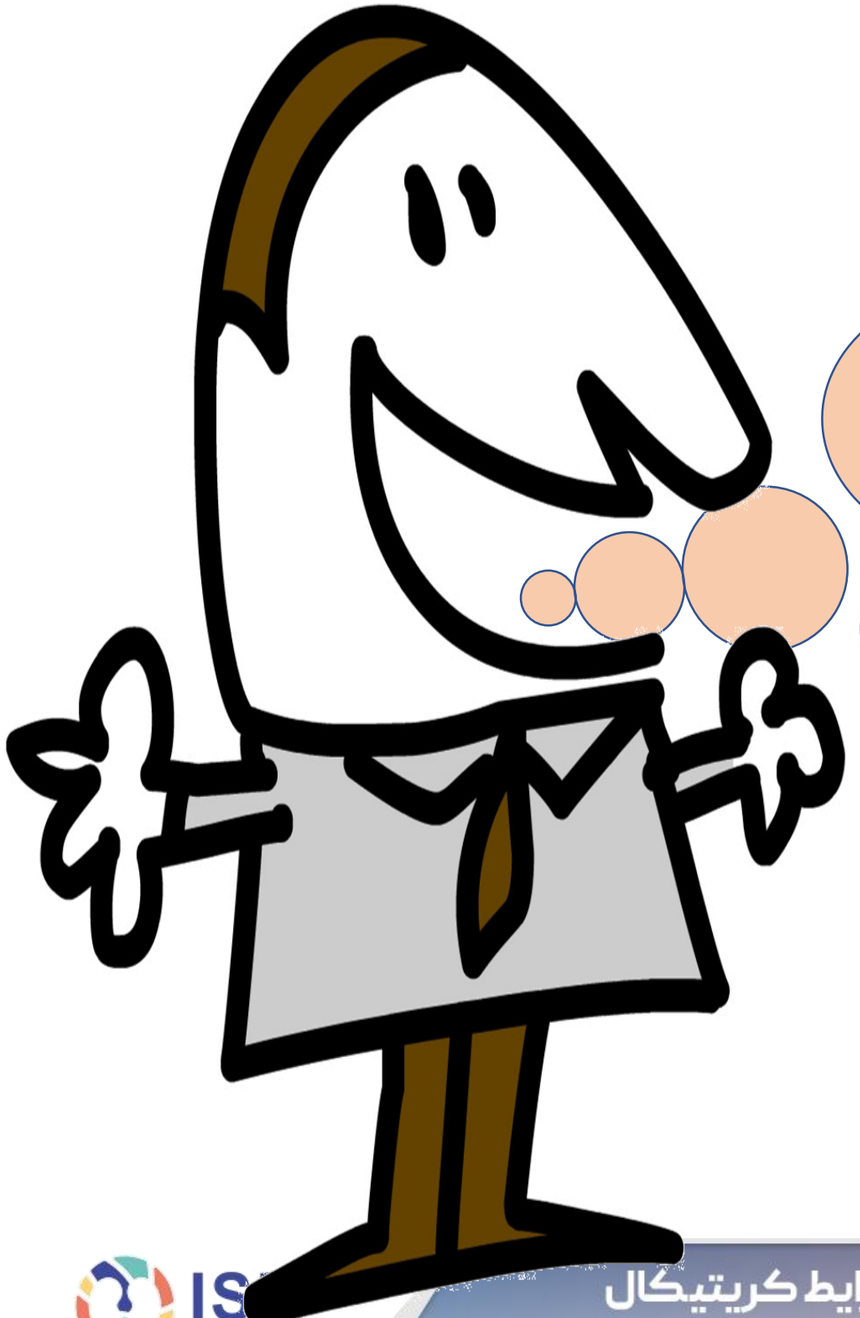
In the name of God

Transplanted patients in ICU

Hassan Argani, Professor of Nephrology



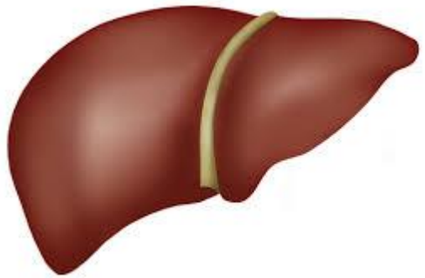
We Need for Sub-Specialized Critical care Unit for RTX

General considerations

- Critical care in solid-organ transplantation (SOT) is complex and vital to patient outcomes.
- About 10% of RTX presented life-threatening conditions requiring intensive care unit (ICU) admission.
- As transplant medicine advances, dedicated critical care units is more necessary.
- The main causes of admission of RTX patients in ICU are related to acute respiratory failure and sepsis.
- In the ICU setting, acute graft pyelonephritis is the leading cause of around 20% of sepsis cases

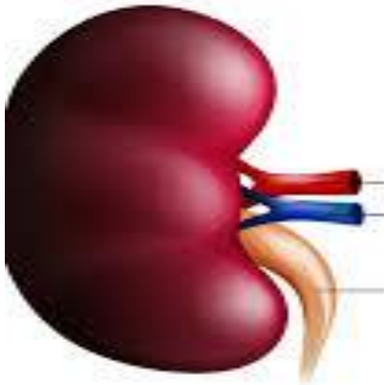
ICU Utilization for Transplantation

Liver Transplants



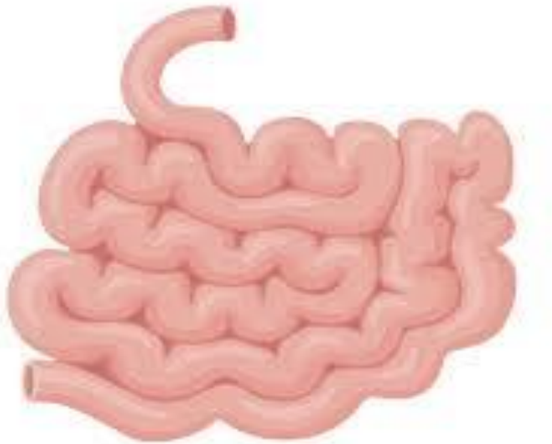
- 12.6% hospitalized in ICU pre-transplant.
- 45.7% require immediate post-transplant ICU care.

Kidney Transplants



- 6.6% require ICU admission, often for respiratory failure.
- Higher mortality than general ICU population.

Intestinal Transplants



- Mean ICU stay of 16 days post-transplant.

