



HAL
open science

Risk factors and outcomes of early acute kidney injury in infective endocarditis: A retrospective cohort study

Florent von Tokarski, Adrien Lemaiguen, Antoine Portais, Laurent Fauchier, Fanny Hennekinne, Bénédicte Sautenet, Jean-Michel Halimi, Annick Legras, Frédéric Patat, Thierry Bourguignon, et al.

► To cite this version:

Florent von Tokarski, Adrien Lemaiguen, Antoine Portais, Laurent Fauchier, Fanny Hennekinne, et al.. Risk factors and outcomes of early acute kidney injury in infective endocarditis: A retrospective cohort study. *International Journal of Infectious Diseases*, 2020, 99, pp.421 - 427. 10.1016/j.ijid.2020.08.022 . hal-03491149

HAL Id: hal-03491149

<https://hal.science/hal-03491149>

Submitted on 14 Sep 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Risk factors and outcomes of early acute kidney injury in infective endocarditis: a retrospective cohort study

Florent Von Tokarski^{1,2*}, Adrien Lemaïgnen^{1*}, Antoine Portais¹, Laurent Fauchier³, Fanny Hennekinne⁴, Bénédicte Sautenet², Jean-Michel Halimi², Annick Legras⁵, Frédéric Patat⁶, Thierry Bourguignon⁷, Christian Mirguet⁸, Anne Bernard³ and Louis Bernard¹

1 : Service de Médecine interne et Maladies Infectieuses, 2 : Service de Néphrologie-HTA, Dialyses, Transplantation Rénale, 3 : Service de Cardiologie, 4 : Service de Gériatrie, 5 : Service de Médecine Intensive, 6 : Service d'échographie, 7 : Service de chirurgie cardio-vasculaire, 8 : Service de réanimation cardio-vasculaire, CHRU de Tours, France

* Florent Von Tokarski and Adrien Lemaïgnen contributed equally for this work

Corresponding author:

Doctor Adrien LEMAIGNEN, MD

Service de Médecine interne et maladies infectieuses, Hôpital Bretonneau, CHRU de Tours

2, Boulevard Tonnellé, 37 044 CEDEX 9, Tours, France

Tel : +33.2.47.47.37.14 - Fax : +33.2.47.47.37.31

E-mail: adrien.lemaïgnen@univ-tours.fr

Short Title: acute kidney injury in infective endocarditis

Keywords: Infective endocarditis, Acute Kidney Injury, Outcome, Infectious diseases team

Text word count: 2.991

Abstract word count: 207

Number of figures and tables: 5

Supplementary data: 3

Number of references: 27

Abstract

Objectives: The incidence of acute kidney injury (AKI) in infective endocarditis (IE), its risk factors and consequences on patient and renal survival remain debated.

Methods: Patients hospitalized for a first episode of IE (possible or definite according to modified Duke criteria) between 2013 and 2016 were included. The primary endpoint was to determine risk factors for early AKI (E-AKI) during the first week of management of IE.

Results: 276 patients were included. 220 patients (79.7%) had definite IE and 56 (20.3%) had possible IE. E-AKI occurred in 150 patients included (53%). IE due to *Staphylococcus aureus* (*S. aureus*, Odd Ratio (OR): 3.41 [95% Confidence interval (CI): 1.83-6.39], $p < 0.01$), history of diabetes (OR: 2.34 [1.25-4.37], $p < 0.01$), peripheral arterial disease (OR: 2.59 [1.07-6.23], $p < 0.05$), immunological manifestations (OR: 3.11 [1.31-7.39], $p = 0.01$) and use of norepinephrine (OR: 3.44 [1.72-7.02], $p < 0.01$) were associated with E-AKI. In subgroup analysis, infectious disease consultation was associated with a lower risk of AKI at day 7 (OR: 0.41 [0.16-0.88], $p = 0.04$). E-AKI was associated with one-year mortality (OR: 1.65 [1.03-2.64], $p = 0.04$) and chronic kidney disease progression (OR: 2.23 [1.30-3.82], $p < 0.01$).

Conclusions: E-AKI is common in IE and often associated with non-modifiable variables. Multidisciplinary management should be mandatory, and awareness of AKI diagnosis and etiological explorations should be raised.

List of abbreviations

AKI: acute kidney injury

ANCA: anti-neutrophil cytoplasmic antibodies

CKD: chronic kidney injury

CKD-EPI: Chronic Kidney Disease - Epidemiology Collaboration

eGFR: estimated glomerular filtration rate

IE: infective endocarditis

IDC: infectious disease consultation

KDIGO: Kidney Disease: Improving Global Outcomes

NSAID: non-steroidal anti-inflammatory drugs

RAASi: renin angiotensin aldosterone system inhibitor

S. aureus: Staphylococcus aureus

SC: serum creatinine

Introduction

Infective endocarditis (IE) is a severe infectious disease with a high long-term mortality, up to 33% at 4 years [1]. Its annual incidence was estimated at 33.8 per million inhabitants in France [2]. Acute kidney injury (AKI) is a common complication of IE, which was recently estimated to occur in 39.8% of cases [3].

AKI has been identified as a predictive factor for mortality. Buchholtz et al. showed that risk for mortality was increased by 23.1% for every decrease of 10 mL/min in estimated endogenous creatinine clearance using Cockcroft and Gault formula [4]. However, risk factors for AKI at onset of IE are still debated.

Management of IE is challenging and needs identification and removal of infectious foci, collection of repeat blood cultures until resolution of bacteremia, echocardiography, and selection of appropriate intravenous (IV) treatment and duration. This management is greatly influenced by AKI, *i.e.* the choice of antibiotic drug, doses, and modalities of administration.

The aim of the present study was to determine the risk factors associated with acute kidney injury (AKI) during IE management and to evaluate the impact of AKI on patient survival and late kidney function.

