ISHLT September 2024 | Infectious Diseases
JOURNAL WATCH

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European Study of Cerebral Aspergillosis treated with Isuvaconazole: an EFISG Study

Serris et al. *Clinical Infectious Diseases 2024.* | https://doi.org/10.1093/cid/ciae371

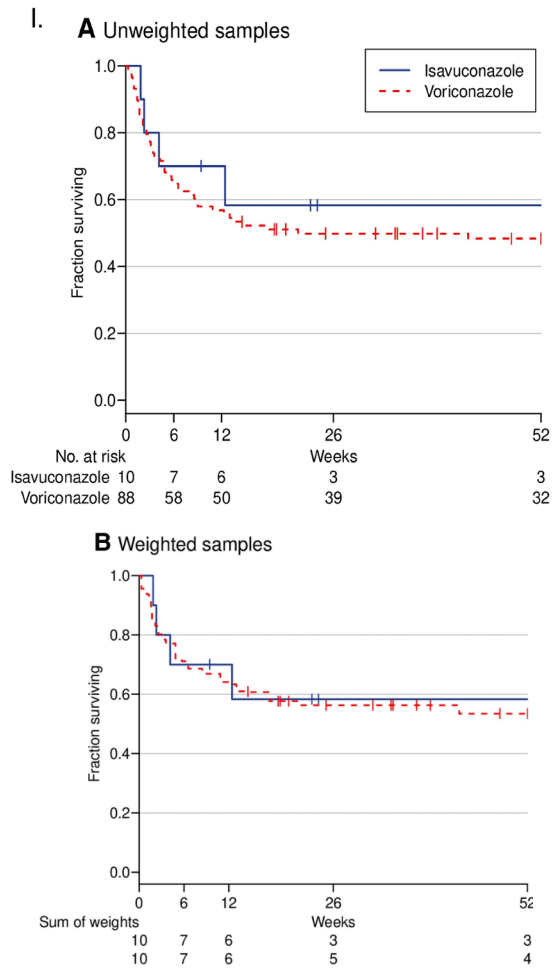
Study Highlights

Objective: Cerebral aspergillosis (CA) is associated with high mortality. According to ECIL-6 and ESCMID guidelines, the recommended first-line treatment for all forms of aspergillosis is voriconazole or isuvaconazole. However, little is known about the safety and efficacy of isuvaconazole in CA.

Methods: The authors conducted a European multi-center retrospective study of patients treated with isuvaconazole for proven or probably CA between 2014 and 2022 and compared the outcomes to those of weighted control groups from the previously published French national cohort of CA, the Cerebral Aspergillosis Lesional Study.

Results: Forty patients from 10 countries were included. The main underlying conditions were hematologic malignancy (53%) and solid organ transplantation (20%). Isuvaconazole was administered as first-line treatment to 10 patients, primarily in combination therapy, resulting in control of CA in 70% of these cases. Thirty patients received isuvaconazole after a median of 65 days on another therapy, mostly because of side effects (50%) or therapeutic failure (23%) of the previous treatment. Predominantly given as monotherapy, it achieved control of CA in 73% of the patients. Seventeen patients (43%) underwent neurosurgery. When measured, isuvaconazole levels were low in cerebrospinal fluid but adequate in serum and brain tissue. Isuvaconazole toxicity led to treatment interruption in 7.5% of the patients. Twelve-week mortality was 18%. Comparison with the CEREALS cohort showed a comparable survival in patients receiving isuvaconazole or voriconazole as a first-line treatment.

Conclusions: Isuvaconazole appears to be a well-tolerated treatment. Mortality associated with isuvaconazole is similar to that reported with voriconazole.



Legend: Survival during the first year after first-line antifungal therapy. Unweighted sample (*A*) and weighted sample (*B*).

Reviewer's Comments

- Current guidelines recommend voriconazole as first-line therapy for cerebral aspergillosis, however toxicity and drug interactions are limiting.
- Isuvaconazole is a more tolerable drug active against *Aspergillus*, however there is little real-world data to support its use as a first-line treatment for CNS disease.
- This study provides further evidence that isuvaconzole is non-inferior to voriconazole for the treatment of cerebral aspergillosis.