Challenges in Transplant Patients

1 ## Pre-Transplant Phase

Management of end-stage organ failure complications like hepatic encephalopathy, spontaneous bacterial peritonitis, and porto-pulmonary hypertension. Maintaining transplant eligibility.

2 ## Peri-Transplant Surgery

Complex surgical procedure with unique physiological challenges.

3 ## Post-Transplant Phase

Balancing immunosuppression, managing infections, and monitoring for allograft dysfunction or rejection.

Pre-Transplant Phase in the ICU

- To resolve acute illnesses.
- To treat complications before transplantation.
- Pre-transplant medical optimization.
- Orchestrating collaborative therapeutic strategies.

Post-Transplant Phase in the ICU

- About 10% of RTx. presented life-threatening conditions requiring ICU admission, mainly related to acute respiratory failure and sepsis/septic shock.
- RTx.s are at higher risk of AKI onset during ICU stay, and a discrete proportion will require renal replacement therapy.

Chest 2016, 149, 1546–1555

Post-Transplant Phase in the ICU

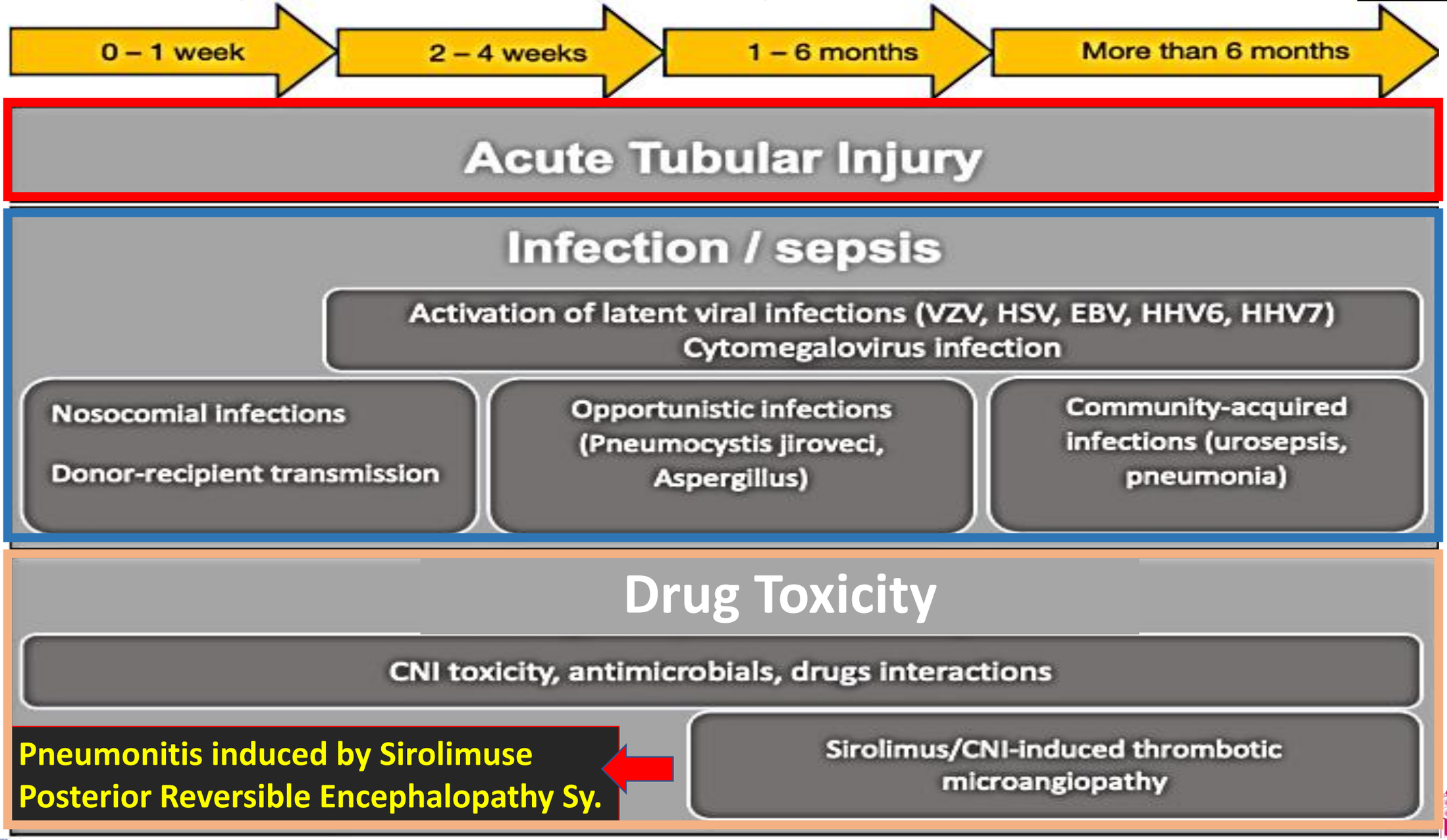
Immediately post-transplant period

- ❖Bleeding.
- ❖Electrolyte imbalances.
- ❖Cardiovascular events.
- ❖Urologic complications: Urinoma, Ureteral kinking.
- ❖ AKI and delayed graft function, need to CRRT.
- ❖Early identification and appropriate management of poorly functioning grafts is a critical aspect of post-transplantation.
- ❖Any suspected vascular compromise, Placement of a central venous line is challenging

Late post-transplant period

- ❖Modifying, tailoring and balancing immunosuppressive regimen
- ❖Sepsis
- ❖Complicated Rejections
- ❖Multi-Organ Failure

The 3 most important causes of RTx patients admitted to ICU **(AID)**



Biomedicines 2023, 11, 1474

Kidney transplantation in the Intensive Care Unit

Table 1 General characteristics of the kidney transplant patients.

Type of donor	Brain-dead donor	Type II non-heart beating donor	Type III non-heart beating donor	Live donor
n (%)	189 (69.2)	26 (9.5)	17 (6.2)	41 (15)
Lactate upon admission to ICU, median (IQR) [mmol/l]	1.4 (1.0–2.0)	1.4 (1.2–1.9)	1.3 (1.1–1.7)	1.5 (1.0–2.1)
Creatinine upon admission to ICU, median (IQR) [mg/dl]	5.86 (4.45–7.23)	6.83 (5.24–7.68)	5.64 (4.78–6.62)	5.5 (4.28–6.23)
Creatinine at hospital discharge, median (IQR) [mg/dl][a]	1.81 (1.36–2.48)	4.26 (2.23–6.17)	2.5 (2.21–3.96)	1.47 (1.05–1.66)
Diuresis during the first 24 h in the ICU (%)				
Polyuria	58.0	38.5	41.2	92.7
Oliguria	31.4	42.3	35.3	7.3
Anuria	10.6	19.2	23.5	0.0

[a] Statistically significant differences. IQR: interquartile range.