Methods

Objectives

The primary objective was to determine factors associated with E-AKI. Secondary objectives were: 1) to define and compare factors associated with D0-AKI; 2) with D7-AKI; 3) to determine factors associated with CKD progression at last follow-up; 4) to assess one-year mortality; and 5) to describe AKI aetiologies.

Study design

We performed this retrospective cohort study in a regional centre for IE in a French University Hospital. Patient screening was performed using a previously described algorithm. IE-related diagnosis code was extracted from the Regional Hospital Discharge Data from January 1st 2013 to December 31st 2016 [5].

Participants

Every consecutive patients aged 18 years or older and hospitalized for a first episode of possible or definite IE according to modified Duke criteria [6] were included in the study. Non-inclusion criteria were chronic kidney failure treated with renal replacement therapy at the time of diagnosis and the lack of available creatinine measurement in the acute phase of IE.

Definitions

Infective Endocarditis: The diagnosis of infective endocarditis was established according to the modified Duke criteria as defined in the 2015 European Society of Cardiology guidelines [6]. The day of high suspicion of IE or confirmed diagnosis of IE was considered as Day 0.

Baseline serum creatinine (SC-B): Baseline serum creatinine was sought in each patient medical record prior to the infection to determine AKI diagnosis. When unavailable, we used the lowest serum creatinine level during hospital stay if the glomerular filtration rate was $> 75\text{mL/minute/1.73m}^2$ [9]. Serum creatinine was collected at baseline (SC-B), admission (SC-D0), day 7 +/- 2 (SC-D7), and at last follow-up (SC-FU). Baseline renal function was defined as eGFR.

Acute kidney injury: an increase in serum creatinine by $26.5\mu\text{mol/L}$ (0.3 mg/L) within 48 hours, 1.5 times baseline serum creatinine or acute renal replacement therapy according to KDIGO (Kidney Disease: Improving Global Outcomes) guidelines [7]. The estimated glomerular filtration rate (eGFR) is not relevant for AKI diagnosis. Urine output was not recorded.

Day 0 AKI (D0-AKI): AKI at the first day (+/- 1 day) of hospital admission.

Day 7 AKI (D7-AKI): AKI at the seventh day (+/- 2 days) of hospital admission.

Early AKI (E-AKI): AKI occurring from admission to the seventh day of IE management. This criterion includes both D0-AKI and D7-AKI. These two variables were not additive, some patients having both D0-AKI and D7-AKI and others only D0-AKI or D7-AKI.

Chronic kidney disease (CKD): an estimated glomerular filtration rate (eGFR) $< 60\text{mL/min/1.73m}^2$.

CKD progression: a 30% reduction of eGFR from baseline to last follow-up using the CKD-EPI (Chronic Kidney Disease - Epidemiology Collaboration) equation [8]. It includes patients with or without history CKD at baseline.

Infectious disease consultation (IDC): IDC was defined by the documentation of a therapeutic advice by an infectious disease specialist in the medical record (hospitalization in Infectious Diseases Unit, bedside or telemedicine advice).

~~Infectious diseases' specialists are available all days of the week during normal working hours.~~

Immunological phenomena: splinter haemorrhages, Roth spots, purpura or arthralgia.

Vancomycin administration protocol: vancomycin treatment used either 1 gram every twelve hours or 30 milligrams per kilo per day after a first infusion of 15 milligrams per kilo, with serum through level monitoring.

Data collection

Data was individually collected by examining each hospital record. Previous valvular heart disease and demographic data including age, sex, and weight were collected. Patients' comorbidities were defined by the Charlson comorbidity index [10]. Clinical setting at admission and biological/microbiological data (especially SC-B, SC-D0, SC-D7 and SC-FU rates), confounding factors such as diuretics, non-steroidal anti-inflammatory drugs, renin angiotensin aldosterone system inhibitors (RAASi), steroids or proton pump inhibitors prescription at admission were evaluated. IV administration of contrast media in the first week of AKI was recorded. Previous use of nephrotoxic treatment was defined as 2 or more nephrotoxic medications (non-steroidal anti-inflammatory, diuretics, renin-angiotensin-aldosterone system blockers and contrast infusion). Use of norepinephrine during the first week was sought: it was either a marker of unstable hemodynamic at onset or post-surgery management.

Presence of infectious disease consultation was recorded for each patient. The antibiotics treatment was recorded, particularly aminoglycoside and glycopeptide duration and highest through level.

Statistical analysis

Continuous variables were presented as median (Interquartile range [IQR]) and non-parametric Mann-Whitney-Wilcoxon test was used for comparison. Categorical variables were presented as numbers with percentage and we used χ^2 -test or Fisher exact test when appropriate for univariate analysis.

Missing data were imputed by multiple imputation with chained equation (MICE package in R) with 10 imputations and 5 iterations. In order to determine factors associated with E-AKI, we used a multivariate analysis by logistic regression conducted on imputed data. Several models were tested, and factors included in the model were those significant in univariate analysis with a p-value under 0.2. Some variables previously described as risk factors for AKI in the literature were forced in the model. Potential interactions between factors were investigated by performing individual bivariate analysis and considered in the analysis when necessary. The final risk model was chosen to select the model with the lowest Akaike Information Criterion in a backward step-by-step comparison. Secondary analysis on patients' survival and CKD progression was made by multivariate analysis with two distinct Cox survival model using significant variables in univariate analysis with log-rank. For survival analysis, the whole population was considered. For CKD progression analysis, we only considered patients alive with available creatinine measurement at last follow-up. The selection of the final

models was made looking for the best goodness-of-fit. Statistical analyses were conducted using R software (3.6.3 version).

Ethics

The study was approved by the regional ethic committee (number 2017 082) and complied with the requirements of the French National Data Protection Agency. No funding was granted for this study.

