Therapeutic Advances in Difficult-to-Treat Infections

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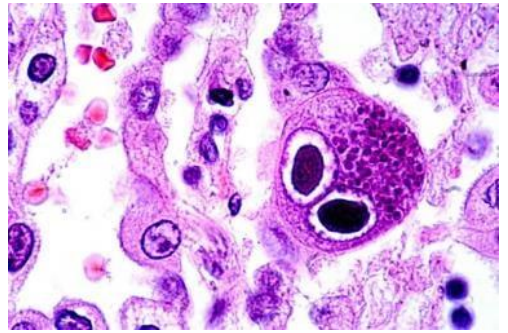
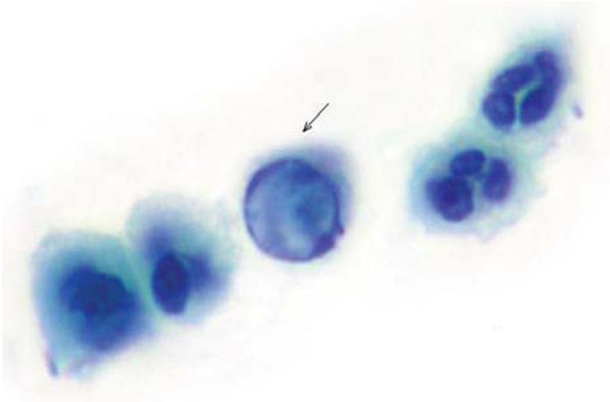
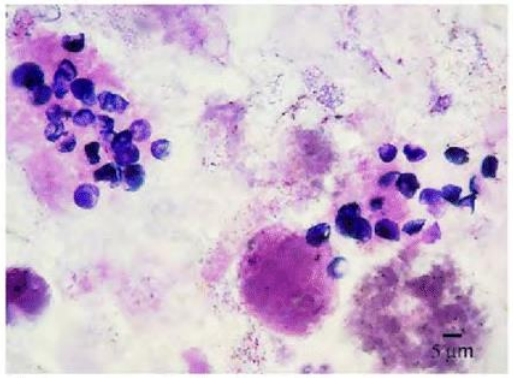
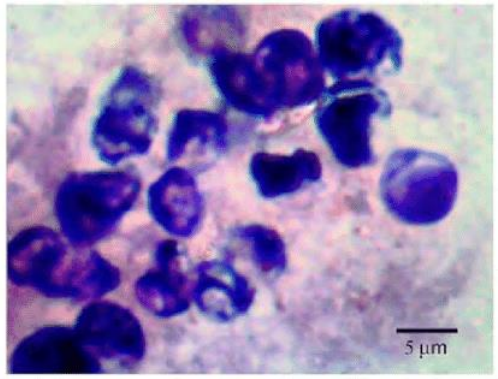
Presentation Plan



- Why are difficult-to-treat infections important?
- Epidemiology
- Mortality rate
- Current treatments







The importance of difficult-to-treat infections in immunosuppressed patients

Why are difficult-to-treat infections important?

- High mortality rates
- Negativities in the transplant procedure
- Treatment side effects
- A risk for GVHD

The importance of difficult-to-treat infections in immunosuppressed patients (Mortality)

Selvey et al. BMC Infectious Diseases (2017) 17:501
DOI 10.1186/s12879-017-2599-y

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Cytomegalovirus viraemia and mortality in renal transplant recipients in the era of antiviral prophylaxis. Lessons from the western Australian experience

Linda A. Selvey[1*], Wai H. Lim[2,3], Peter Boan[4,5], Ramyasuda Swaminathan[6], Claudia Slimings[7], Amy E. Harrison[1] and Aron Chakera[3,8]

Abstract

Background: Cytomegalovirus (CMV) establishes a lifelong infection that is efficiently controlled by the immune system; this infection can be reactivated in case of immunosuppression such as following solid organ transplantation. CMV viraemia has been associated with CMV disease, as well as increased mortality and allograft failure. Prophylactic antivi... cessation of antivi... pact of CMV viraem... al outcomes.

Meth... ...d between 1 Janua... plant registry and v... raemia (≥600 copie... gression.

Resul... ...CMV viraemia with v... donor; and receiving a graft from a donor aged 60 years and over. CMV viraemia with viral loads ≥656 copies/ml was a risk factor for death following renal transplantation, as was being aged 65 years and above at transplant, being Aboriginal and having vascular disease. Importantly 37% of the episodes of CMV viraemia with viral loads ≥656 copies/ml occurred while the patients were expected to be on CMV prophylaxis.