Med Intensiva. 2019;43:384---386.

Common organ dysfunctions and reason for ICU admission in RTx. recipients

Acute Respiratory Failure

- Bacterial infection
- Pneumocystis
- Pulmonary edema

Shock / Sepsis

- Bacterial infection / Pyelonephritis
- Cardiovascular comorbidities (cardiogenic S. / mesenteric isch.)
- Post transplant hemorrhage

Drug toxicity

- Steroids: infection, adrenal insufficiency
- Calcineurin inhibitors: infections, AKI, TMA, cancer
- mTOR inhibitors: sirolimus-associated pneumonitis
- Purine Metabolism inhibitors: neutropenia, cancer
- Drug interaction

AKI

- Underlying CKD
- Acute illness
- Obstruction / Vascular complication

Intensive Care Med (2019) 45:380–383

principles for transplant patients in ICU, Beside of immediate post-transplant period

The best is still to come	Safety profile of drugs in ICU, and assessing long-term allograft outcome
Consider complications of immunosuppression	Adrenal insufficiency, TMA, PRESS, pneumonitis, Hematologic dis.
Limited renal reserve	high susceptibility to AKI and drug Toxicity
Co-operation with other transplant team	Impact of systematic rounds with the transplant team is questionable
Rule out uncommon causes of AKI	ATN, CNI Tox, TMA, Recurrent GN, UTI
Beware of residual long-term complications of CKD	CVD, BMD, HTN
Preserve vascular access	Femoral access is forbidden, AVF effect on CHF
Anti-rejection drugs during critical illness	Time from transplantation, baseline GFR, immunological risks, Reason for ICU admission
Role out fungal and viral infections	CMV,EBV, PCP, Aspergilosis, mycotic aneurysm
Search for bacterial infection and treat promptly	Especially Pneumonia, and Pyelonephritis

Intensive Care Med (2019) 45:380–383

AKI in the RTx who admitted to ICU

Typical causes of AKI following RTx.

Time-Course Transplantation

< 48 hours	48 hours- 1 week	2- 4 weeks	2- 3 months	> 3 months

- Acute Tubular Injury (including reperfusion injury and hemodynamic instability)
- Immunological complication (including Rejection)
- Surgical Complications (Bleeding, Vascular complications, Ureteric obstruction, Urinoma)
- Nephrotoxic exposure (Including Drug toxicity and Radiocontrast)
- Infections
- TTP
- Recurrent Primary GN

Intensive Care Med (2019) 45:380–383

Main studies focusing on AKI incidence and outcomes in RTx recipients

Study ID	Year	Study Design	Patients	AKI Incidence	Mortality Rate	Additional Epidemiological Findings
Mehrotra et al. [19]	2012	Retrospective longitudinal cohort study; AKI incidence and outcomes in KTRs	27,232	11.6%	5.8%	AKI is an independent factor for graft loss (HR 2.74), death with functioning graft (HR 2.36) and graft loss (HR 3.17). AKI paradoxically associates with worse outcomes in early CKD stages.
Filiponi et al. [11]	2015	Single-center, retrospective cohort study; 1-year graft survival in KTRs with AKI	458	82.3%	2.1%	CMV infection being the most common cause of hospitalization (20.3%), followed by urosepsis (14.4%). ICU admission OR: 8.9; contrast media use OR: 9.34.
Panek et al. [17]	2015	Single-center retrospective cohort study; clinical outcomes of KTRs at 1 year post-transplantation	326	21.0%	1.2 deaths/100 PY	CNI toxicity is the leading cause of AKI (33%). The presence of AKI does not have any impact on mortality rate.
Guinault et al. [18]	2019	Multicenter, retrospective observational study; outcomes in ICU admitted KTRs	200	85.1%	26.5%	Death occurring mostly within the first 6 months. CKD progression observed in 45.1% of survivors; 15.1% developed new anti-HLA antibodies.

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Main studies focusing on AKI incidence and outcomes in RTx recipients-Con

Cravedi et al. [26]	2020	International, multicenter, retrospective cohort study; clinical outcomes in COVID-19-positive KTRs	144	51.0%	32.0%	AKI occurred in 52% cases, with respiratory failure requiring intubation in 29%, and the mortality rate was 32%. Risk factors for mortality: older age, lower lymphocyte counts and baseline eGFR, higher serum lactate dehydrogenase, procalcitonin and IL-6.
Camargo-Salamanca et al. [16]	2020	Retrospective cohort study; AKI incidence and risk factors	179	58.1%	3.9%	KTRs with higher baseline serum creatinine (OR, 2.6; 95% CI 1.5–4.5, $p < 0.001$) and hospital admission because of infections (OR, 2.4; 95% CI, 1.1–5.2; $p = 0.020$) were more likely to experience AKI. 19 recipients (10.6%) had graft loss with a significant AKI association ($p = 0.003$).
Kremer et al. [25]	2021	Meta-analysis; clinical outcomes in COVID-19-infected KTRs	5559	50.0%	23.0%	Mortality rates are significantly increased in the early post-transplantation period (15 months post-TX). No differences are reported in AKI risk between early and late post-transplantation periods.

