Gli ultimi studi che potrebbero cambiare la pratica clinica quotidiana

Il paziente immunocompromesso non HIV

Renato Pascale

Università di Bologna

IRCCS Policlinico Sant'Orsola

UO Malattie Infettive

POLICLINICO DI SANT'ORSOLA

ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA

Outline

Viral Infections

Bacterial Infections

Fungal Infections

SOT

HSCT

CMV new drugs

Drug	Mode of action	Advantages	Limitations
Maribavir	Inhibition of viral UL97 kinase	Well tolerated Oral formulation	Dysgeusia in one-third of patients No intravenous formulation **Reduced efficacy with high viral loads** **Poor penetration to CNS/retina** Drug-drug interactions **Recurrences after successful treatment** **Resistances**
Letermovir	Inhibition of viral terminase complex	Well tolerated Oral and intravenous formulation	Approved only for prophylaxis **Reduced efficacy with high viral loads** **Relevant interaction with cyclosporine, sirolimus, tacrolimus** **Recurrences after successful treatment** **Resistances**

Walti CS et al. Transplant International 2023

Clinical Infectious Diseases

MAJOR ARTICLE

Maribavir for Refractory or Resistant Cytomegalovirus Infections in Hematopoietic-cell or Solid-organ Transplant Recipients: A Randomized, Dose-ranging, Dc Phase 2 Study

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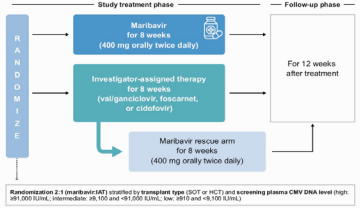
Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial

Robin K. Avery, Sophie Alain, Barbara D. Alexander, Emily A. Blumberg, Roy F. Chemaly, Catherine Cordonnier, Rafael F. Duarte, Diana F. Florescu, Nassim Kamar, Deepali Kumar, Johan Maertens, Francisco M. Marty, Genovefa A. Papanicolaou, Fernanda P. Silveira, Oliver Witzke, Jingyang Wu, Aimee K. Sundberg, and Martha Fournier, for the SOLSTICE Trial Investigators

INTRODUCTION

This was a phase 3, multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of maribavir compared with IAT in HCT and SOT recipients with CMV infections refractory to most recent treatment, with or without resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir.

STUDY DESIGN



STUDY ENDPOINTS

The primary endpoint was confirmed CMV viremia clearance at the end of Week 8 (regardless of premature treatment discontinuation).

The key secondary endpoint was a composite of confirmed CMV viremia clearance and symptom control at the end of **Week 8, maintained through Week 16 after receiving exclusively** study-assigned treatment.

RESULTS

352 patients were randomized (maribavir, n=235; IAT, n=117)

PRIMARY ENDPOINT (WEEK 8)

Adjusted difference (95% CI): 32.8 (22.80–42.74)

A significantly higher proportion of patients treated with maribavir achieved the primary endpoint of confirmed CMV viremia clearance at Week 8 compared with IAT.

KEY SECONDARY ENDPOINT (WEEK 16)

Adjusted difference (95% CI): 9.5 (2.02–16.88)

A greater proportion of patients treated with maribavir achieved the composite key secondary endpoint of CMV viremia clearance and symptom control at Week 8, with maintenance through Week 16 compared with IAT.

SAFETY

Median (range) duration of exposure was 57 (2–64) days with maribavir and 34 (4–64) days with IAT.

Fewer patients discontinued maribavir than IAT due to TEAEs (13.2% vs 31.9%).

Dysgeusia was the most frequently reported TEAE in the maribavir group (maribavir: 37.2%; IAT: 3.4%).

Maribavir was associated with less acute kidney injury versus foscarnet (8.5% vs 21.3%) and neutropenia versus valganciclovir/ganciclovir (9.4% vs 33.9%).

One patient per treatment group had fatal treatment-related TEAEs.

CONCLUSIONS

Maribavir was superior to IAT for cytomegalovirus viremia clearance, and viremia clearance plus symptom control, with maintenance of these effects post-therapy in transplant recipients with refractory cytomegalovirus infections with or without resistance.

Maribavir demonstrated an improved safety profile versus valganciclovir/ganciclovir for myelotoxicity and versus foscarnet for nephrotoxicity, with fewer patients discontinuing maribavir than IAT.

The availability of an orally bioavailable therapy without the tolerability issues associated with current therapies may confer patient management benefits.

CMV, cytomegalovirus; HCT, hematopoietic-cell transplant; IAT, investigator-assigned therapy; SOT, solid-organ transplant; TEAE, treatment-emergent adverse event.

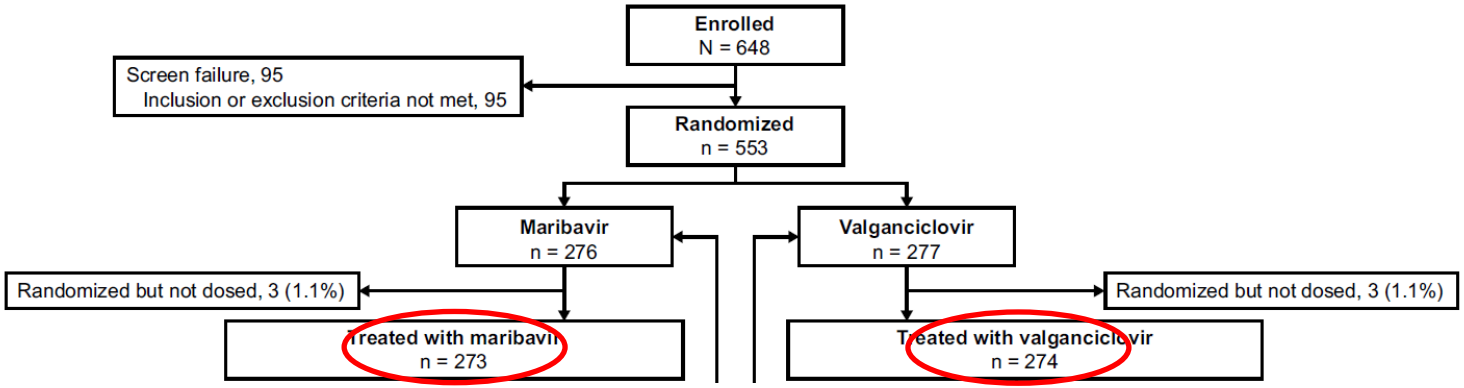
ClinicalTrials.gov: NCT02931539

This study was funded by Takeda Development Center Americas, Inc., Lexington, MA

Treatment for First Cytomegalovirus Infection Post-Hematopoietic Cell Transplant in the AURORA Trial: A Multicenter, Double-Blind, Randomized, Phase 3 Trial Comparing Maribavir With Valganciclovir

Papanicolau G et al. Clin Infect Dis 2024 20;78(3):562-572.