Results

Cohort description and univariate analysis

During the retrospective study period, a total of 276 consecutive patients presented with IE and satisfied the inclusion criteria (Figure 1). Two-hundred twenty patients (79.7%) had definite IE and 56 patients (20.3%) had possible IE. Mean time between first symptoms and IE diagnosis was 22.3 days (± 27.7) and did not differ between the E-AKI and no AKI groups. E-AKI occurred in 150 patients (54.3%). Twenty patients (13.3%) required renal replacement therapy during hospitalization. Patients' characteristics at baseline are described in Table 1. Microbiology and patients' management are resumed in Table 2. To note, *Staphylococcus aureus* (*S. aureus*) was the most common species (n=91, 33%) and 14 patients (5%) had methicillin-resistant *S. aureus*. The mean time between first day of treatment and adapted treatment for IE was of 4.1 days in E-AKI group versus 4.3 days in no-AKI group (p=0.9). IDC was sought in 108 patients (72.0%) with E-AKI and 106 patients (84.1%) without AKI. Forty patients (14.5%) had CKD with eGFR <60mL/min/1.73m² at baseline.

Primary objective

The univariate analysis and the final model of multivariate analysis of factors associated with E-AKI are presented in Table 3: *S. aureus* infection, immunological manifestations, history of diabetes, peripheral arterial disease and administration of norepinephrine were positively associated with E-AKI (OR: 3.41 [95%-Confidence interval (CI): 3.41 [1.83-6.39], 3.11 [1.31-7.39], 2.34 [1.25-4.37], 2.59 [1.07-6.23] and 3.44 [1.72-7.02] respectively). Conversely, embolic events (whatever their localization) were associated with a lower risk of E-AKI (OR: 0.54 [0.30-0.96]). There was no impact of IE localisation on the incidence of E-AKI.

Secondary objectives

AKI occurred in 118 patients (42.7%) at day 0 and in 51 (18.5%) patients at day 7 (missing data: 2/276 and 17/276 patients, respectively). E-AKI differed from the sum of D0-AKI and D7-AKI since some patients presented with AKI at both moments. Age, records of diabetes and peripheral arterial disease, nephrotoxic

treatment prescription before admission, *S. aureus*-associated IE and use of norepinephrine were significantly associated with occurrence of D0-AKI but were not risk factors for D7-AKI (Appendix 1).

IDC was significantly associated with less D7-AKI whereas the occurrence of acute heart failure was associated with D7-AKI. In multivariate analysis, nor aminoglycoside neither glycopeptides administration were associated with E-AKI.

Fifty-six out of the 150 patients presenting E-AKI had no urine dipstick test done, and no data about proteinuria. In patients with E-AKI versus no E-AKI, 64 (42.7%) versus 33 (26.2%) had proteinuria (missing data=104, $p<0.01$) and 72 (48.0%) versus 35 (27.8%) had haematuria (missing data=72, $p<0.01$), respectively. Sixty-three patients had bacteriological analysis of urine, of which 13 patients had urinary crystals. Eosinophiluria was never sought.

One patient had possible acute interstitial nephritis and one had amoxicillin-induced crystal nephropathy. Explorations of urine electrolytes in other patients did not conclude on prerenal AKI or intrinsic AKI secondary to sepsis, nor toxic. One hundred and thirty-three patients had a computerized-tomography-scan with contrast injection in the first week. Renal emboli were found in 11 patients with E-AKI versus 12 ($p=0.63$). Only five patients underwent kidney biopsy. The results were: one acute tubular necrosis with chronic interstitial nephritis, one post-infectious glomerulonephritis, one AA amyloidosis, one cryoglobulinemia glomerulonephritis and one diabetic nephropathy.

In-hospital mortality rate was of 27.3% (41 patients) in the E-AKI group versus 12.7% (16 patients) in the no-AKI group ($p<0.01$).

The median time of follow-up was 491 days (IQR: 926, minimal: 0 days, maximal: 1905 days). Eighty-six patients (31.1%) died and median time to death was 26 days (IQR: 68.5). Overall, one-year survival was 65.6% (Figure 2).

E-AKI was significantly associated with increased mortality at 1 year (HR: 1.65 [1.03-2.64], $p=0.04$) but did not affect length of hospital stay. The median length of hospital stay in E-AKI versus no E-AKI were of 21 days (IQR: 21) versus 23 days (IQR: 19) respectively ($p=0.6$).

Among the 161 surviving patients with available long-term follow-up data, 64 (39.7%) presented with CKD progression at the last follow-up. Seventeen patients had eGFR of less than 30 mL/min/1.73m², 47 between 30 and 60 mL/min/1.73m², 97 more than 60 mL/min/1.73m² (missing data n=19) and none on chronic dialysis. E-AKI and patients older than 70 years old were significant factors associated with CKD progression. Being a woman seemed protective for CKD progression (Appendix 3).

Discussion

We present here one of the largest cohorts assessing the specific risk of AKI during IE.

E-AKI was a common condition during IE management in our study. E-AKI appeared being associated with baseline background (record of diabetes, peripheral arterial disease) and severity of infection (immunological manifestations, need for norepinephrine use and *S. aureus*-associated infection [2]). IDC appeared as a protective factor for D7-AKI.

Factors associated with E-AKI in our study were mostly non-modifiable variables: at the time of IE diagnosis, those variables could not be changed by clinicians. Our complementary data showed a difference from those factors at day 0 and day 7. We did not find an association with some expected factors such as age, baseline renal function, use of oxacillin, aminoglycoside or vancomycin, and heart surgery. ~~contrast media injection and nephrotoxic.~~ Contrast media injection was associated with less AKI but this association appeared to be biased as patients with AKI at diagnosis were contra-indicated for contrast injection during the first week and therefore this variable was not retained. Difference in use of diuretics was significant in univariate but not in the multivariate analysis possibly due to a lack of power. It could also be related to the higher median age in our cohort, with patients presenting more known risk factors for AKI increasing the weight of these variables in the occurrence of AKI. The higher incidence of E-AKI (51%) comparing to other studies goes in the same way. Moreover, a recent French retrospective study found that 68.8% of patients with IE had AKI [11]. ~~420 patients had no baseline serum creatinine and estimation was done in 97 patients as defined in methods.~~

Twenty-seven per cent patients underwent heart valve surgery. It is consistent with recent data on French epidemiology and a recent prospective study in older patients (mean age of 83 years old) showed that surgery was performed in 16% of cases [12,13].