Conclusions: CMV viraemia (≥656 copies/ml) was associated with all-cause mortality in multivariable analysis, and CMV viraemia at ≥656 copies/ml commonly occurred during the period when renal transplant recipients were expected to be on antiviral prophylaxis. A greater vigilance in monitoring CMV levels if antiviral prophylaxis is stopped prematurely or poor patient compliance is suspected could protect some renal transplant recipients from adverse outcomes such as premature mortality.

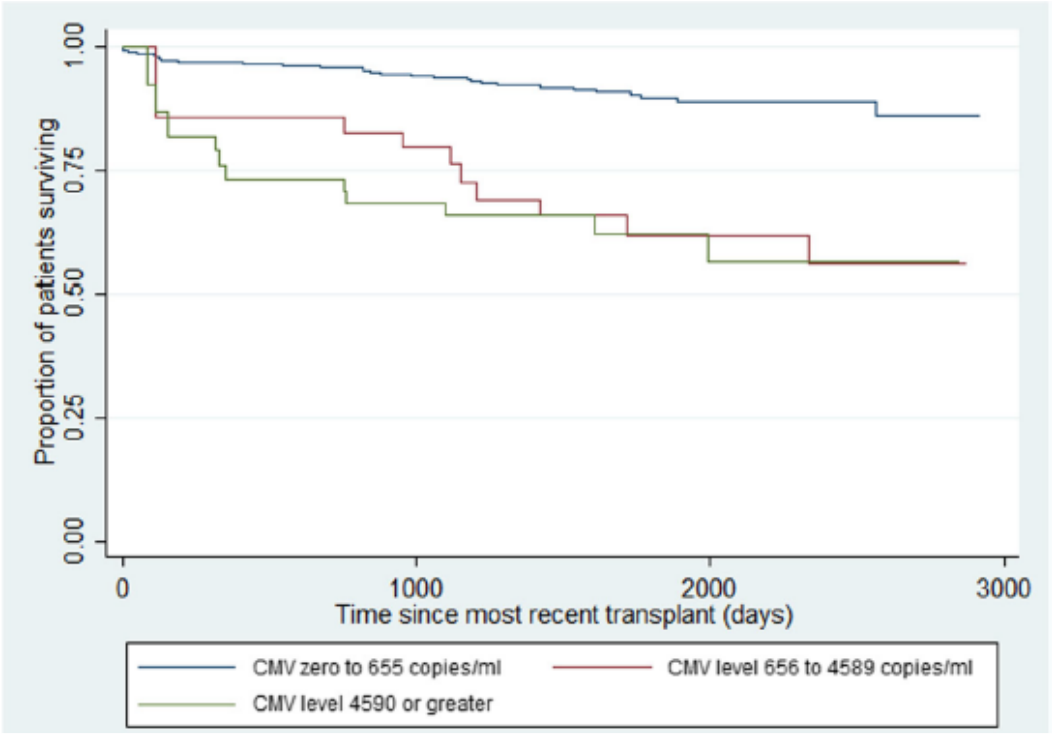
Keywords: Cytomegalovirus reactivation, Renal transplantation, Mortality, Risk factors

- 438 renal transplant patients
- Routine prophylaxis were addministrated for guides
- Donor positive /recipient negative status

The importance of difficult-to-treat infections in immunosuppressed patients (Mortality)

Table 5 Final Cox Proportional Hazards regression model for death

Variable	Adjusted Hazard Ratio (95% CI)	*p*-value
CMV viral load		
Less than 656 copies/ml (reference)	-	
656–4590 copies/ml	3.25 (1.42, 7.44)	0.007
≥ 4590 copies/ml	3.94 (1.75, 8.89)	0.012
Aboriginal	3.39 (1.74, 6.63)	<0.001
Age ≥ 65 at transplant	2.39 (1.10, 5.18)	0.027
Cerebrovascular disease	4.21 (1.81, 9.78)	0.001
Other vascular disease	2.21 (1.19, 4.09)	0.012



The importance of difficult-to-treat infections in immunosuppressed patients (Mortality)