- **Study design**: multicenter, double-blind, phase 3 study,
- **Population**: pts with first **asymptomatic** CMV infection post-HCT
- **Intervention**: randomized 1:1 to **maribavir** 400 mg twice daily or **valganciclovir** for 8 weeks with 12 weeks of follow-up.
  - ✓ The **primary endpoint** was **confirmed CMV viremia clearance at week 8** (primary hypothesis of **non inferiority margin of 7.0%**).
  - ✓ Secondary endpoint: **composite endpoint**: primary endpoint + no findings of CMV tissue-invasive disease at week 8 through week 16.



Treatment for First Cytomegalovirus Infection Post-Hematopoietic Cell Transplant in the AURORA Trial: A Multicenter, Double-Blind, Randomized, Phase 3 Trial Comparing Maribavir With Valganciclovir

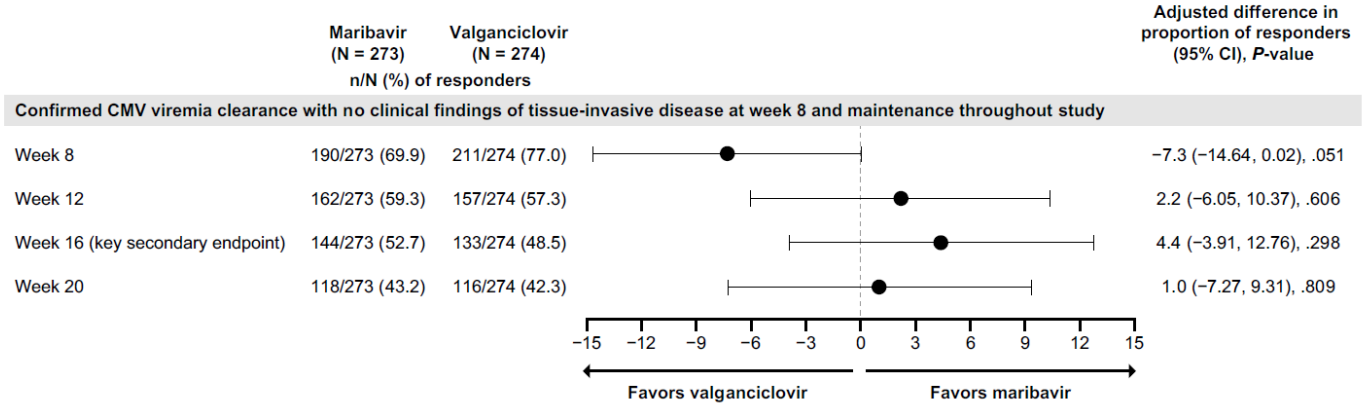
Papanicolau G et al. Clin Infect Dis 2024 20;78(3):562-572.

Primary endpoint:

- Confirmed CMV viremia clearance **At week 8**:
  - ✓ **Maribavir** (**69.6%**) vs **Valganciclovir** (**77.4%**) (**adj diff: −7.7%**; 95% CI: −14.98, −.36). The criterion for noninferiority of maribavir to valganciclovir for the primary endpoint **was not met**

- For patients with high viral load, acute GVHD, and those who had undergone T-cell depletion at baseline, the treatment effect of maribavir was below the group average.

Secondary endpoint:



Treatment for First Cytomegalovirus Infection Post-Hematopoietic Cell Transplant in the AURORA Trial: A Multicenter, Double-Blind, Randomized, Phase 3 Trial Comparing Maribavir With Valganciclovir

Papanicolau G et al. Clin Infect Dis 2024 20;78(3):562-572.

Treatment-Emergent Resistance

Maribavir 8.8% (24/273)

87.5% (21/24) did not achieve the primary endpoint

- 19 R to only maribavir
- 1 R to only valganciclovir
- 1 R to both maribavir and valganciclovir

Valganciclovir 2.9% (8/274)

50% (4/8) did not achieve the primary endpoint

- 3 R to only valganciclovir
- 1 R to both maribavir and valganciclovir

Supplementary Table 2. Identified Treatment-Emergent[a] Known or Suspected RASs to Conventional Anti-CMV Therapies[b]

	Associated resistance	Valganciclovir (N=274) n (%)	Maribavir (N=273) n (%)
Single GCV/FOS/CDV RAS in only pUL97			
M460I	GCV	1 (0.4)	0
M460V	GCV	1 (0.4)	0
C480F	GCV (also MBV)	0	1 (0.4)
C480R	GCV (also MBV)	1 (0.4)	0
H520Q	GCV	1 (0.4)	0
C592G	GCV	0	1 (0.4)
A594V	GCV	2 (0.7)	0
L595S	GCV	1 (0.4)	0
Multiple GCV/FOS/CDV RAS in only pUL97			
A594P+**C603W**	Ganciclovir	1 (0.4)	0

Supplementary Table 3. Identified Treatment-Emergent[a] Known or Suspected RASs to Maribavir[b]

	Valganciclovir (N=274) n (%)	Maribavir (N=273) n (%)
Single maribavir RAS in only pUL97		
T409M	0	12 (4.4)
H411Y	0	6 (2.2)
Multiple maribavir RASs in only pUL97		
T409M+H411Y	0	5 (1.8)
T409M+C480F	0	1 (0.4)
T409M+C480R	1 (0.4)	0

Efficacy and safety of extended duration letermovir prophylaxis in recipients of haematopoietic stem-cell transplantation at risk of cytomegalovirus infection: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

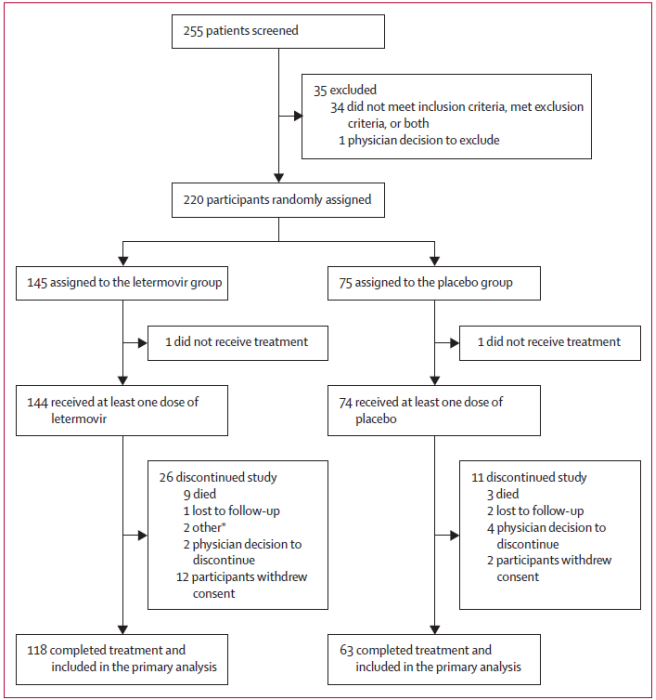
Russo D et al. Lancet Haematology 2024

- **Aim**: the efficacy and safety of 200 days letermovir prophylaxis for clinically significant CMV infection following HSCT