Glycopeptides and aminoglycosides were not associated with E-AKI in our study. Glycopeptides' use was included in our multivariate model. Short duration of administration of these drugs comparatively with other studies, and low occurrence of overdoses for glycopeptides could explain this difference. Indeed, if these antibiotic classes were commonly used at onset, the low incidence of methicillin-resistant *S. aureus* and *Enterococcus faecium* permitted in most cases a quick antibiotic switch with less nephrotoxic drugs. It also corroborates the protective effect of IDC on D7-AKI but not E-AKI. Indeed, IDC in bacteraemia due to *S. aureus* was associated elsewhere with decreased in-hospital mortality [14]. These results are in line with Chirillo et al. who reported a favourable impact of multidisciplinary management on renal function [15]. IDC has been associated with greater adherence to these quality-of-care indicators, with some studies also demonstrating lower

mortality rates. The implementation of an ID team for the early management of sepsis in the Emergency Department improved the adherence to Surviving Sepsis Campaign recommendations, appropriateness of initial antibiotic therapy and patient survival [16]. Nowadays, management of IE typically requires a multidisciplinary team including, at least, an infectious disease specialist, a cardiologist and a cardiac surgeon, with a proven benefit [17–19].

Beta-lactams were equally used in both groups. Cloxacillin was more often used than cefazolin in methicillin-susceptible *S.aureus* infection according to European Society of Cardiology (ESC) guidelines, even though Flynt et al. showed a higher risk of AKI with nafcillin. Our study was not powered to show this difference so we cannot make any conclusions about this risk factor for E-AKI [20].

Presence of septic emboli, whatever their localization, appeared to be associated with less AKI in our study. This surprising result could be due to an earlier diagnosis of IE with a more aggressive management in the presence of cutaneous or neurological emboli.

Mechanism of renal toxicity secondary to *S. aureus* remains unknown. An hypothesis is the greater severity of IE due to *S.aureus* [2]. Another hypothesis is a tubular toxicity caused by mitochondrial DNA damage [21]. Otherwise glomerulonephritis related to *S.aureus* infection is a well-described entity [22]. *S.aureus* antigen was identified within the glomeruli without immunoglobulin which stems from a T-cell mediated injury and lesion closer to pauci-immune glomerulonephritis, and differs from the immune-complex mediated glomerulonephritis usually described [23–25]. A retrospective study on renal biopsy (n=20) and necropsy (n=42) showed mostly localised infarction (n=19), acute glomerulonephritis (n=16) and pure acute tubular necrosis (n=12) [26]. Glomerulonephritis was associated with *S.aureus* but also *Streptococcus species* and 12 patients were hospitalized in nephrology unit before diagnosis of IE.

Exploration of AKI was not enough to draw any conclusion upon interstitial, tubular or glomerular origin. Renal emboli were often diagnosed since abdominal CT-scan is highly recommended by ESC guidelines even if AKI may be considered a contraindication to perform it. A lack of exploration of AKI will not permit a better understanding in its mechanisms and its therapeutics. Renal biopsy is never an emergency and should not prevail over cardiac and neurological complications, but simple biologic specimen collection such as urine dipstick test, serum complement C3 and C4, anti-neutrophil cytoplasmic antibodies (ANCA) should be encouraged [27].

Moreover, the fact that immunological phenomena were associated with E-AKI suggested that glomerulonephritis associated with IE were not diagnosed. These results are of clinical relevance, since we showed an independent association between E-AKI and one-year survival and CKD progression, with a non-negligible economic burden and worsening quality of life.

Our study presented some limitations. The retrospective design of our cohort could have resulted in a selection bias and missing data. However, the screening by Discharge Hospital Database allowed an exhaustive detection of consecutive IE cases [5]. Missing data were considered using multiple imputation by chained equation. We preferred to include patients with possible IE according Dukes criteria (i.e treated as IE) in order to better represent the real-life management of IE. Lastly, the monocentric character of our study limits its external validity. However, the study population was comparable to the literature in terms of microbiology, patients' comorbidities and characteristics of the IE [3,9].

E-AKI is common in IE and seems most often associated with non-modifiable variables: background, initial use of norepinephrine and *S.aureus* infection. E-AKI also seems to increase one-year mortality and CKD progression at last follow up. Multidisciplinary management should be mandatory. As the main actors of IE management, ID team's awareness of AKI diagnosis and etiological explorations should be raised.

Acknowledgments

We thank all the patients for their participation in this study. We also thank the staff (physicians, nurses, medical microbiologists, secretaries, and assistants) of each participating centre for their cooperation, particularly Claire Hobson, Sophie Derolez, Anne-Laure Piton, Léa Lefeuvre, Charlotte Jaulerry and Elisabeth Depoutot. We thank Pierre Bernard and Clemence Jacq for English editing. LB, FVT and AL conceived and designed the study. FVT, AL, AP, LF, FH, BS, JMH, ALeg, FP, TB, CM, AB and LB took care of the patients included. FVT, AP and FH recorded the data. AL was responsible for the statistical analyses. FVT and AL wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Funding None

Competing interests None.

Ethics approval Tours Research Ethics Committee (CPP TOURS - Region Centre - Ouest 1, 2017 082).

References

- [1] Martínez-Sellés M, Muñoz P, Estevez A, del Castillo R, García-Fernández MA, Rodríguez-Créixems M, et al. Long-term outcome of infective endocarditis in non-intravenous drug users. *Mayo Clin Proc* 2008;83:1213–7. <https://doi.org/10.4065/83.11.1213>.