- *Clostrioides difficile* infections account for 16% of 90-day post-transplant mortality*
- CMV viremia is a risk factor for PJP and the presence of PJP is a risk factor for transplant failure**
- The presence of BK viremia in patients with renal transplantation has been stated as a risk factor for organ survival and patient survival***

*Hosseini-Moghaddam SM. Incidence and Outcomes Associated With *Clostridioides difficile* Infection in Solid Organ Transplant Recipients. JAMA Netw Open. 2021;4(12):e2141089
**Kim, J.E. Impact of Pneumocystis jirovecii pneumonia on kidney transplant outcome. BMC Nephrol 20, 212 (2019). https://doi.org/10.1186/s12882-019-1407-x.
Malik O. Prevalence, Risk Factors, Treatment, and Overall Impact of BK Viremia on Kidney Transplantation. Transplant Proc. 2019 Jul-Aug;51(6):1801-1809.

Bone Marrow Transplantation (2014) 49, 664–670

www.nature.com/bmt

ORIGINAL ARTICLE

High burden of BK virus-associated hemorrhagic cystitis in patients undergoing allogeneic hematopoietic stem cell transplantation

323 patients followed for 5 years after allogeneic transplantation

Aim: Medico-economic complications after BK viremia and hemorrhagic cystitis

BK virus-associated HC developed in 43 patients

BK viremia is directly related to the advanced stage of HC

Hospital stay is longer in patients with BK-related HC

Platelet transfusion is more common in patients with BK-related HC

Financial costs are higher in patients with BK-related HC

Keywords: BK virus; hemorrhagic cystitis; allogeneic hematopoietic SCT; PCR; cidofovir

Bone Marrow Transplant. 2014 May;49(5):664-70.

Therapeutic Advances in CMV Infections

- One of the most common opportunistic infections
- CMV disease affects 5%–15% of patients
- Up to one-third of patients experience recurrent CMV
- The first line antiviral drug for CMV prevention and treatment is intravenous **ganciclovir** or its oral prodrug **valganciclovir**
- Neutropenia is a major toxicity occurring in 18%–47%
- Foscarnet and cidofovir are second-line treatments

Ljungman P. Lancet Infect Dis 2019; 19: e260–72

Therapeutic Advances in CMV Infections

- Ganciclovir requires phosphorylation by a viral kinase (UL97) for activation and inhibits the viral DNA polymerase (UL54)
- Ganciclovir-resistant CMV occurs in around 1%–3% of SOT or 6%–18% of SOT recipients treated for CMV
- Mutations in the UL97 gene are most frequent
- UL54 mutations usually emerge upon extended pre-treatment and can confer cross resistance with cidofovir and foscarnet

Ljungman P. Lancet Infect Dis 2019; 19: e260–72

Therapeutic Advances in CMV Infections (Guidelines)

CMV antiviral resistance should be suspected and testing performed

- Patients in whom the viral load increase > 1 log10 after at least two weeks appropriate antiviral therapy
- Patients in whom the viral load does not decrease > 1 log10 after at least three weeks appropriate antiviral therapy
- Patients who has CMV disease and whose symptoms worsen after at least 2 weeks appropriate antiviral therapy

Ljungman P. Lancet Infect Dis 2019; 19: e260–72

Therapeutic Advances in CMV Infections (Guidelines)

Pre-emptive treatment

- Either iv ganciclovir or foscarnet can be used for first line preemptive therapy
- Valganciclovir can be used in place of iv ganciclovir or foscarnet
- The choice of drug depends on time after HSCT, risk of toxicity, and previous antiviral drug exposure

Ward KN, P; 2017 European Conference on Infections in Leukaemia (ECIL). Haematologica. 2019;104(11):2155-2163

Therapeutic Advances in CMV Infections (Guidelines)

Pre-emptive treatment

- **Cidofovir** can be considered for second/third line pre-emptive therapy (3-5 mg/kg/week) but careful monitoring of the renal function is required
- The **combination of ganciclovir and foscarnet** might be considered for second/third line pre-emptive therapy
- **Reduce immunosuppression if possible**
- **Leflunomide or artesunate** can be considered in patients resistant/refractory to available antiviral drugs

Ward KN, P; 2017 European Conference on Infections in Leukaemia (ECIL). Haematologica. 2019;104(11):2155-2163

Therapeutic Advances in CMV Infections (Guidelines)