- **Study design**: multicentre, randomised, double-blind, placebo-controlled, phase 3 trial at 32 sites in 6 European and USA countries

- **Population**:
  - ✓ CMV+ HSCT recipients receiving letermovir prophylaxis for up to 100 days following HSCT randomly assigned (2:1) to receive either an additional 100 days or 100 days of a placebo comparator for letermovir

- **The primary efficacy endpoint**: was the proportion of participants to week 28 (200 days after HSCT) with clinically significant cytomegalovirus infection.



Efficacy and safety of extended duration letermovir prophylaxis in recipients of haematopoietic stem-cell transplantation at risk of cytomegalovirus infection: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Russo D et al. Lancet Haematology 2024

- Results: 220 patients enrolled:
  - 145 (66%) in the letermovir group vs 75 (34%) in the placebo group.

4 (**3%**) of 144 **letermovir group** Developed clinically CMV infection

14 (**19%**) of 74 **placebo group** developed clinically CMV infection

treatment difference: **-16,1%** (95% CI -25,8 to − 6,5]; p=0,0005).

Key secondary endpoints				
Clinically significant cytomegalovirus infection§				
From week 14 to week 38	19 (13%)	14 (19%)	−5·7 (−16·8 to 5·4)	0·16
From week 14 to week 48	19 (13%)	14 (19%)	−5·7 (−16·8 to 5·4)	0·16
Failures¶ from week 14 to week 28	3 (2%)	12 (16%)	−14·1 (−23·3 to −5·0)	0·0012
Initiation of PET based on documented cytomegalovirus viraemia	1 (<1%)	11 (15%)	..	..
Discontinued from study with cytomegalovirus viraemia before week 28	2 (1%)	1 (1%)	..	..
All-cause mortality				
From week 14 to week 28	3 (2%)	1 (1%)	0·7 (−3·8 to 5·3)	0·62
From week 14 to week 48	12 (8%)	6 (8%)	0·3 (−7·9 to 8·4)	0·53

Safety	Letermovir group (n=144)	Placebo group (n=74)	Difference (95% CI)*
Any adverse event	128 (89%)	69 (93%)	−4·4 (−11·8 to 4·7)
GVHD	43 (30%)	23 (31%)	−1·2 (−14·5 to 11·2)
Diarrhoea	17 (12%)	9 (12%)	−0·4 (−10·7 to 8·2)
Nausea	16 (11%)	13 (18%)	−6·5 (−17·6 to 2·9)
Pyrexia	13 (9%)	9 (12%)	−3·1 (−13·3 to 5·0)
Decreased appetite	6 (4%)	9 (12%)	−8·0 (−17·8 to −0·8)

Data are n (%), unless otherwise indicated. Most common adverse events defined as adverse events of any severity that were reported in at least 10% of participants in either treatment group. Information on AE grades was not collected in this trial. GVHD=graft-versus-host disease. *Based on Miettinen and Nurminen's method.[10]

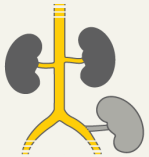
Table 3: **Adverse events in the safety population**

JAMA

QUESTION Is letermovir noninferior to valganciclovir prophylaxis for cytomegalovirus (CMV) disease prevention in high-risk adult CMV-seronegative kidney transplant recipients who receive an organ from a CMV-seropositive donor?

CONCLUSION Letermovir was noninferior to valganciclovir for prophylaxis of CMV disease over 52 weeks among adult CMV-seronegative recipients who received an organ from a CMV-seropositive donor.

POPULATION



422 Men
167 Women

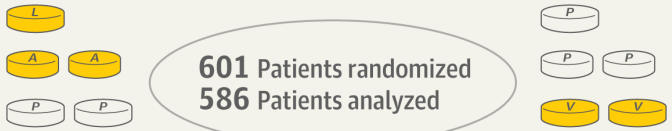
Adult CMV-seronegative kidney transplant recipients receiving an organ from a CMV-seropositive donor

Mean age: **50** years

LOCATIONS

94
Hospitals worldwide

INTERVENTION



601 Patients randomized
586 Patients analyzed

301
Letermovir
480 mg of letermovir orally daily, 400 mg of acyclovir twice daily, and a valganciclovir placebo

300
Valganciclovir
900 mg of valganciclovir orally daily with letermovir and acyclovir placebos

PRIMARY OUTCOME

CMV disease through 52 weeks after transplant

FINDINGS

Patients with committee-confirmed CMV through week 52

Letermovir
10.4% (30 of 289 patients)

Valganciclovir
11.8% (35 of 297 patients)

Letermovir was noninferior to valganciclovir:
Stratum-adjusted difference, −1.4%
(95% CI, −6.5% to 3.8%)

Limaye AP, Budde K, Humar A, et al. Letermovir vs valganciclovir for prophylaxis of cytomegalovirus in high-risk kidney transplant recipients: a randomized clinical trial. *JAMA*. Published online June 6, 2023. doi:10.1001/jama.2023.9106

Use of letermovir for cytomegalovirus primary prophylaxis in lung transplant recipients.