- [2] Selton-Suty C, C elard M, Le Moing V, Doco-Lecompte T, Chirouze C, Iung B, et al. Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-based survey. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2012;54:1230–9. <https://doi.org/10.1093/cid/cis199>.
- [3] Ritchie BM, Hirning BA, Stevens CA, Cohen SA, DeGrado JR. Risk factors for acute kidney injury associated with the treatment of bacterial endocarditis at a tertiary academic medical center. *J Chemother Florence Italy* 2017:1–7. <https://doi.org/10.1080/1120009X.2017.1296916>.
- [4] Buchholtz K, Larsen CT, Hassager C, Bruun NE. In infectious endocarditis patients mortality is highly related to kidney function at time of diagnosis: a prospective observational cohort study of 231 cases. *Eur J Intern Med* 2009;20:407–10. <https://doi.org/10.1016/j.ejim.2008.12.017>.
- [5] Sunder S, Grammatico-Guillon L, Baron S, Gaborit C, Bernard-Brunet A, Garot D, et al. Clinical and economic outcomes of infective endocarditis. *Infect Dis Lond Engl* 2015;47:80–7. <https://doi.org/10.3109/00365548.2014.968608>.
- [6] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;36:3075–128. <https://doi.org/10.1093/eurheartj/ehv319>.
- [7] Summary of Recommendation Statements. *Kidney Int Suppl* 2012;2:8–12. <https://doi.org/10.1038/kisup.2012.7>.
- [8] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–12.
- [9] Legrand M, Pirracchio R, Rosa A, Petersen ML, Van der Laan M, Fabiani J-N, et al. Incidence, risk factors and prediction of post-operative acute kidney injury following cardiac surgery for active infective endocarditis: an observational study. *Crit Care Lond Engl* 2013;17:R220. <https://doi.org/10.1186/cc13041>.
- [10] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
- [11] Gagneux-Brunon A, Pouvaret A, Maillard N, Berthelot P, Lutz MF, Cazorla C, et al. Acute kidney injury in infective endocarditis: A retrospective analysis. *Med Mal Infect* 2019;49:527–33. <https://doi.org/10.1016/j.medmal.2019.03.015>.
- [12] Sunder S, Grammatico-Guillon L, Lemaigen A, Lacasse M, Gaborit C, Boutoille D, et al. Incidence, characteristics, and mortality of infective endocarditis in France in 2011. *PloS One* 2019;14:e0223857. <https://doi.org/10.1371/journal.pone.0223857>.
- [13] Forestier E, Roubaud-Baudron C, Fraisse T, Patry C, Gavazzi G, Hoen B, et al. Comprehensive geriatric assessment in older patients suffering from infective endocarditis. A prospective multicentric cohort study. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2019;25:1246–52. <https://doi.org/10.1016/j.cmi.2019.04.021>.
- [14] Bai AD, Showler A, Burry L, Steinberg M, Ricciuto DR, Fernandes T, et al. Impact of Infectious Disease Consultation on Quality of Care, Mortality, and Length of Stay in *Staphylococcus aureus* Bacteremia: Results From a Large Multicenter Cohort Study. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2015;60:1451–61. <https://doi.org/10.1093/cid/civ120>.
- [15] Chirillo F, Scotton P, Rocco F, Rigoli R, Borsatto F, Pedrocco A, et al. Impact of a multidisciplinary management strategy on the outcome of patients with native valve infective endocarditis. *Am J Cardiol* 2013;112:1171–6. <https://doi.org/10.1016/j.amjcard.2013.05.060>.
- [16] Viale P, Tedeschi S, Scudeller L, Attard L, Badia L, Bartoletti M, et al. Infectious Diseases Team for the Early Management of Severe Sepsis and Septic Shock in the Emergency Department. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2017;65:1253–9. <https://doi.org/10.1093/cid/cix548>.

- [17] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:e57-185. <https://doi.org/10.1016/j.jacc.2014.02.536>.
- [18] Holland TL, Baddour LM, Bayer AS, Hoen B, Miro JM, Fowler VG. Infective endocarditis. *Nat Rev Dis Primer* 2016;2:16059. <https://doi.org/10.1038/nrdp.2016.59>.
- [19] Camou F, Dijos M, Barandon L, Cornolle C, Greib C, Laine M, et al. Management of infective endocarditis and multidisciplinary approach. *Med Mal Infect* 2019;49:17–22. <https://doi.org/10.1016/j.medmal.2018.06.007>.
- [20] Flynt LK, Kenney RM, Zervos MJ, Davis SL. The Safety and Economic Impact of Cefazolin versus Nafcillin for the Treatment of Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections. *Infect Dis Ther* 2017;6:225–31. <https://doi.org/10.1007/s40121-017-0148-z>.
- [21] Bartz RR, Fu P, Suliman HB, Crowley SD, MacGarvey NC, Welty-Wolf K, et al. *Staphylococcus aureus* sepsis induces early renal mitochondrial DNA repair and mitochondrial biogenesis in mice. *PloS One* 2014;9:e100912. <https://doi.org/10.1371/journal.pone.0100912>.
- [22] Wang S-Y, Bu R, Zhang Q, Liang S, Wu J, Liu X-GZS-W, et al. Clinical, Pathological, and Prognostic Characteristics of Glomerulonephritis Related to Staphylococcal Infection. *Medicine (Baltimore)* 2016;95:e3386. <https://doi.org/10.1097/MD.0000000000003386>.
- [23] Pertschuk LP, Woda BA, Vuletin JC, Brigati DJ, Soriano CB, Nicastrì AD. Glomerulonephritis due to *Staphylococcus aureus* antigen. *Am J Clin Pathol* 1976;65:301–7.
- [24] Cunningham MA, Huang XR, Dowling JP, Tipping PG, Holdsworth SR. Prominence of cell-mediated immunity effectors in “pauci-immune” glomerulonephritis. *J Am Soc Nephrol JASN* 1999;10:499–506.
- [25] Lusco MA, Fogo AB, Najafian B, Alpers CE. AJKD Atlas of Renal Pathology: Subacute Bacterial Endocarditis-Associated Glomerulonephritis. *Am J Kidney Dis Off J Natl Kidney Found* 2016;68:e11–2. <https://doi.org/10.1053/j.ajkd.2016.06.001>.
- [26] Majumdar A, Chowdhary S, Ferreira MA, Hammond LA, Howie AJ, Lipkin GW, et al. Renal pathological findings in infective endocarditis. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc* 2000;15:1782–7.
- [27] Hirai K, Miura N, Yoshino M, Miyamoto K, Nobata H, Nagai T, et al. Two Cases of Proteinase 3-Anti-Neutrophil Cytoplasmic Antibody (PR3-ANCA)-related Nephritis in Infectious Endocarditis. *Intern Med Tokyo Jpn* 2016;55:3485–9. <https://doi.org/10.2169/internalmedicine.55.7331>.