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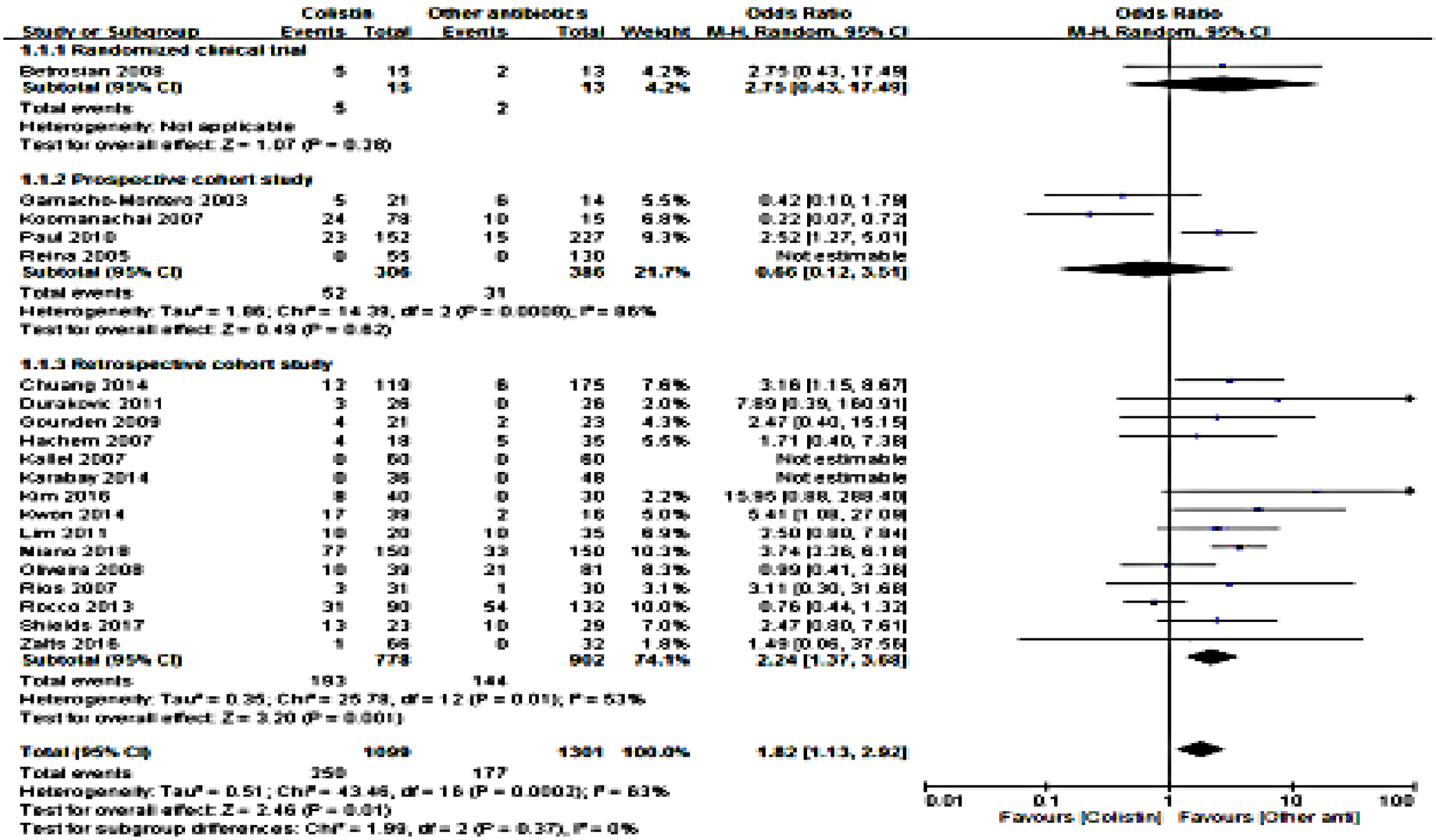
AKI among patients receiving Colistin monotherapy versus combination therapy



H.-T. Chien. et al. / International Journal of Antimicrobial Agents 55 (2020) 105889

Conclusion

- Colistin was associated with an ~2-fold higher incidence of acute kidney injury (AKI) than other antibiotics.
- Colistin-associated AKI was usually mild and reversible without higher rates of mortality or renal replacement therapy.
- Colistin combined with a carbapenem was associated with a lower incidence of AKI.

Guinault *et al. BMC Anesthesiology* (2019) 19:130
https://doi.org/10.1186/s12871-019-0800-0

BMC Anesthesiology

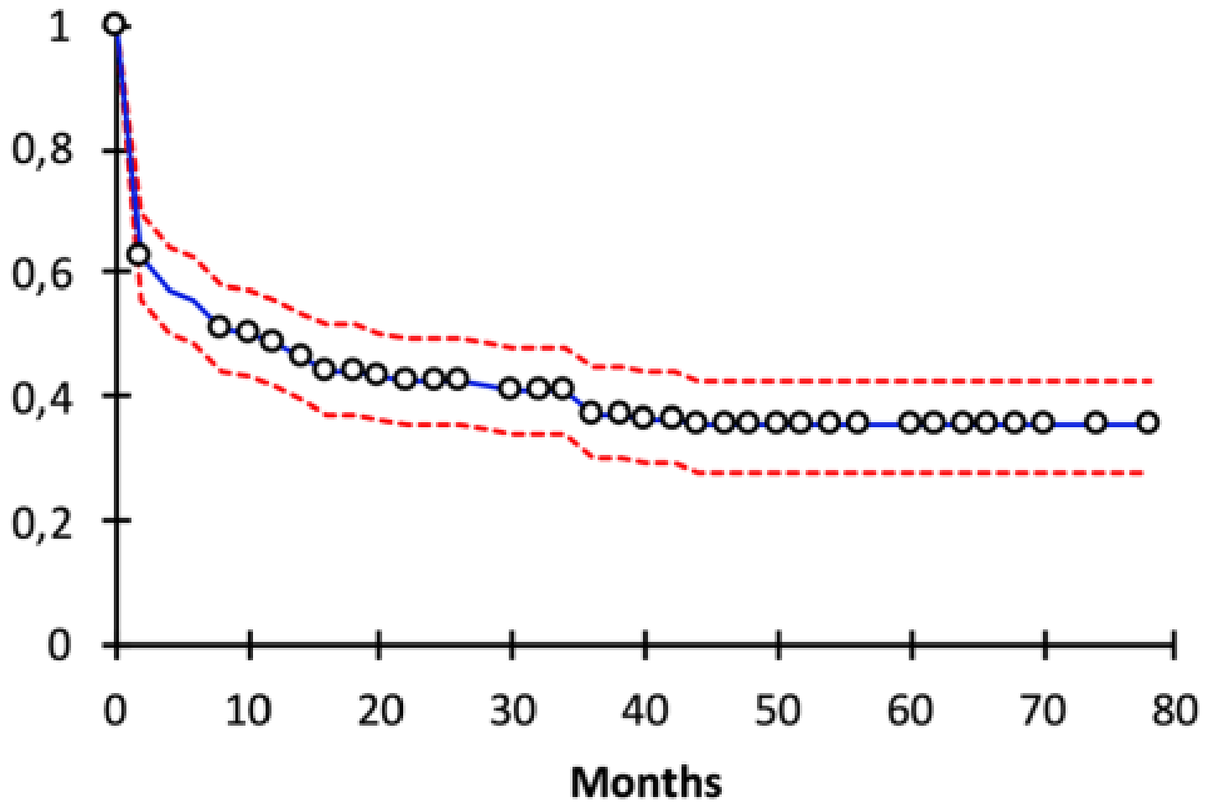
RESEARCH ARTICLE Open Access

Outcomes of kidney transplant recipients admitted to the intensive care unit: a retrospective study of 200 patients