Kleiboeker HL et al. Transpl Infect Dis. 2024 Oct;

Use of Letermovir for Cytomegalovirus Primary Prophylaxis in Lung Transplant Recipients

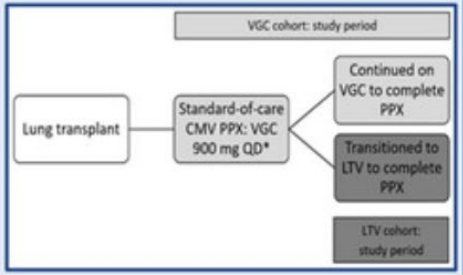
@TheTxIDJournal @NM_Lung @KleiboekerHanna

Kleiboeker *et al. Transplant Infectious Diseases.* 2024

Methods

Single center, retrospective cohort study

Adult lung transplant recipients (1/1/2015-7/30/2022) with risk of post-transplant CMV (D+ and/or R+)



Results

204 patients on CMV PPX:

- 175 patients on VGC
- 29 patients on LTV

Antiviral PPX

- VGC cohort: 331 days (mean)
- LTV cohort: 168 days on VGC → 168 days on LTV (mean)

	VGC	VGC to LTV	p
Leukopenia (WBC < 3.0 x 10^9/L); n (%)	144 (82.3)	17 (58.6)	0.008
Severe leukopenia (WBC < 2.0 x 10^9/L); n (%)	100 (57.1)	9 (31.0)	0.016
Neutropenia (ANC ≤ 1500 cells/uL) requiring GCSF; n (%)	124 (70.9)	15 (51.7)	0.048

Results

- Breakthrough infections: VGC 5.7% vs. LTV 3.4% (P=0.955)
- Post-prophylaxis infections: VGC 24.6% vs. LTV 37.9% (P=0.199)

Subgroup analysis (D+/R-): similar outcomes

Conclusions

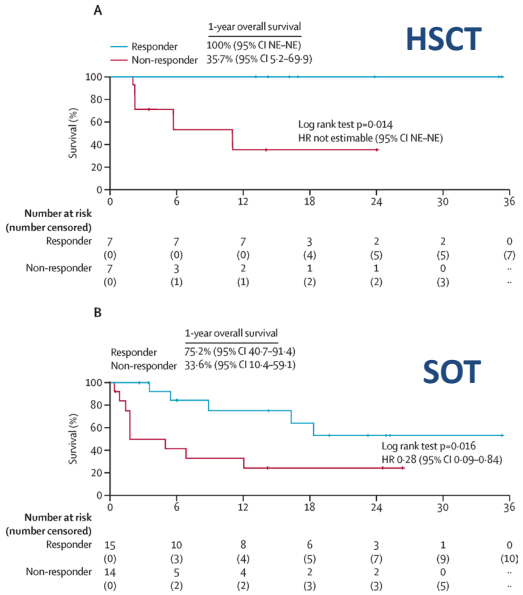
- Incidence of leukopenia, neutropenia reduced in lung transplant recipients converted to LTV vs. VGC for CMV PPX
- Comparable incidence of breakthrough and post-prophylaxis infections

Tabelecleucel for allogeneic haematopoietic stem-cell or solid organ transplant recipients with Epstein-Barr virus-positive post-transplant lymphoproliferative disease after failure of rituximab or rituximab and chemotherapy (ALLELE): a phase 3, multicentre, open-label trial

Mahadeo KM et al. Lancet Oncol 2024;25:376-387

- Patients with EBV-PTLD relapsed and/or refractory to rituximab after HSCT (n = 14) or to rituximab ± chemotherapy after SOT (n = 29) received three tabelecleucel infusions (2×10^6 cells per Kg) based on a partially matched HLA profile (restriction switch allowed)
- Median number of cycles 3 (IQR 2-4) in HSCT, and 2 (IQR 1-3) in SOT

	HSCT (n=14)	SOT (n=29)	All (n=43)
Objective response	7 (50%, 23–77)	15 (52%, 33–71)	22 (51%, 36–67)
Complete response	6 (43%)	6 (21%)	12 (28%)
Partial response	1 (7%)	9 (31%)	10 (23%)
Stable disease	3 (21%)	2 (7%)	5 (12%)
Progressive disease	2 (14%)	7 (24%)	9 (21%)
Not evaluable	2 (14%)	5 (17%)	7 (16%)
Median response duration	23 months	15.2 months	23 months



- Treatment-related AE of any grade in 29%, grade 3–4 in 4% of patients (erythematous rash, hypotension and hypoxia in 1 patient each)

Tabelecleucel for EBV+ PTLD after allogeneic HCT or SOT in a multicenter expanded access protocol

Nikiforow S. et al. Blood Advances, April 2024

- Multicenter expanded access protocol in 14 HSCT and 12 SOT recipients treated with tabelecleucel for EBV+ PTLD relapsed/refractory (R/R) to rituximab with/without chemotherapy.
- The Median number of cycles 3 (IQR 2-4) in HSCT, and 2 (IQR 1-3) in SOT.
- Patients were treated with intravenous tabelecleucel on days 1, 8, and 15, without any prior lymphodepleting therapy.
- Treatment continued until maximal response, unacceptable toxicity, patient or investigator decision, or withdrawal of consent.

- ✓ Pediatric (aged <16 years; 23.1%) and adult (76.9%) patients were included.
- ✓ Median age was 36.0 years (range, 2-74).
- ✓ SOT: Median time from transplant to diagnosis of EBV+ PTLD was 5.1 months (range, 1.4-275.9).
- ✓ HSCT: Median time from initial EBV+ PTLD diagnosis to first administration of tabelecleucel was 2.3 months (range, 0.2-67.6).

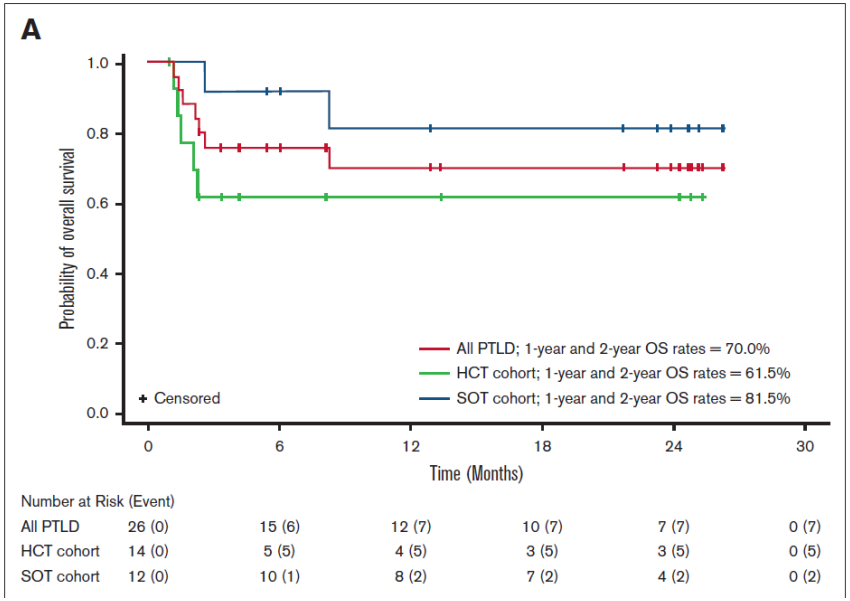
Tabelecleucel for EBV+ PTLD after allogeneic HCT or SOT in a multicenter expanded access protocol

Nikiforow S. et al. Blood Advances, April 2024

Table 2. ORRs

	HCT (n = 14)	SOT (n = 12)	Total (N = 26)
Best overall response, n (%)			
CR	4 (28.6)	6 (50.0)	10 (38.5)
PR	3 (21.4)	4 (33.3)	7 (26.9)
SD	2 (14.3)	1 (8.3)	3 (11.5)
PD	4 (28.6)	1 (8.3)	5 (19.2)
NE	1 (7.1)*	0	1 (3.8)*
Responders, n (%)	7 (50.0)	10 (83.3)	17 (65.4)
95% CI	23.0-77.0	51.6-97.9	44.3-82.8

A patient is considered a responder if the best overall response is either CR or PR.
NE, not evaluable; PD, progressive disease.
*No disease assessment obtained.