Treatment of CMV pneumonia

- Antiviral therapy with iv ganciclovir is recommended
- Foscarnet might be used in place of ganciclovir
- The addition of immune globulin/hyperimmuneglobulin to antiviral therapy can be considered
- Cidofovir or the combination of foscarnet and ganciclovir can be used as 2nd/3rd line therapy

Ward KN, P; 2017 European Conference on Infections in Leukaemia (ECIL). Haematologica. 2019;104(11):2155-2163

Therapeutic Advances in CMV Infections (Guidelines)

Immune therapy

Adoptive CMV-directed T Cell Therapy: Reconstitution of an antiviral T cell response prevents CMV reactivation/disease

- **Prophylactic Adoptive Transfer**: Cloned donor-derived T cells sensitized in vitro with autologous CMV-infected fiboblasts reduced CMV reactivation and disease post-transplant
- **Phase I/II trials Therapeutic Applications** CMV-specific T cell lines transferred to small patient cohorts of recipients of an allo-graft (including CBT/Haplo-transplant recipients) were safe and at least partially effective in chemotherapy-refractory CMV infection/disease
- Different selection strategies for CMV-specific T cells applied (stimulation with APC pulsed with viral peptides/MHC multimers/cytokine catch assay)

Therapeutic Advances in CMV Infections (Guidelines)

Solid organ Transplantation

For adults, children and young people who develop CMV infection or disease following solid organ transplantation:

- Oral **valganciclovi**r for a duration of at least 2 weeks
- **Be aware of the potential development of ganciclovir resistance**
- Assess CMV viral load after 2 weeks of treatment and repeat at a minimum interval of 7days
- Consider stopping treatment for CMV disease after resolution of symptoms AND two consecutive, CMV viral load tests that confirm that CMV is not detected

https://bts.org.uk/uk-guideline-on-prevention-and-management-of-cytomegalovirus-cmv-infection-and-disease-following-solid-organ-transplantation/