Limitations

- The small sample size (n=40) used in this study limits generalizability of the findings.
- The majority of patients received an alternate drug as first-line treatment and were subsequently changed to isuvaconazole, limiting the applicability of this study to initial treatment regimens.
- The retrospective nature of this study raises concern for underlying bias in the results, further limiting clinical application of the study.

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Donor-derived *Mycoplasma* and *Ureaplasma* infections in lung transplant recipients: A prospective study of donor and recipient respiratory tract screening and recipient outcomes

P. C. K. Tam, *et al*. *American Journal of Transplantation*. Jul 2024. | https://doi.org/10.1016/j.ajt.2024.07.013

Study Highlights

Objective: Mollicutes are fastidious bacteria that can cause pulmonary and extrapulmonary donor-derived infections after lung transplant. Best practice for screening and recipient surveillance is unknown. This study assesses the value and comparative performance of culture and polymerase chain reaction (PCR) screening in predicting mollicute infection in lung transplant recipients.

Methods: Single-center, blinded, prospective study occurring between 10/5/20–9/25/21 (n=99). Specimens from donor and recipient bronchoalveolar lavage (BAL) performed at time of transplant were screened for *M. hominis* and *Ureaplasma* spp. using culture and PCR.

Results: 18/99 donor lungs had ≥1 positive mollicute screening test. 9/99 recipients developed post-transplant mollicute infection, of whom, 7 (78%) had a positive donor screen. All recipients with severe infection post-transplant received lungs from donors who were culture screen positive.

Conclusion: Donor BAL culture screening predicted all serious recipient mollicute infections and culture had better PPV than PCR.

Results

Performance of donor BAL mollicute screening tests to predict post-transplant recipient mollicute infection

Testing modality	SN	SP	PPV	NPV
Culture	6/9 (67%)	88/90 (98%)	6/8 (75%)	88/91 (97%)
PCR	5/9 (56%)	80/90 (89%)	5/15 (33%)	80/84 (95%)
Culture OR PCR	7/9 (78%)	79/90 (88%)	7/18 (39%)	79/81 (98%)
Culture AND PCR	4/9 (44%)	89/90 (99%)	4/5 (80%)	89/94 (95%)

SN=sensitivity; **SP**=specificity; **PPV**=positive predictive value; **NPV**=negative predictive value

- Positive donor culture predicted all 6 cases of definite mollicute infections, including 3 cases with extrapulmonary involvement
- Donor culture was negative in 3 cases of possible/probable mollicute pulmonary infection
- Donor PCR failed to predict 2 cases of serious mollicute infection

Reviewer's Comments

- This study demonstrates the utility of universal lung donor mollicute screening at time of transplant.
- Donor BAL mollicute screening by culture had similar sensitivity as PCR screening, but higher PPV.
- Neither donor BAL mollicute culture nor mollicute PCR screens at time of transplant predicted all mollicute infections.
- Clinicians should maintain a high index of suspicion for mollicute infection after lung transplant despite a negative screening test.

Limitations

- Generalizability is limited by single-center study design and cohort size.
- Local diagnostic test availability, as well as variability in mollicute culture techniques and PCR tests may impact findings.
- Further investigation comparing outcomes between immediate universal mollicute prophylaxis initiated before screening results vs delayed pre-emptive antibiotics started after a positive screening is needed.

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Cardiac allograft vasculopathy in heart transplant recipients from hepatitis C viremic donors

Kadosh B, et al. *Clinical Transplantation* 2024. |https://doi.org/10.1111/ctr.15294