- CR: Complete response
- PR: Partially response
- PD: progressive disease
- NE: Not evaluable
- SD: Stable disease

- 1-2 year Overall Survival: 70.0% (95% CI, 46.5-84.7)
- HSCT :61.5% (CI, 30.8-81.8)
- SOT: 81.5% (CI, 43.5-95.1)

Outline

Viral Infections

Bacterial Infections

Fungal Infections

SOT

HSCT

Stepdown oral treatment in Bloodstream Infections

- **Oral antibiotics** for treatment of uncomplicated bacteremia in immunocompetent patients has become increasingly common in clinical practice.

- Agents such as **fluoroquinolones**, t**rimethoprim-sulfamethoxazole** (TMP/SMX), and broad-spectrum **oral beta-lactams** due to their good bioavailability are the preferred agents

- Robust evidences to support the oral step-down therapy (7 RCT, 4 retrospective)
  - ✓ equivalent or higher rates of treatment success oral vs intravenous
  - ✓ fewer adverse events in the oral
  - ✓ reduced length of stay

No studies focused on the solid-organ transplant population.

Tamma PD. JAMA Intern Med 2019; 179: 316–23.

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Oral Antibiotics for Treatment of Gram-Negative Bacteremia in Solid Organ Transplant Recipients: A Propensity Score Weighted Retrospective Observational Study

Nussbaum EZ et al. CID, 2024

- **Aim:** to assess the safety and efficacy of oral antibiotic step-down therapy for uncomplicated GN-BSI in SOT recipients.

- ***Study design:*** *retrospective observational study of* all SOT recipients within the Massachusetts General and Brigham and Women's Hospital systems from 2016 to 2021 with uGNBSI treated with oral stepdown therapy

- **Primary endpoints**: **mortality**, **bacteremia recurrence**, and reinitiation of IV antibiotics.
- **Secondary endpoints**: length of stay, *Clostridioides difficile* infection, treatment-associated complications, and tunneled central venous catheter placement.

- **Oral group: 120 patients**

- **Intravenous group: 42 patiens**

Oral Antibiotics for Treatment of Gram-Negative Bacteremia in Solid Organ Transplant Recipients: A Propensity Score Weighted Retrospective Observational Study

Nussbaum EZ et al. CID, 2024

Table 1. Baseline Patient Characteristics

	IV (N = 42)	PO (N = 120)	*P* Value
Age, median (IQR; range)	64.5 (56, 70; 34, 82)	62 (54, 70; 22, 95)	.49
Female sex (N, %)	26 (62)	58 (48)	.09
Transplanted organ (N, %)			
Kidney	29 (69)	84 (70)	.97
Liver	4 (10)	13 (11)	
Lung	2 (5)	7 (6)	
Heart	3 (7)	7 (6)	
Bowel	0 (0)	1 (1)	
Combined[a]	4 (10)	8 (7)	
Years from transplant, median (IQR; range)	2.5 (1, 10; 0.02–25)	3 (0.67, 10; 0.02–42)	.80
Pitt bacteremia score, median (IQR; range)[b]	0 (0, 1; 0–4)	0 (0, 1; 0–6)	.65
Charlson comorbidity score, median (IQR; range)[c]	5.5 (3, 7; 1–11)	6 (4, 7; 1–15)	.93
CMV viremia in the 90 d before hospital discharge (N, %)	3 (7)	2 (2)	.11
Treatment for rejection in the 90 d before hospital discharge (N, %)	2 (5)	4 (3)	.17

Oral Antibiotics for Treatment of Gram-Negative Bacteremia in Solid Organ Transplant Recipients: A Propensity Score Weighted Retrospective Observational Study

Nussbaum EZ et al. CID, 2024

Table 4. Clinical Outcomes in Oral and IV Antibiotic Treatment Groups

	Oral Group, N (%)*	IV Group, N (%)
Mortality	0 (0)	0 (0)
30-d bacteremia recurrence	2 (2)	2 (5)
Transition back to IV therapy[b]	6 (5)	4 (9)
Total antibiotic duration (median days)	15 (range, 7–36) IV duration: 4 (range, 1–15)	16 (range, 12–29)
Length of hospitalization (median days)	5 (range, 3–16)	7 (range, 4–18)
Development of *Clostridium difficile*	2 (2)	5 (12)
Other treatment-related complications	3 (3)[c]	4 (10)[d]

*of patients in oral arm: 33% were within the 1 year of transplant 30% within the first 6 months, and **15% within the first 3 months**.

Oral Antibiotics for Treatment of Gram-Negative Bacteremia in Solid Organ Transplant Recipients: A Propensity Score Weighted Retrospective Observational Study

Nussbaum EZ et al. CID, 2024

Inverse probability of treatment-weighted models, using propensity scores	Odds Ratio Or Quantitative Difference In IV Versus PO Group[a] (95% CI, *P* Value)
Mortality	-
30-d bacteremia recurrence	3.1 (0.4–23.1; .27)
Transition back to IV therapy[b]	1.7 (0.6–8.8; .38)
Total antibiotic duration (median days)	0.7 d (–0.6 to 2.1; .27)
Length of hospitalization (median days)	1.97 d (0.4–3.6; .005)
Development of *Clostridium difficile*	8.4 (1.5–46.5; .015)
Other treatment-related complications	6.4 (1.9–20.9; .002)

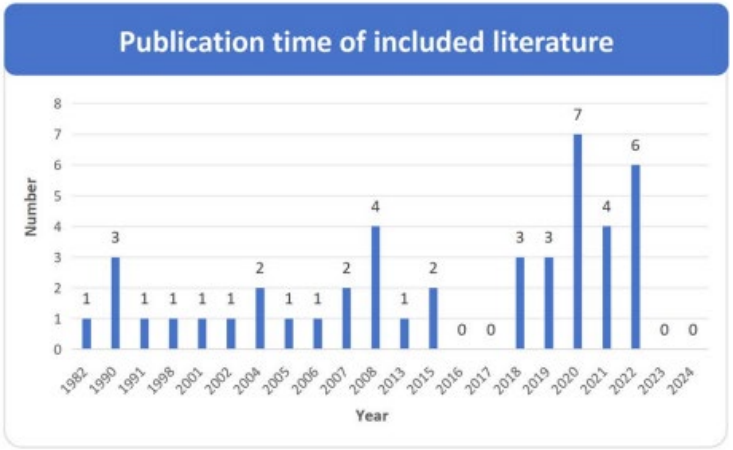
Adjusted for: age, sex, transplant type, time from transplant, Pitt bacteremia score, Charlson comorbidity score, CMV viral load >500 IU/mL, rejection within 90 days preceding hospital discharge