Therapeutic Advances in CMV Infections

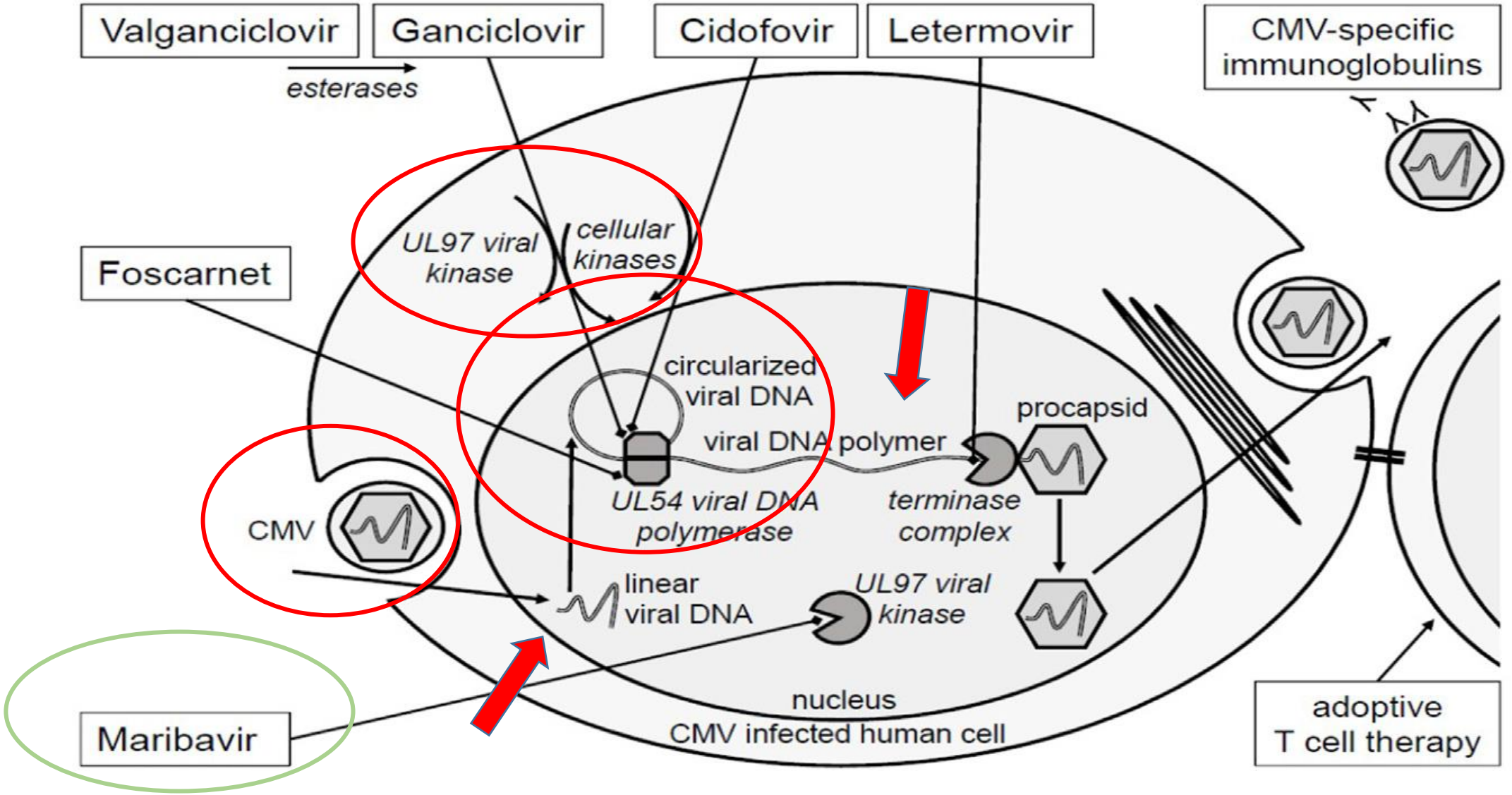
Ganciclovir resistance

- Newer agents **Letermovir** and **Maribavir** may be associated with less drug resistance than Ganciclovir
- The use of Maribavir for treating refractory or resistant CMV infection following solid organ transplantation has been assessed in phase 3 studies and reported to be superior to Ganciclovir, Cidofovir and Foscarnet

https://bts.org.uk/uk-guideline-on-prevention-and-management-of-cytomegalovirus-cmv-infection-and-disease-following-solid-organ-transplantation/

New Treatment Options For R/R CMV

Maribavir



Clinical Infectious Diseases
MAJOR ARTICLE

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

- Hematopoietic-cell or solid-organ transplant recipients
- ≥12 years old
- RR CMV infections
- Plasma CMV DNA ≥1000 copies/Ml
- Randomized (1:1:1) to twice-daily dose-blinded
- Maribavir 400, 800, or 1200 mg for up to 24 weeks
- The primary efficacy endpoint was the proportion of patients with confirmed undetectable plasma CMV DNA within 6 weeks of treatment
- Safety analyses included the frequency and severity of treatment-emergent adverse events

Papanicolaou GA.Clin Infect Dis. 2019 Apr 8;68(8):1255-1264

Clinical Infectious Diseases
MAJOR ARTICLE

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

Outcome	(n = 40)	(n = 40)	(n = 40)	(N = 120)
Primary efficacy endpoint: patients with confirmed undetectable plasma CMV DNA within 6 weeks, n (%)[a]				
Yes[b]	28 (70.0)	25 (62.5)	27 (67.5)	80 (66.7)
No				
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Patients				
Yes[d]				
No[e,f]				
Treatment effect estimate by group				
Estimated rate[c]	0.24	0.41	0.40	0.35
95% CI	0.10–0.44	0.22–0.61	0.23–0.59	0.25–0.46
Patients with CMV recurrence on treatment, n (%)[c]	6 (20.7)	9 (33.3)	10 (33.3)	25 (29.1)
Patients with CMV recurrence off treatment, n (%)[c,g]	1 (3.4)	2 (7.4)	2 (6.7)	5 (5.8)

- Undetectable CMV DNA within 6 weeks of treatment with rates of 70%, 63%, and 68%, respectively, for maribavir 400, 800, and 1200 mg twice daily
- Recurrent on-treatment CMV infections occurred in 25 patients; 13 developed mutations conferring maribavir resistance
- Maribavir was discontinued due to adverse events in 41/120 (34%) patients, and 17/41 discontinued due to CMV infections
- During the study, 32 patients died, 4 due to CMV disease
- Dysgeusia was the most common TEAE (78/120; 65%) and led to maribavir discontinuation in 1 patient