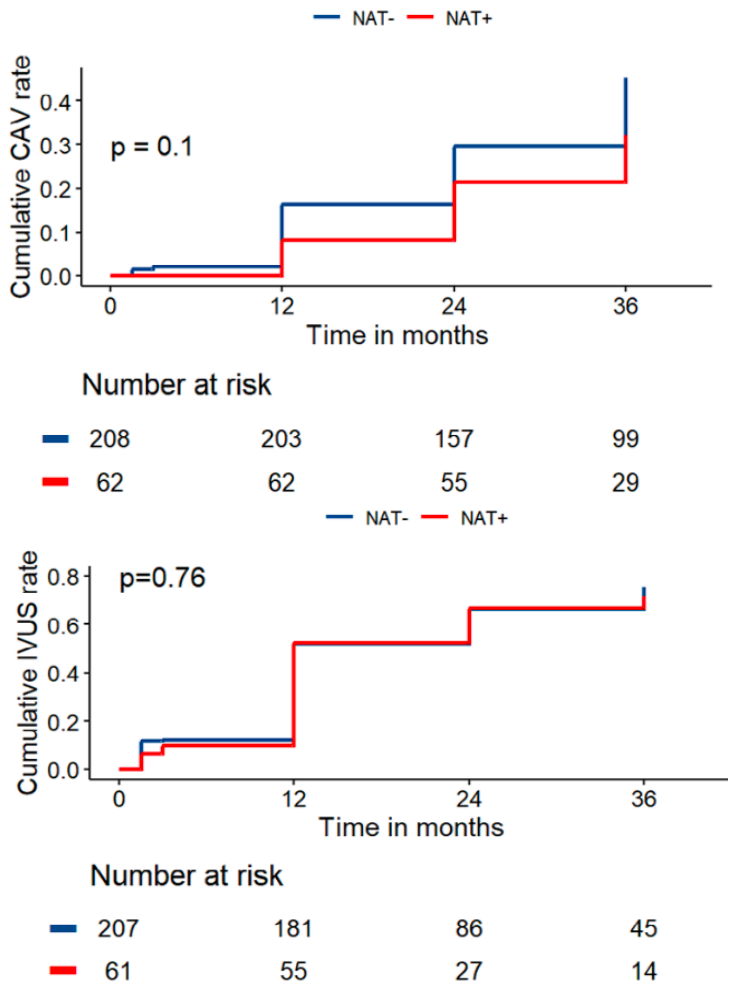
Study Highlights

Objective: HCV viremia is a known risk factor for atherosclerosis, but its impact on cardiac allograft vasculopathy (CAV) is unclear. This study compared CAV incidence in heart transplant recipients from HCV+ and HCV− donors.

Methods: A retrospective review was conducted on heart transplant recipients at two large centers. Patients with at least one surveillance angiogram at one-year post-transplant were included. Data from years 2 and 3 were included if available. CAV was graded (1, 2, or 3) per ISHLT guidelines. IVUS ≥ 0.5 mm was considered subclinical disease.

Results: Of 270 patients, 62 received a heart from an HCV+ donor and 208 from an HCV− donor. CAV incidence was 8.8% in the HCV+ group versus 16.8% in the HCV− group at 1 year, 20.0% versus 28.8% at 2 years, and 33.3% versus 41.5% at 3 years. Multivariate analysis, controlling for donor age, smoking history, BMI, hypertension, and diabetes showed no significant difference in CAV risk (adjusted HR 0.80; 95% CI 0.45–1.40, p = 0.43). Hazard modeling revealed no difference in the cumulative rate of significant IVUS lesions (OR 0.95; 95% CI 0.67–1.34, p = 0.76).

Conclusions: There was no significant difference in the incidence of CAV or subclinical disease (IVUS) between heart transplant recipients from HCV+ and HCV− donors.



Rate of CAV by HCV (NAT) donor status (Top). Rate of any IVUS lesion ≥ 5 mm by HCV donor status (Bottom).

Reviewer's Comments

- Since the advent of direct-acting antiviral therapy, outcomes between HCV+ and HCV- recipients have become comparable.
- This study, conducted at two large transplant centers, is the second of its kind, following a 2023 Vanderbilt study which also found no difference in CAV outcomes at 1 year between HCV+ and HCV- recipients.
- Ongoing research is needed to explore long-term outcomes and optimize HCV treatment timing and strategies for this vulnerable patient population.

Limitations

- The study was retrospective and observational in nature.
- CAV is a cumulative, progressive disease. Although the study provided comparisons at years 2 and 3 post transplantation, it was not powered to detect significant differences at these time points.
- Although statistical analysis adjusted for known CAD risk factors, only a quarter of patients had baseline angiography prior to transplantation making donor derived CAD burden difficult to quantify.