Guinault et al. BMC Anesthesiology (2019) 19:130

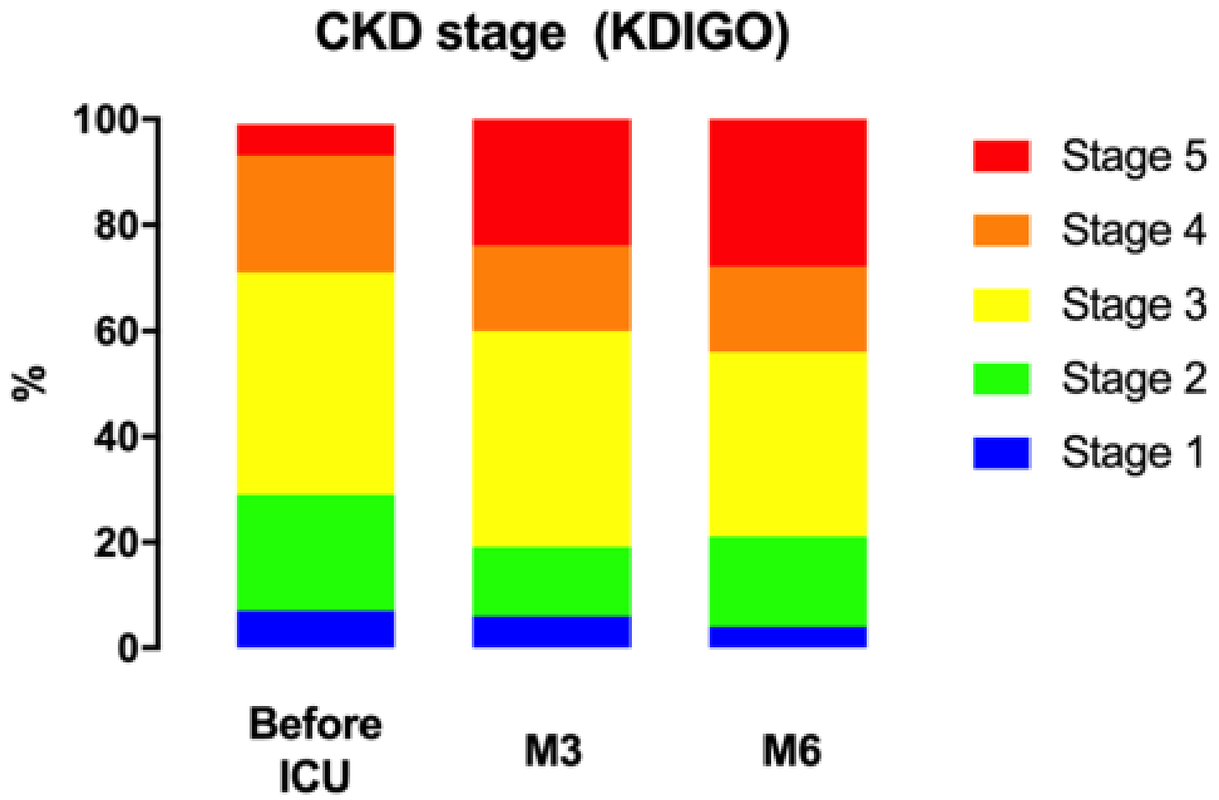
Renal outcome of the 200 kidney transplant recipients admitted to the ICU