Clinical Infectious Diseases
MAJOR ARTICLE

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

Robin K. Avery,[1] Sophie Alain,[2] Barbara D. Alexander,[3] Emily A. Blumberg,[4] Roy F. Chemaly,[5] Catherine Cordonnier,[6] Rafael F. Duarte,[7] Diana F. Florescu,[8] Nassim Kamar,[9] Deepali Kumar,[10] Johan Maertens,[11] Francisco M. Marty,[12,a] Genovefa A. Papanicolaou,[13,14] Fernanda P. Silveira,[15] Oliver Witzke,[16] Jingyang Wu,[17] Aimee K. Sundberg,[18] and Martha Fournier[18]; for the SOLSTICE Trial Investigators[b]

- In this phase 3, open-label study, hematopoietic-cell and solid-organ transplant recipients
- R/R CMV were randomized 2:1 to maribavir 400 mg twice daily or investigator-assigned therapy
- 12 weeks of follow-up
- The primary endpoint was confirmed cytomegalovirus clearance at end of week 8
- The key secondary endpoint was achievement of cytomegalovirus clearance and symptom control at end of week 8, maintained through week 16

Avery RK et al. Clin Infect Dis. 2022 Sep 10;75(4):690-701

Clinical Infectious Diseases

MAJOR ARTICLE

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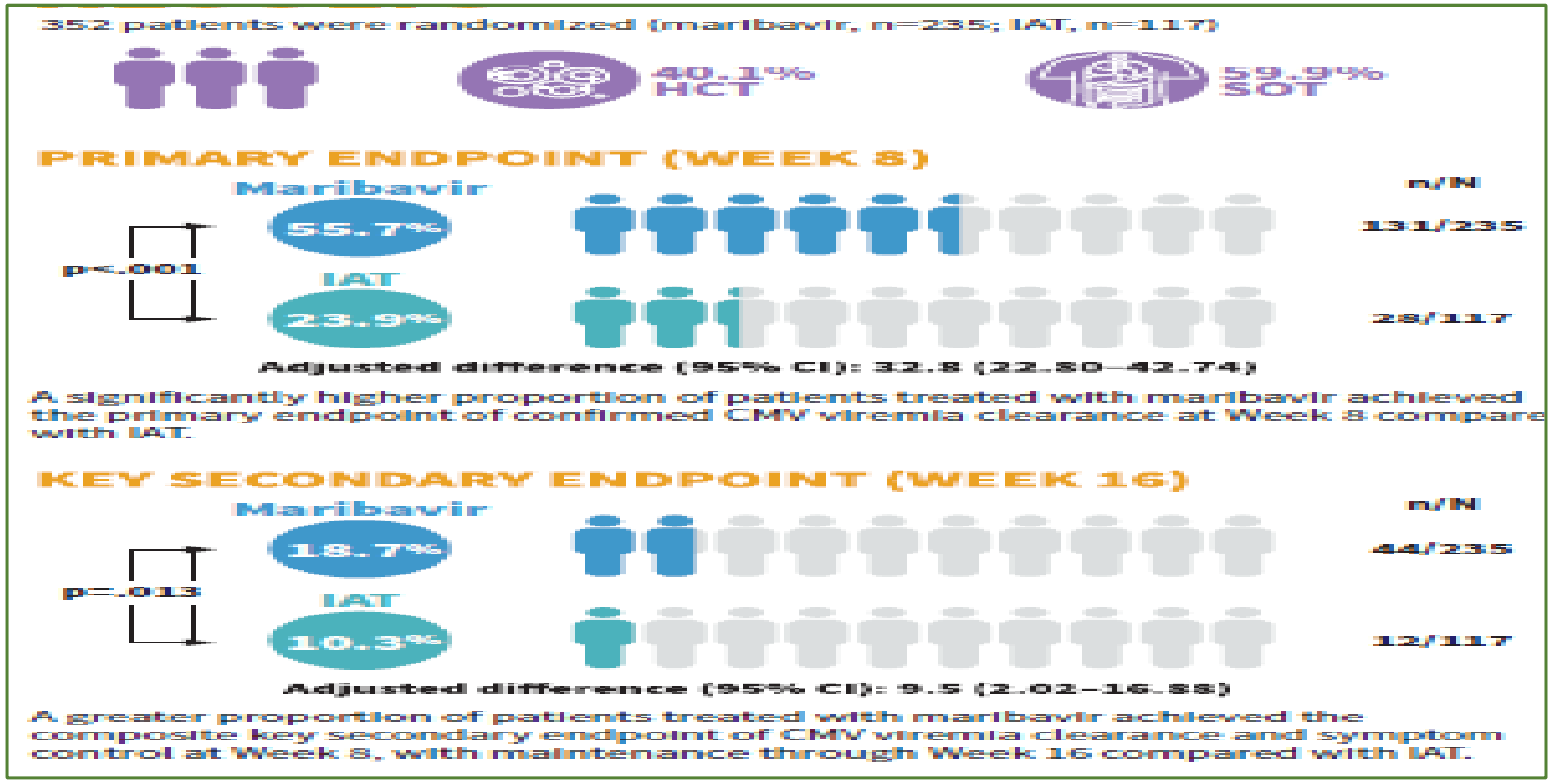