Figures

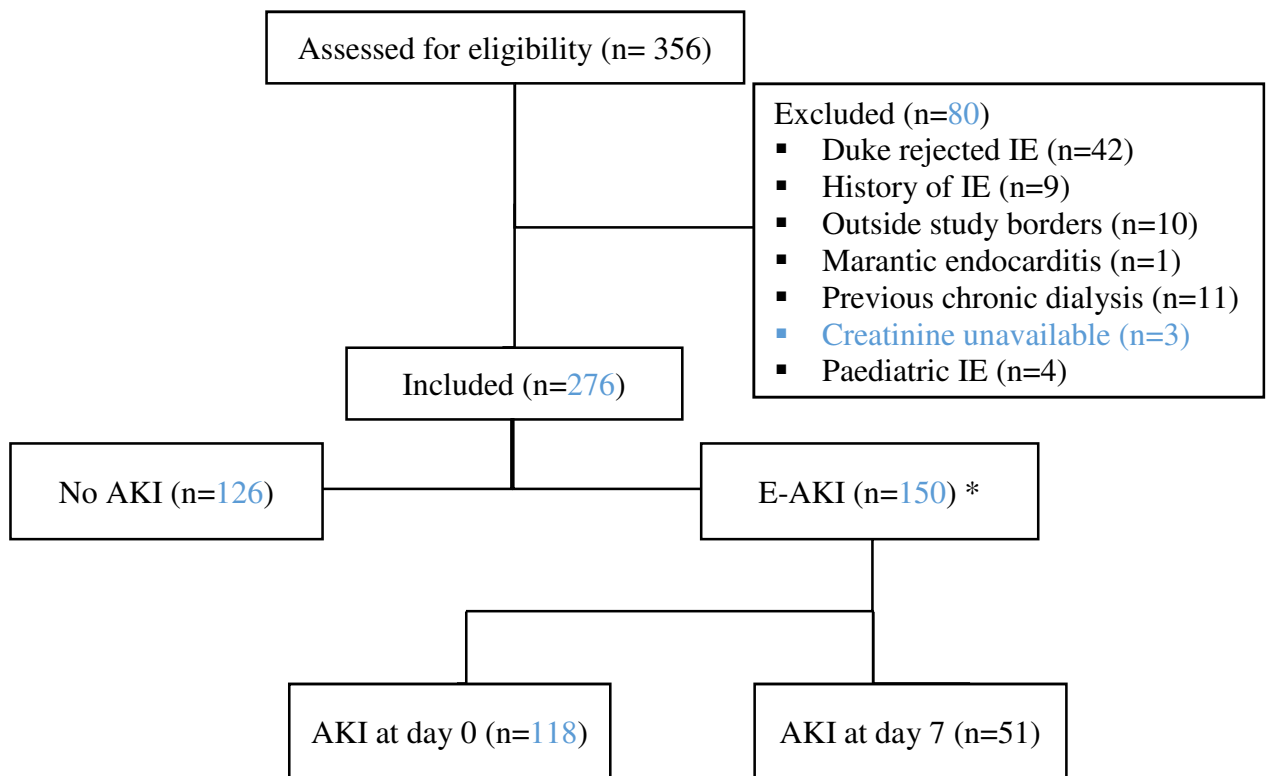


Figure 1: Flowchart

IE = Infective endocarditis; AKI = Acute Kidney injury; E-AKI = early AKI;

* E-AKI includes patients with AKI during the first week. 19 patients had AKI at D0 and worsening renal function at D7, so they were included in both D0-AKI and D7-AKI.