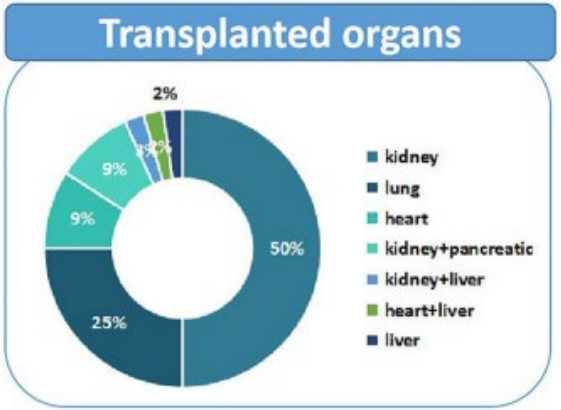
Ureaplasma urealyticum infection following organ transplantation: a case report and narrative review

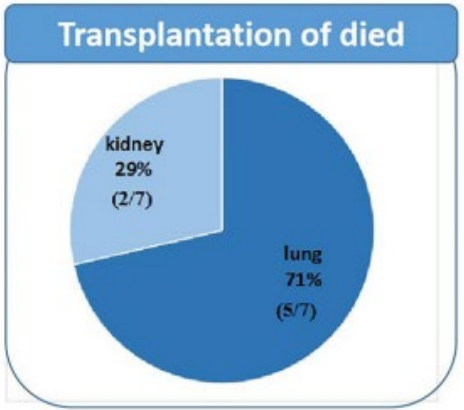
Zhang H. Renal Failure, 2024

- About 25%–40% of men and **80% of women** have asymptomatic Ureaplasma urealyticum (UU) colonization in the urinary tract. In patients with immunodeficiency, UU is more predisposed to causing **disseminated infection**

- Ureaplasma urealyticum can induce **hyperammonaemia** through the **hydrolysis of urea into ammonia**, catalyzed by **cytoplasmic urease**.
- No clinical repercussions in genitourinary infections. However, in disseminated infections:
  - ✓ Elevated and persistent hyperammonemia → Cerebral edema → Death.







Ureaplasma urealyticum infection following organ transplantation: a case report and narrative review

Zhang H. Renal Failure, 2024

Table 3. Summary of dead patients infected with *Ureaplasma urealyticum* after transplantation in review.

Trans organ	Author/year	Gender	Age	Symptom	Time post transplant	Anomaly index	Drug /course
Lung	Bharat, A. 2015 [8]	Male	44	Acute mental status changes	7 d	Routine blood, urine, and BAL fluid cultures were negative	Azithromycin (500 mg daily for 5 days)
Lung	Chan, P.G. 2021 [17]	Male	34	Shock liver	3 d	Hypotensive, elevated ammonia levels	CRRT, lactulose; 13d
Lung	McLaughlin, D. C. 2018 [31]	Male	65	Refractory status epilepticus	7 d	Ammonia level of 830 µmol/L	Mannitol and 23.4% hypertonic saline, CRRT
Lung	Shrestha, K. 2022 [48]	Female	30	Decreased responsiveness	7 d	Ammonia levels 353 mmol/l	CRRT, lactulose, polyethylene glycol, levocarnitine, rifaximin, acarbose & sodium benzoate
Kidney	Legouy, C. 2020 [35]	Female	65	Refractory status epilepticus	3 months	Serum ammonia 671 µmol /L	Levofloxacin(500 mg, qd) and doxycyline(200 mg, bid); 4 w
Lung	Wylam, Mark E. 2013 [53]	Female	64	Fever to 38.4 °C, and became less alert.	4 d	POD7d ammonia was greater than 704 µmol/L	Ciprofloxacin (400 mg IV twice daily), replaced by efepime later
Kidney	Kiberenge, R. K. 2015 [38]	Male	35	Nausea, vomiting, and altered mental status	9 d	Ammonia level of 646 µmol/L repeat level 3 h later was 939 µmol/L	CRRT, sodium phenylbutyrate, and sodium benzoate

CRRT: continuous renal replacement therapy.

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

Tam PCK. et al. Am. J. Transp. 2024

- Best practices for mollicute screening remain unknown.
- **Study design**: single-center prospective study analyzing lung transplants from 2020-2021
- **Intervention**: donor and recipient BAL samples obtained at time of transplant underwent mollicute screening (culture and PCR).
- **Results**: 115 total lung transplants:
  - 99 (86%) donors: 18 (18%) positive.
  - 92 (93%) recipients: 3 (3%) positive results.

- **9 (9%) recipients developed mollicute infection.**
- Sensitivity of donor screening: 67% (6/9) via culture and 56% (5/9) via PCR.
- Positive predictive value for donor culture was 75% (6/8), compared with 33% (5/15) for PCR.

Donor screening via culture predicted all serious recipient mollicute infections and had better positive predictive value than PCR;

However, neither screening test predicted all mollicute infections.