A



Graft Survival curve

B

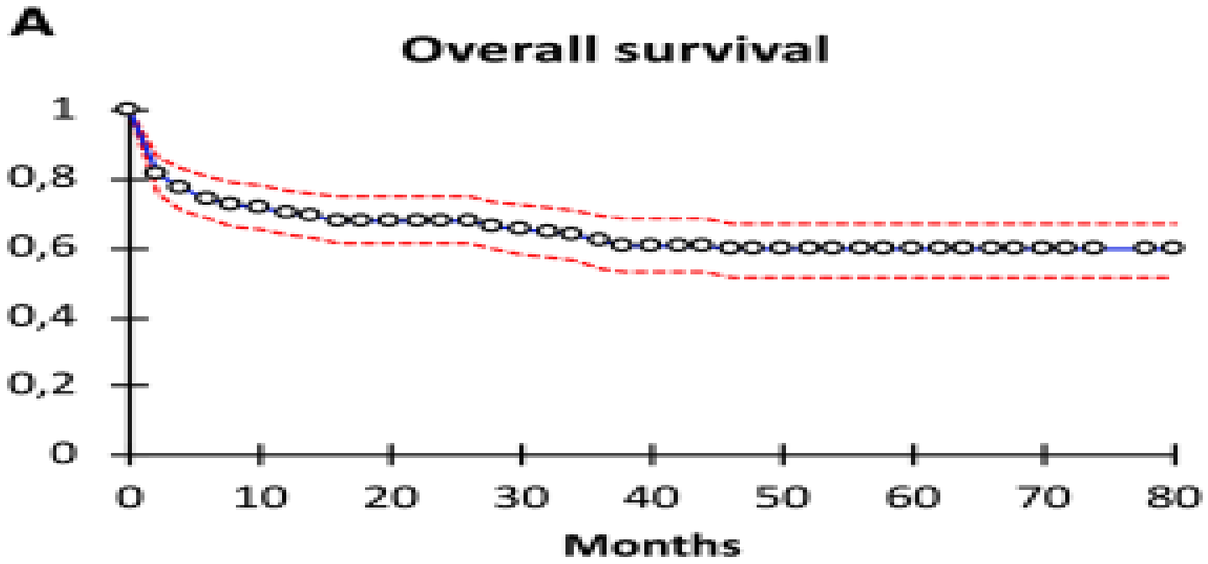


Progression of CKD following admission to the ICU

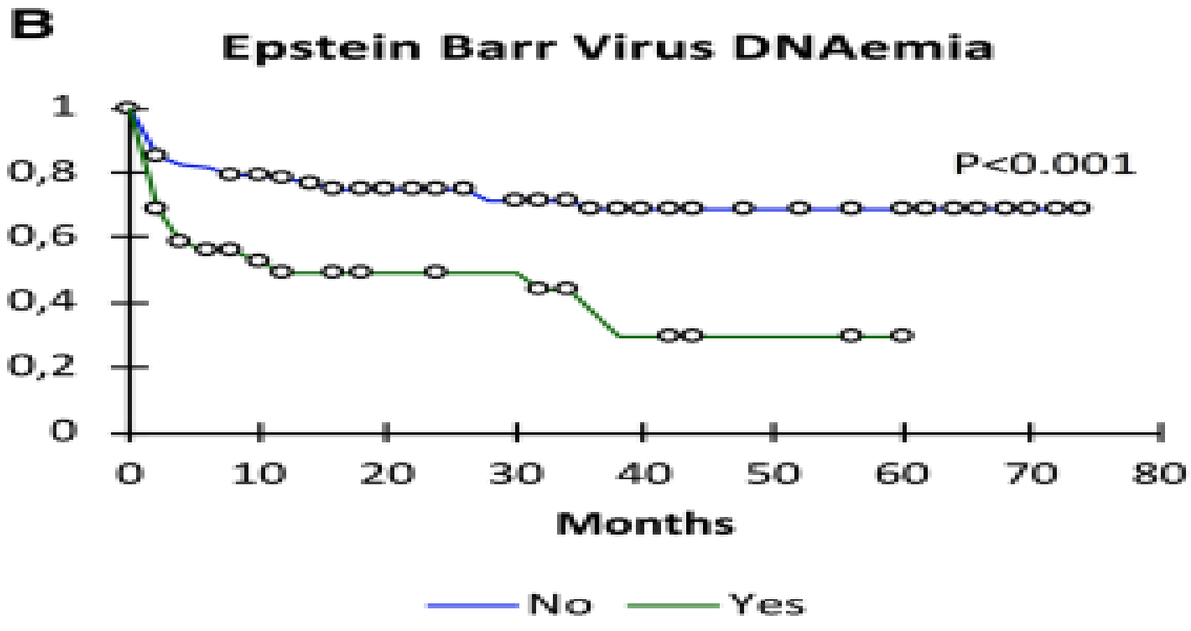
Guinault et al. BMC Anesthesiology (2019) 19:130

Survival curves following admission to the ICU

Overall population



Survival according to EBV replication before admission



Guinault et al. BMC Anesthesiology (2019) 19:130

Conclusion

- ARF and sepsis are the main causes of ICU admission in KTR
- More than 14% of the RTX patients had at least two concomitant infections.
- Management of KTR in ICUs specialized in the field of transplantation may improves the outcome of these patients.
- EBV replication in the months preceding the admission of KTR to the ICU was associated with a poorer outcome.