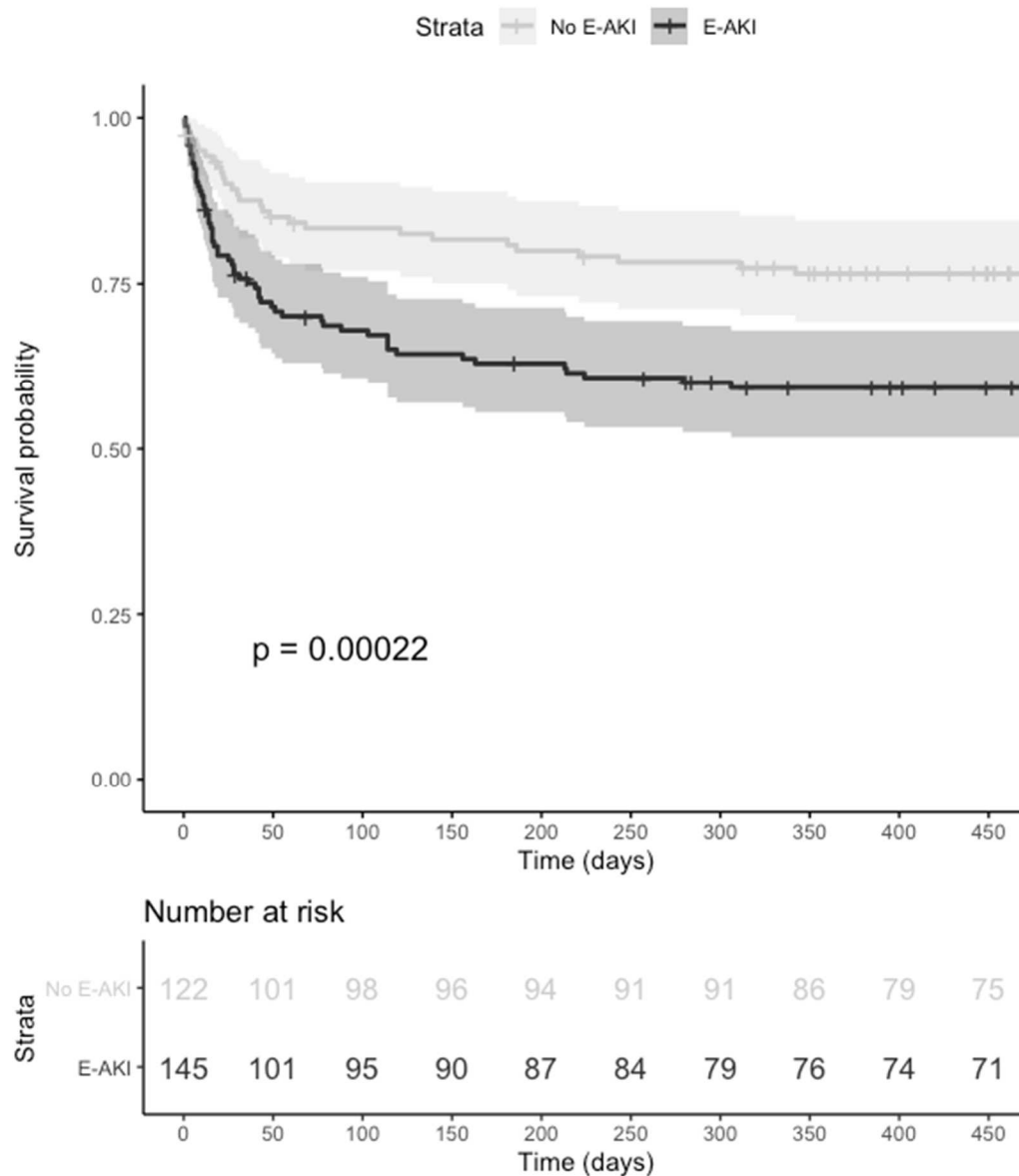


Figure 2: One-year survival after infective endocarditis according to the presence of early acute kidney injury

Survival was estimated using Kaplan-Meier survival curve, comparing patients presenting E-AKI or not. Confidence intervals are presented for each group, as well as the p-value of the log-rank test. E-AKI = Early Acute Kidney Injury. Survival data was missing for 9 patients (5 in the E-AKI group).

Tables

Table 1: Baseline characteristics of patients

P-values were defined by univariate analysis comparing both groups of patients, as described in the Methods section. *E-AKI: early acute kidney injury; **GFR: glomerular filtration rate; ***RAAS: renin angiotensin aldosterone system; ****NSAID: non-steroidal anti-inflammatory drugs; IQR: interquartile range; SD: standard deviation. **NA: absolute count of missing data by variable in the whole population. The missing data were harmoniously distributed among groups.**

	Total patients		No E-AKI*	E-AKI	P-value
	n=276	NA	n=126	n=150	
Background					
Age, years, <i>median (IQR)</i>	70 (19)	-	68.5 (19.7)	71 (20)	0.20
Men, <i>n (%)</i>	206 (74.6)	-	99 (78.6)	107 (71.3)	0.22
Weight, Kg, <i>median (IQR)</i>	74 (23)	5	74 (22)	75 (24)	0.57
Baseline GFR**, mL/min/1,73m ² <i>median (IQR)</i>	87.0 (29.9)	21	89.6 (26.2)	85.0 (29.1)	0.05
RAAS inhibitor***, <i>n (%)</i>	130 (47.1)	2	55 (43.7)	75 (50)	0.42
NSAID ****, <i>n (%)</i>	35 (13.0)	2	16 (12.7)	19 (12.7)	1
Diuretics, <i>n (%)</i>	122 (44.2)	2	45 (35.7)	77 (51.3)	0.02
Contrast injection, <i>n (%)</i>	132 (52.2)	12	73 (57.9)	71 (47.3)	0.11
≥ 2 nephrotoxic drugs, <i>n (%)</i>	147 (53.3)	13	58 (46.0)	89 (59.3)	0.09
IV drug user, <i>n (%)</i>	10 (3.6)	-	6 (4.8)	4 (2.7)	0.52
Charlson comorbidity index, <i>median (IQR)</i>	5 (4)	4	5 (4)	6 (3)	0.03
Peripheral arteriopathy, <i>n (%)</i>	42 (15.2)	-	10 (7.9)	32 (21.3)	0.002
Stroke, <i>n (%)</i>	56 (20.3)	-	30 (23.8)	26 (17.3)	0.30
Diabetes, <i>n (%)</i>	87 (31.5)	-	25 (19.8)	62 (41.3)	<0.001
Congestive heart failure, <i>n (%)</i>	104 (37.7)	-	39 (31.0)	65 (43.3)	0.04
Hypertension, <i>n (%)</i>	176 (63.8)	-	74 (58.7)	102 (68.0)	0.14
Prosthetic valve, <i>n (%)</i>	85 (30.8)	-	43 (34.1)	42 (28)	0.33
Pacemaker (PM) or defibrillator, <i>n (%)</i>	55 (19.9)	-	21 (16.7)	34 (22.7)	0.22
Characteristics of infective endocarditis					