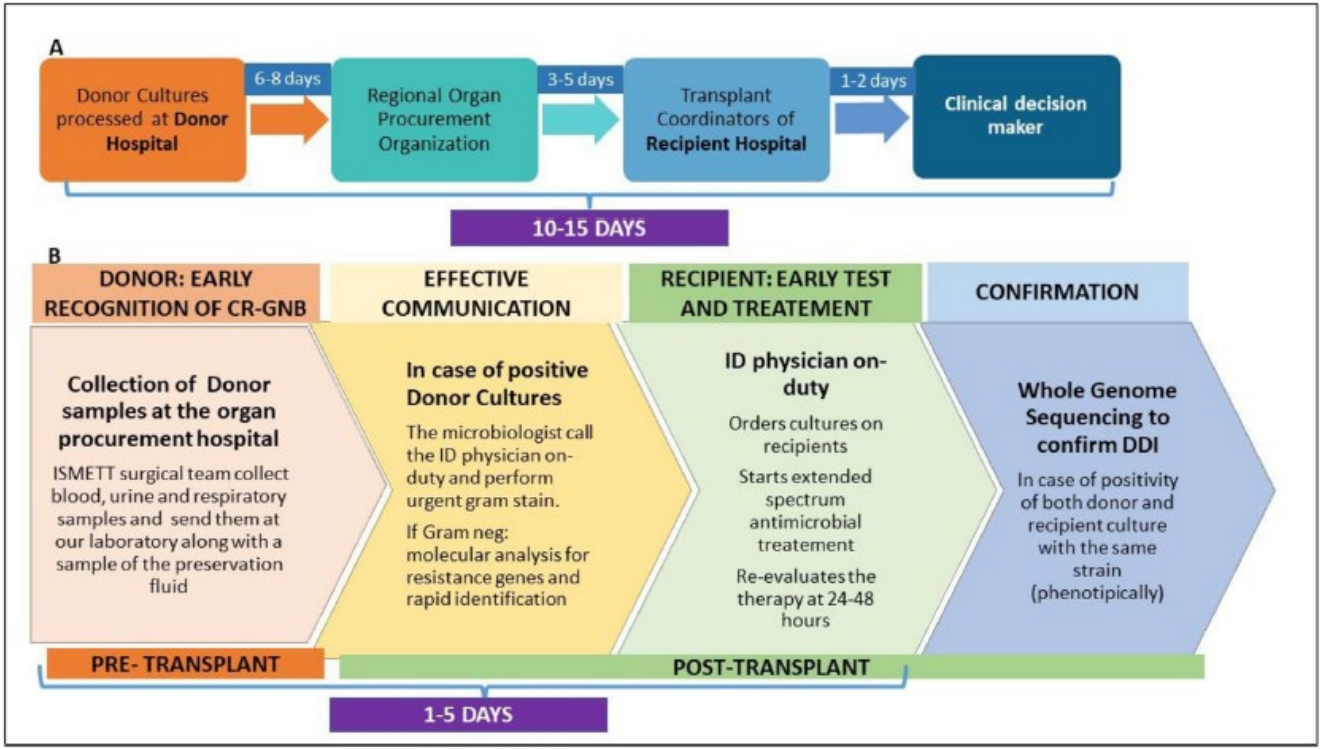
– Ricerca di Ureaplasma e Mycoplasma con metodica molecolare o colturale su BAL o secrezioni respiratorie profonde per i donatori di polmone (i risultati di tale test non sono vincolanti ai fini della procedura di prelievo e successivo trapianto ma devono essere acquisiti appena possibile). Il campione per il test deve essere prelevato dal donatore dall'equipe di prelievo.

Targeted prophylaxis VS Universal prophylaxis?

Donor-derived carbapenem-resistant gram-negative bacterial infections in solid organ transplant recipients: Active surveillance enhances recipient safety

Mularoni A. et al. Am. J. Transp. 2024

- **Study design**: prospective cohort study. All consecutive patients who underwent SOT from December 2015 to July 2021
- **Aims**: to evaluate the incidence, factors associated with transmission, and the outcome of recipients with unexpected CR-GNB DDIs after the implementation of local active surveillance system
- LASS provides for early detection of unexpected donor CR-GNB infections, prophylaxis of recipients at high risk, and early diagnosis and treatment of DDIs.



Donor-derived carbapenem-resistant gram-negative bacterial infections in solid organ transplant recipients: Active surveillance enhances recipient safety

Mularoni A. et al. Am. J. Transp. 2024

- **Results:**
  - 791 recipients: **38 (4.8%)** were at high risk of unexpected CR-GNB DDI: 25 CRE, 13 CRAB
  - Incidence of CR-GNB DDI was **1.4%** (9 of 25 of CRE and 2 of 13 of CRAB), and **29% in HR recipients**
  - No **difference in length of hospital stay or survival in patients with and without CR-GNB DDI**.

Table 1
Risk stratification according to the organ transplanted and the positive donor sample.

Positive donor sample / Organ transplanted	Blood	Urine	Respiratory specimen	Preservation fluid
Liver	High Risk	Low Risk	Low Risk	High Risk
Kidney	High Risk	High Risk	Low Risk	High Risk
Heart	High Risk	Low Risk	Low Risk	High Risk
Lung	High Risk	Low Risk	High Risk	High Risk
Pancreas	High Risk	Low Risk	Low Risk	High Risk

- The type of donor specimen was the **only significant predictor of CR-GNB DDI.**
- Growth of CR-GNB in **preservation fluid led to DDI in 87% of cases**, in the case of donor blood positivity, the rate of DDI was only 18%.
- CR-GNB, Liver transplant recipients had a higher, but not statistically significant, risk of developing CR-GNB DDI compared with other organ recipients (9/22 [40.9%] vs 2/16 [12.5%], P <0.08).

Outline

Viral Infections

Bacterial Infections

Fungal Infections

SOT

HSCT

Isavuconazole for the Treatment of Invasive Mold Disease in Solid Organ Transplant Recipients: A Multicenter Study on Efficacy and Safety in Real-life Clinical Practice

Fernandez-Ruiz M et al. Transplantation 2023;107: 762–773

Which is the impact on the management of immunosuppressive therapy of first-line or salvage therapy with isavuconazole?

- Multicenter retrospective cohort of 81 patients treated with isavuconazole for IA (n=71) or mucormycosis (n=10)
- IA: IPA (n=61), probable (n=49), *A. fumigatus* (n=39), *A. flavus* (n=3), *A. terreus* (n=3), ***A. lentulus* (n=2)**
- Mucormycosis: proven (n=10), deep soft tissue infection (n=3), lung (n=2)
- Isavuconazole use
  - First-line (n=59) 72.8%
  - Salvage therapy (n=22)
    - Treatment-emergent toxicity (n=9)
    - Refractory diseases (n=6)
    - Oral stepdown therapy (n=5)
    - PK optimization (n=2)

Antifungal susceptibility testing	
Voriconazole, no. tested isolates	23
MIC values, geometric mean and range, mg/L	0.57 (0.19–16.00)
Isavuconazole, no. tested isolates	9
MIC values, geometric mean and range, mg/L	1.13 (0.50–16.00)
Posaconazole, no. tested isolates	18
MIC values, geometric mean and range, mg/L	0.12 (0.06–16.00)