Guinault et al. BMC Anesthesiology (2019) 19:130

Respiratory failure in the RTx admitted to ICU

Canet et al. Critical Care 2011, 15:R91
http://ccforum.com/content/15/2/R91

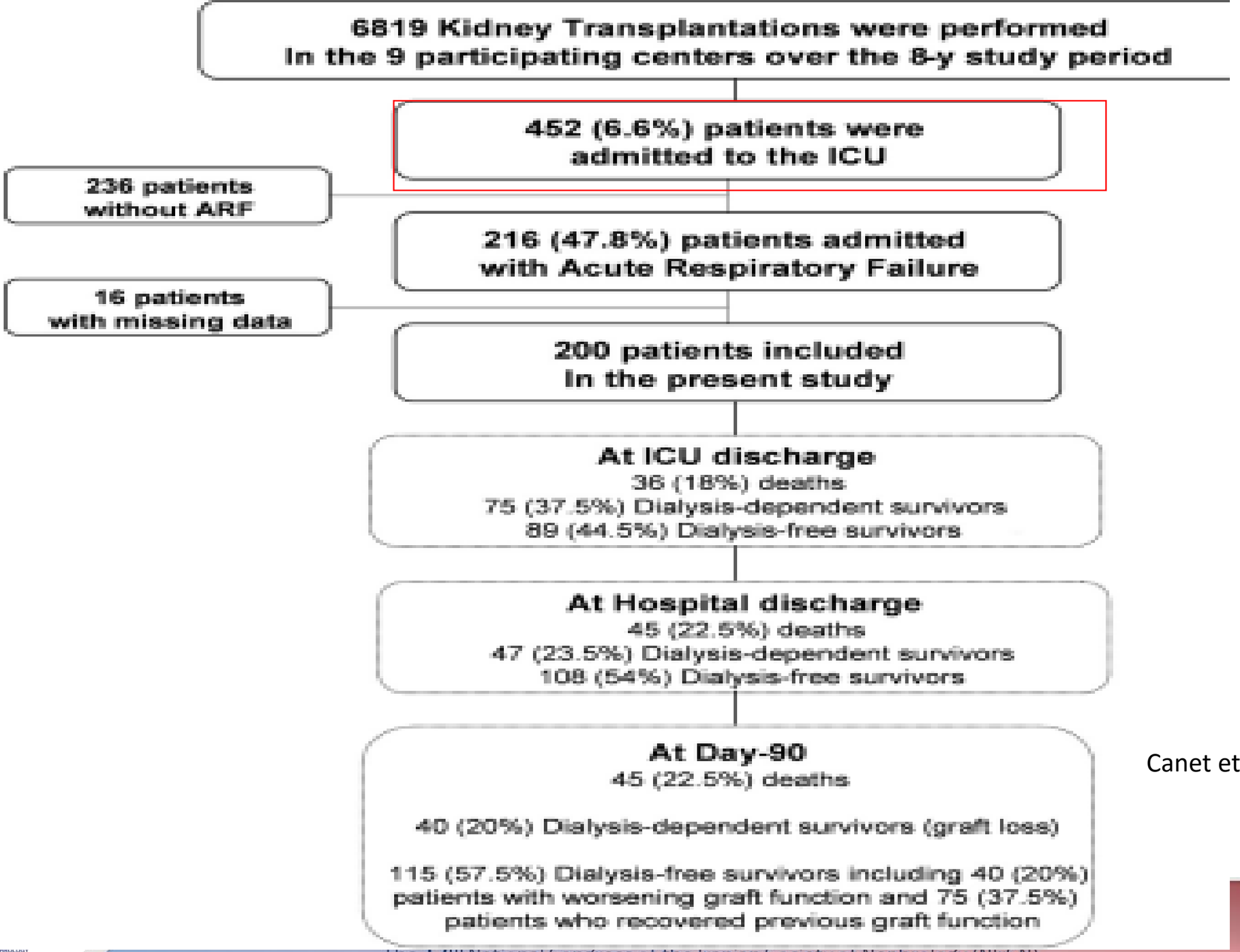
CRITICAL CARE

RESEARCH Open Access

Acute respiratory failure in kidney transplant recipients: a multicenter study

Emmanuel Canet[1], David Osman[2], Jérome Lambert[1], Christophe Guitton[3], Anne-Elisabeth Heng[4], Laurent Argaud[5], Kada Klouche[6], Georges Mourad[6], Christophe Legendre[7], Jean-François Timsit[8], Eric Rondeau[9], Maryvonne Hourmant[10], Antoine Dunbach[11], Denis Glotz[12], Bertrand Souweine[4], Benoit Schlemmer[1], Elie Azoulay[1*]

Canet et al. Critical Care 2011, 15:R91



Canet et al. Critical Care 2011, 15:R91

Table 4 Diagnosis of acute respiratory failure according to the delay between transplantation to ICU admission[a]

Diagnosis	Number of patients	Time from transplantation to ICU admission			
		< 1 month	1 to 3 months	3 to 6 months	> 6 months
All patients	200	27 (14%)	30 (15%)	14 (7%)	129 (65%)
Bacterial infection					
Bacterial pneumonia	71	7 (24%)	15 (39%)	3 (19%)	46 (32%)
Extrapulmonary ARDS	31	3 (10%)	6 (15%)	4 (25%)	18 (13%)
Cardiogenic pulmonary edema	49	14 (48%)	7 (18%)	2 (13%)	26 (18%)
Opportunistic fungal infection					
Pneumocystis pneumonia	23	0	3 (8%)	2 (13%)	18 (13%)
Invasive aspergillosis or Candidemia	6	0	2 (5%)	2 (13%)	2 (1%)
Viral pneumonia	6	0	3 (8%)	0	3 (2%)
Drug-related pulmonary toxicity	6	0	1 (3%)	0	5 (4%)
Other	11	2 (7%)	1 (3%)	0	8 (6%)
No diagnosis	25	3 (10%)	1 (3%)	3 (19%)	18 (13%)

Higher risk of returning to dialysis

Canet et al. Critical Care 2011, 15:R91

Table 5 Multivariable analysis: predictors of in-hospital mortality[a]

Predictor of hospital mortality	Odds ratio	95% confidence interval	P value
Shock at ICU admission	8.70	3.25 to 23.29	0.00002
Opportunistic fungal infection[b]	7.08	2.32 to 21.60	0.0007
Bacterial infection	2.53	1.07 to 5.96	0.034
Lung infiltration ≥3 quadrants on chest-X ray	2.50	0.98 to 6.37	0.051
Extrapulmonary ARDS	2.30	0.83 to 6.38	0.11
Oxygen flow at ICU admission (per liter)	1.05	0.97 to 1.15	0.24

Canet et al. Critical Care 2011, 15:R91

Conclusions:

- In kidney transplant recipients, ARF is associated with high mortality and graft loss rates.
- Acute respiratory failure accounts for one-half of the ICU admissions in recipients of kidney transplantation.
- In the early post-transplant period (< 1 month) cardiogenic pulmonary edema accounted for one-half of the diagnoses, while opportunistic fungal infections and drug-related pulmonary toxicity were mostly diagnosed in the late post-transplant period (> 6 months)
- Early ICU admission might prevent graft loss.
- 90-day mortality is 22.5%, but a one-fourth of survivors have lost their graft.

Canet et al. Critical Care 2011, 15:R91

Admission of COVID-19-infected RTX in ICU

- The patients have 2-fold increased risk of AKI
- The patients have prolonged ICU stay and death.
- The patients have 4-fold increase for RRT
- The severity of infection was correlated with a worse graft outcome and increased fatality rate

Aziz, F etal. Transplant. Proc. 2020, 52, 2659–2662.

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SAUNDERS

CRITICAL
CARE
CLINICS

Crit Care Clin 24 (2008) 949–981

Psychiatric Aspects of Organ Transplantation in Critical Care

Andrea DiMartini, MD[a,*], Catherine Crone, MD[b], Marian Fireman, MD[c], Mary Amanda Dew, PhD[d]

- Following transplant up to 20% of kidney recipients, 30% of liver recipients, and 63% of heart recipients develop Psychiatric disorders especially during the first post-transplant year.

- It is exaggerated in the Transplanted patients need to be admitted to ICU

Crit Care Clin 24 (2008) 949–981

sciendo

The Journal of Critical Care Medicine 2018;4(3):83-89

REVIEW

DOI: 10.2478/jccm-2018-0014

Transplant Critical Care: Is There A Need for Sub-specialized Units? — A Perspective

- Hospitals incur substantial costs due to repetitive, redundant and frequently unnecessary physician consultations and diagnostic tests in the ICU

BUN cost:22000 T, Cr cost=27000 T

The Journal of Critical Care Medicine 2018;4(3):83-81

Benefits of Specialized Transplant ICUs

Patient Care

- Focused expertise in managing complex transplant physiology and complications.
- Improved pre-transplant optimization and post-transplant monitoring.

Program Development

- Ability to take on higher-risk donors and recipients.

Research & Innovation

- Opportunity to develop specialized protocols and advance the field of transplant critical care.