Duke definite IE, <i>n</i> (%)	220 (79.7)	-	104 (82.5)	116 (77.3)	0.36
PM or prosthetic valve infection, <i>n</i> (%)	113 (40.9)	-	54 (42.9)	59 (39.3)	0.64
Vegetation, <i>n</i> (%)	178 (64.5)	3	78 (61.9)	100 (66.7)	0.44
Emboli (Renal, Cerebral, Osteo-articular), <i>n</i> (%)	157 (56.9)	-	78 (61.9)	79 (52.7)	0.15
Immunological manifestations, <i>n</i> (%)	37 (13.4)	-	12 (9.5)	25 (16.7)	0.11
Acute heart failure, <i>n</i> (%)	124 (44.9)	2	44 (34.9)	80 (53.3)	0.005
Norepinephrine use, <i>n</i> (%)	62 (22.5)	2	16 (12.7)	46 (30.7)	< 0.01
Albumin, g/L, median (IQR)	31 (8)	73	31 (8)	30 (9)	0.04
Positive blood cultures after 48h of treatment, <i>n</i> (%)	55 (20.0)	56	18 (14.3)	37 (24.7)	0.02

Table 2: Microbiology and treatment of infective endocarditis

P-values were defined by univariate analysis comparing both groups of patients, as described in the Methods section. *E-AKI: early acute kidney injury; IQR: interquartile range; SD: standard deviation. NA: absolute count of missing data by variable in the whole population. The missing data were harmoniously distributed among groups.

	Total patients		No E-AKI*	E-AKI*	P-value
	n = 276	NA	n = 126	n = 150	
Microbiology					
<i>Staphylococcus</i> species	108 (39.1)	-	38 (30.2)	70 (46.7)	0.007
<i>Staphylococcus aureus</i> , n (%)	91 (33.0)	-	28 (22.2)	63 (42.0)	< 0.001
Coagulase-negative staphylococci, n (%)	17 (6.1)	-	10 (7.9)	7 (4.7)	0.32
<i>Streptococcus</i> species, n (%)	101 (36.6)	-	53 (42.1)	48 (32.0)	0.11
<i>Enterococcus</i> species, n (%)	38 (13.8)	-	21 (16.7)	17 (11.3)	0.22
Other bacterium, n (%)	22 (8.0)	-	14 (11.1)	8 (5.3)	0.12
Undocumented, n (%)	12 (4.3)	-	3 (2.4)	9 (6.0)	0.23
Multibacterial, n (%)	5 (1.8)	-	3 (2.4)	2 (1.3)	0.67
Treatment					
Infectious disease consultation, n (%)	214 (77.5)	5	106 (84.1)	108 (72.0)	0.01
Aminoglycoside, n (%)	22 (80.1)	1	97 (77.0)	124 (82.7)	0.36
Aminoglycoside duration, days, median (IQR)	4 (6)	8	4 (7.5)	4 (5)	0.62
β-lactam, n (%)	255 (92.4)	1	115 (91.3)	140 (93.3)	0.81
β-lactam duration, days, median (IQR)	28 (27)	16	32 (23)	28 (28)	0.03
Glycopeptide, n (%)	85 (30.8)	1	30 (23.8)	55 (36.7)	0.03
Glycopeptide duration, days, median (IQR)	3 (10)	5	3 (14)	3 (8.7)	0.27
Vancomycin maximal trough level, mg/L, median (IQR)	29 (22)	48	29 (23)	29 (20)	0.75
Vancomycin mean trough level, mg/L median (IQR)	22.5 (8.2)	44	23.5 (9.2)	21 (10.1)	0.26
Glycopeptide and aminosides combination, n (%)	72 (26.1)	1	24 (19.0)	48 (32.0)	0.02
Quinolones, n (%)	33 (12.0)	1	15 (11.9)	18 (12.0)	1
Rifampicin, n (%)	73 (26.4)	1	30 (23.8)	43 (28.7)	0.44
Total antibiotics duration, days, median (IQR)	42 (14)	17	42 (14)	40 (18)	0.006
Heart valve surgery, n (%)	77 (27.9)	3	33 (26.2)	44 (29.3)	0.69

Table 3: Variables associated with early acute kidney injury

Univariate and multivariate analysis by logistic regression conducted on imputed data. Factors included in the model were those significant in univariate analysis with a p-value under **0.2**. Missing data was treated with multiple imputation by chained equations.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.01	0.99-1.03	0.182	-		
Masculine gender	1.47	0.85-2.58	0.170	-		
Charlson comorbidity index	1.08	0.98-1.20	0.121	-		
Peripheral arteriopathy	3.15	1.53-7.01	0.003	2.59	1.07-6.23	0.03
Diabetes	2.85	1.67-4.97	<0.001	2.34	1.25-4.37	0.008
Congestive heart failure	1.71	1.04-2.82	0.035	-		
Hypertension	1.49	0.91-2.45	0.111	-		
Baseline GFR (mL/mn/1.73m ²)	0.99	0.98-1.00	0.051	-		
Positive blood cultures > 48h	1.67	0.99-2.85	0.055	-		
<i>Staphylococcus aureus</i>	2.53	1.50-4.35	0.001	3.41	1.83-6.39	<0.001
<i>Streptococcus</i> species	0.65	0.40-1.06	0.085	-		
Other bacterium	0.45	0.17-1.09	0.084	-		
Immunological manifestations	1.90	0.93-4.08	0.086	3.11	1.31-7.39	0.01
Emboli	0.68	0.42-1.11	0.123	0.54	0.30-0.96	0.03
≥ 2 nephrotoxic drugs	1.70	1.04-2.79	0.034	1.67	0.96-2.91	0.07
Diuretics	1.83	1.13-2.99	0.014	-		
Glycopeptide	1.85	1.10-3.17	0.022	-		
Glycopeptide and aminosides	1.90	1.10-3.35	0.024	-		
Acute heart failure	2.06	1.27-3.36	0.004	-		
Norepinephrine use	3.04	1.65-5.85	0.001	3.44	1.72-7.02	<0.001
Infectious Disease consultation	0.46	0.24-0.84	0.013	-		