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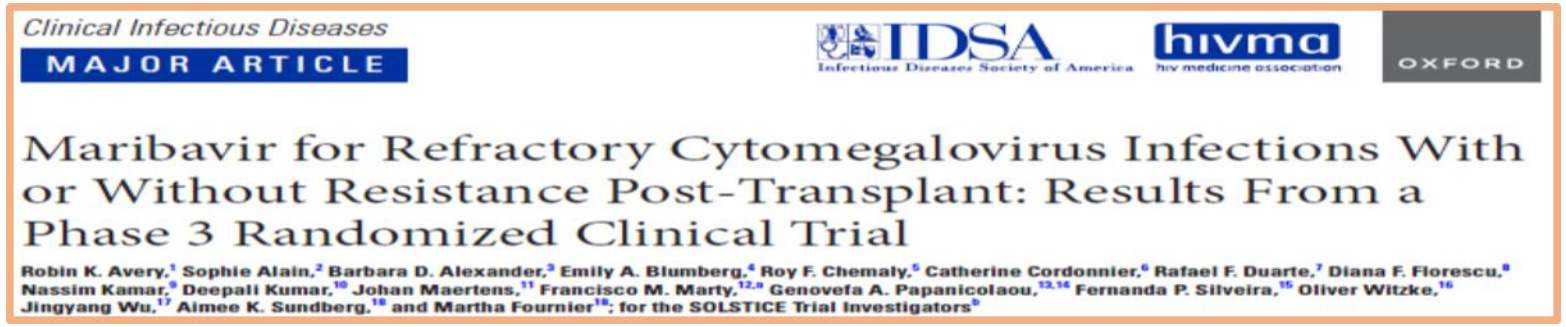
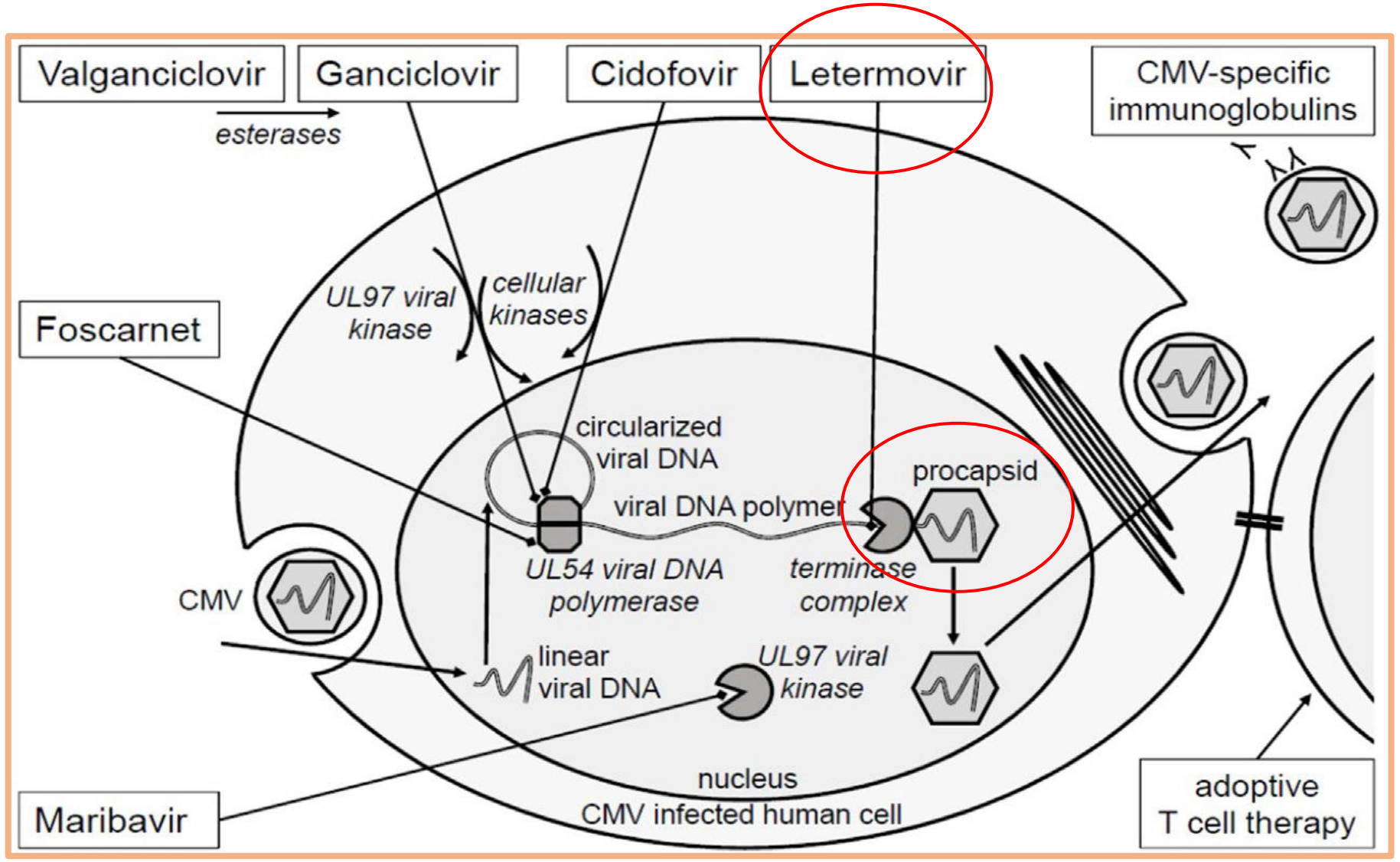