Multidisciplinary Approach

Medical Specialists

Transplant surgeons, intensivists, hepatologists, nephrologists, infectious disease experts

Nursing and Supportive cares

Specialized transplant nurses, pharmacists, respiratory therapists, nutritionists

Coordinators

Transplant coordinators, social workers, psychologists

Collaborative Care

Integrated team approach for comprehensive patient management

Resource Utilization and Cost Considerations

Dedicated Transplant ICU	Designated ICU Beds
High-volume centers	Low to moderate volume centers
Concentrated resources	Flexible overflow capacity
Specialized staff and equipment	Shared resources with general ICU

Training and Workforce Development

1	2	3	4
Expanded Fellowship Training Include intensive care curriculum in transplant surgery fellowships	**Critical Care Skills** Train transplant surgeons in advanced ICU procedures and management	**Transplant Rotations** Incorporate transplant-specific rotations in critical care fellowships	**Dual-Trained Specialists** Develop workforce skilled in both transplant and intensive care

Management of immunosuppression in the ICU RTx. Patients and AKI

Management of immunosuppression in critically ill KTRs with AKI

INFECTION
Confirmed or suspected Infection + SIRS criteria (Temp > 38°, HR > 90 bpm, RR > 20/min, WBC < 4 or > 12, Mental confusion)

- Routine assessment of renal function and graft ultrasound
- Avoid nephrotoxic drugs and contrast agents, when possible
- Close monitoring of immunosuppressive therapy
- Consider potential drug interactions
- CNI trough levels close to lower limit of therapeutic range

SEPSIS
(Sepsis + one or more organ dysfunction, with SOFA ≥ 2)

- Routine assessment of renal function and graft ultrasound
- Avoid nephrotoxic drugs and contrast agents, when possible
- Consider potential drug interactions
- Close monitoring of immunosuppressive therapy. Consider discontinuing temporarily some immunosuppressive drugs (antiproliferative), lowering CNI trough levels
- Do not delay ICU admission in case of worsening clinical conditions

SEPTIC SHOCK
(Sepsis + persistent hypotension requiring vasopressors to mantain MAP≥ 65 mmHg and serum lactate > 2 mmol/L)

- Do not delay ICU admission
- Routine assessment of renal function and graft ultrasound
- Routine assessment of respiratory and cardiac function
- Consider bloodstream infections
- Consider potential drug interactions
- Discontinue immunosuppressive treatment, with introduction of corticosteroids ev

Biomedicines 2023, 11, 1474

Journal of Critical Care 64 (2021) 37–44

Contents lists available at ScienceDirect

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Care for the organ transplant recipient on the intensive care unit

Journal of Critical Care 64 (2021) 37–44

Immunosuppressive therapy in solid organ transplantation admitted to ICU

- ❖ Efficacy of drugs➔ Trough level at least 2 times per week
- ❖ Drugs interactions
- ❖ Drugs Side-effects in the ICU patients
- ❖ Route of administration
- ❖ Immunosuppression during severe infection

Journal of Critical Care 64 (2021) 37–44

ARTICLE

Clinical Pharmacokinetics of Oral Versus Sublingual Administration of Tacrolimus in Adult Liver Transplant Recipients

Zahra Nasiri-Toosi,[1] Simin Dashti-Khavidaki,[2] Mohsen Nasiri-Toosi,[3] Hossein Khalili,[2] Ali Jafarian,[3] Hamideh Irajian,[3] Alireza Abdollahi,[4] Sima Sadrai[2]

Experimental and Clinical Transplantation (2012) 6: 586-591

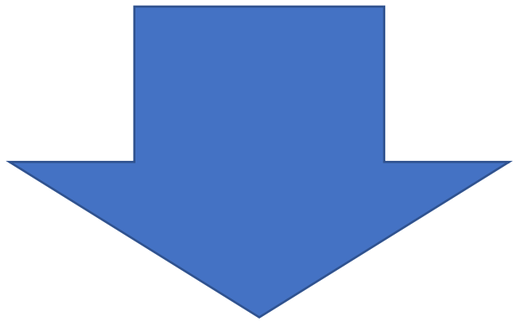
Table 2. Mean TAC Pharmacokinetics Parameters After Oral and Sublingual Administration

Parameters	Sublingual Administration	Oral Administration	*P*
AUC*(ng.h/mL)	160.8 ± 115.9	181.5 ± 114.1	.19
k_e† (h^{-1})	0.05	0.03	
$T_{1/2}$‡ (h)	14.8	24.6	
k_a§ (h^{-1})	0.9	2.2	
Vd¶/F# (L)	222.2 ± 41.8	220.4 ± 45	
Cl**/F (L/h)	10.4 ± 1.9	6.2 ± 1.3	
C_{trough}†† (ng/mL)	11.2 ± 11.3	10.4 ± 7.4	.37
T_{max}‡‡ (h)	1.4 ± 0.7	1.9 ± 1.2	.21
C_{max}§§ (ng/mL)	17.2 ± 11.7	19.9 ± 10.8	.3

Experimental and Clinical Transplantation (2012) 6: 586-591

Conclusion

- Sublingual administration of TAC suspension prepared from its available capsules does provide therapeutic drug concentration and may be considered confidently for those patients who are unable to swallow their drugs.



- What about in the ICU patients???????

Experimental and Clinical Transplantation (2012) 6: 586-591

Sublingual Administration of Tacrolimus: Current Trends and Available Evidence

Survey of 8 studies

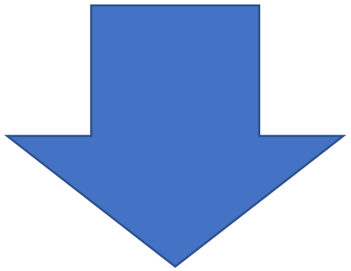
Christina Teeter Doligalski,* Esther C. Liu, Chelsea M. Sammons, Andrew Silverman, and Angela Tong Logan

Department of Pharmacy, Tampa General Hospital, Tampa, Florida

Pharmacotherapy 2014;34(11):1209–1219

Conclusion

- Favorable utilization of sublingual tacrolimus in seven of the eight available reports
- only one study reported unfavorably on sublingual administration



No consensus about the sublingual dosage compared to oral dose

Pharmacotherapy 2014;34(11):1209–1219

Conclusion

- With an increasing number of more frail transplant candidates on the waiting list, increasing number of patients requiring ICU care before transplantation can be anticipated.
- AKI, sepsis and Respiratory failure are most complications after RTx patients who need to ICU admission.
- Sub-specialized ICU for organ transplanted patients with own multidisciplinary approach is needed for each transplant center.
- Professional staffs, sophisticated imaging and laboratory tests should be available for 24 hours.
- Co-operation is very important!

Tank you for your attention