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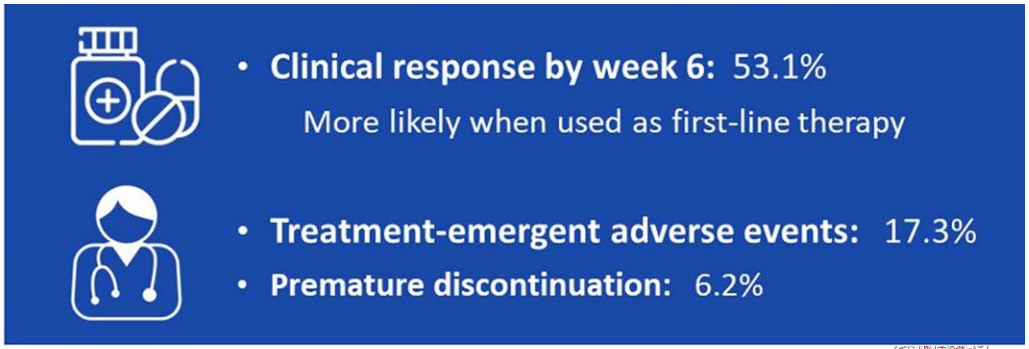

European Study of Cerebral Aspergillosis treated with Isavuconazole (ESCAI): A study by the ESCMID Fungal Infection Study Group

Serris A. et al. CID, 2024

- **Aim**: to compared the outcomes of patients treated with isavuconazole vs voriconazole (from historical control groups from the previously published French national cohort of CA)
- **Study design**: European multicenter retrospective study of patients treated with isavuconazole for proven or probable CA between 2014 and 2022

- **Results**: 40 patients from 10 countries were included:
  - Haematological: 21/40, **53**%
  - SOT: 8/40, **20**%.

- **10 patients** (25%) received **isavuconazole as a first-line treatment** for its ease of use (oral drug, better tolerance, less drug interactions, activity against several molds)

- Reasons for 2nd line isavuconazole:
  - therapeutic failure (7/30, 23.3%)
  - adverse events from a previous treatment (15/30, 50%)
  - ease of use (3/30, 10%)
  - drug–drug interactions/inadequate plasma concentration (4/30, 13.3%)
  - fungal coinfection (1/30, 3.3%)

Table 2. Description of Antifungal Treatment in 40 Patients Who Received Isavuconazole for Cerebral Aspergillosis Treatment

	Values
CA treatment before isavuconazole introduction, n (%)	30 (75%)
• Median [IQR] number of treatment lines	2 [1–2]
• Median [IQR] duration of antifungal treatments before isavuconazole introduction, d	65 [21–157]
First-line treatment for CA (n = 30), n	
Voriconazole	14
Voriconazole + echinocandin	2
Voriconazole + liposomal amphotericin B	2
Liposomal amphotericin B	8
Liposomal amphotericin B + echinocandin	2
Echinocandin	2
Neurosurgery, n (%)	17 (43%)
• Previous to isavuconazole treatment	12 (30%)

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Serris A. et al. CID, 2024

Outcome at the end of isavuconazole treatment or at the date of the latest consultation if ongoing treatment	
• Complete response	18 (45%)
• Partial response	5 (12.5%)
• Stable	6 (15%)
• Progressive disease or death	11 (27.5%)

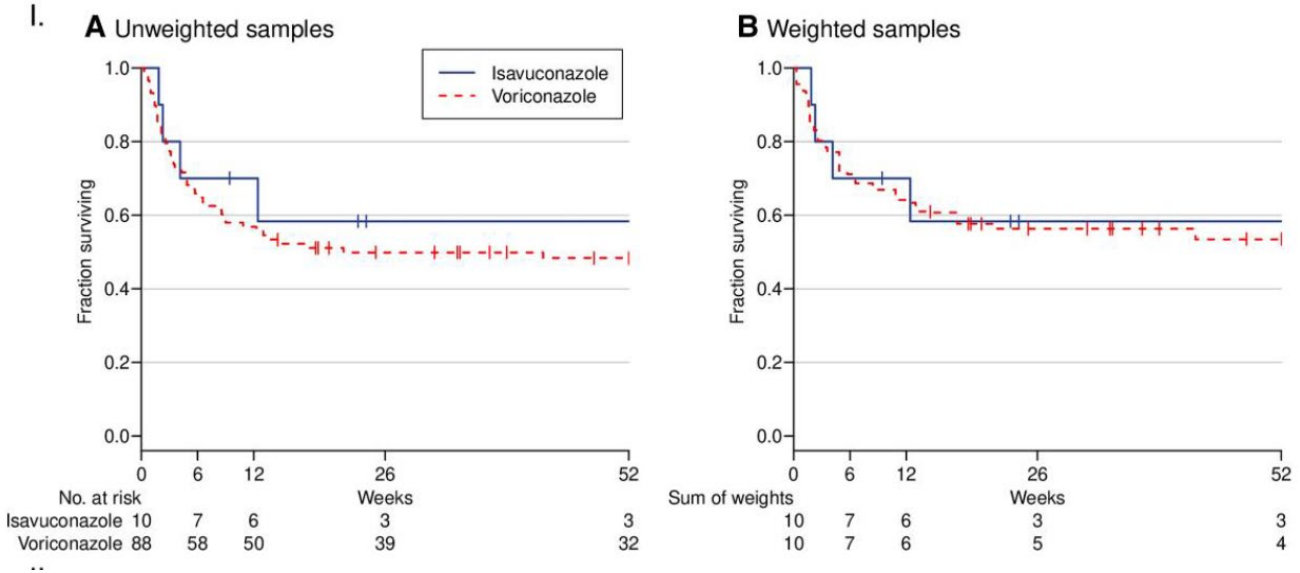
- The median follow-up duration from isavuconazole initiation was 262 days (IQR, 98–737 days).

- Univariate analysis: progression of CA under isavuconazole was not associated with:
  - first-line versus second-or-more treatment line (30% vs 27%, P = 1)
  - mono versus dual therapy (32% vs 42%, P = .7),
  - neurosurgical treatment or not (42% vs 32%, P = .56)
  - species of Aspergillus (A. fumigatus [38%] vs other species [43%]; P = 1)
  - **The only factor associated with a higher mortality rate was the absence of TDM**

European Study of Cerebral Aspergillosis treated with Isavuconazole (ESCAI): A study by the ESCMID Fungal Infection Study Group

Serris A. et al. CID, 2024

Survival comparison between ESCAI and CEREALS patients during the first year after first-line antifungal therapy



Comparison with CEREALS data suggests that isavuconazole might be as effective as voriconazole as a first-line treatment.

Take home messages

- Maribavir potrebbe essere un'opzione terapeutica anche per le infezioni da CMV GCV-S, ma necessario selezionare attentamente il paziente
- Letermovir è una strategia di profilassi con sempre più prospettive, sia in HSCT che SOT
- Step-down oral therapy potrebbe essere una strategia terapeutica efficiacie nei pazienti con BSI non complicate
- DDI restano un campo ancora da esplorare nel panorama dei pazienti sottoposti a SOT
- Isavuconazolo si sta affermando sempre di più nel setting del paziente immunodepresso per il trattamento delle IFI

Grazie