- Median duration of exposure was 57 (2–64) days with maribavir and 34 (4–64) days with IAT
- Fewer patients discontinued maribavir than IAT due to TEAEs (13.2% vs 31.9%)
- Dysgeusia was the most frequently reported TEAE in the maribavir group (maribavir: 37.2%; IAT: 3.4%)
- Maribavir was associated with less acute kidney injury versus foscarnet (8.5% vs 21.3%) and neutropenia versus valganciclovir/ganciclovir (9.4% vs 33.9%)
- Maribavir demonstrated an improved safety profile versus valganciclovir/ganciclovir for myelotoxicity and versus foscarnet for nephrotoxicity, with fewer patients discontinuing maribavir than IAT

Avery RK et al. Clin Infect Dis. 2022 Sep 10;75(4):690-701

New Treatment Options For R/R CMV
Letermovir



New Treatment Options For R/R CMV
Letermovir

- Letermovir was approved in 2017 for prophylactic use in adult CMV-seropositive allogeneic HSCT recipients
- 6 June 2023, the US FDA approved letermovir for the new indication of CMV prophylaxis in D+/ R−kidney transplant recipients

Walti CS. New Treatment Options for Refractory/Resistant CMV Infection. Transpl Int. (2023) 36:11785.

Author/journal/ year	Type of SOT and number of patients	Reason for LTV treatment	Dose of LTV	Outcomes
Linder et al. [46] Transplant Infect Dis 2021	27 SOT (13 lung, 6 kidney, 2 heart, 1 liver, 5 other) In addition, 21 HCT included	Intolerance to other antivirals (77%), resistance concerns (33%)	480 mg OD: 87% 720 mg OD: 13% (titrated up to 960 mg in two patients) Oral: 89% Intravenous: 11%	Good virologic outcomes if viral load <1,000 IU/mL at starting LTV; if > 1,000 IU/mL at starting, only approx. 40% reached DNAemia <1,000 IU/mL
Veit et al. [47] Am J Transplant 2021	28 SOT (all lung)	Refractory infection (57%), confirmed antiviral resistance (43%)	480 or 240 mg OD (based on tacrolimus or cyclosporine use)	Decrease in viral load within median 17 days and subsequent clearance in 82%; treatment failure in 18%
Schubert et al. [48] Eur J Clin Microbiol Infect Dis 2021	5 SOT (3 kidney, 2 heart) In addition, two HSCT and two other immunosuppressed patients included	refractory infection (11%), intolerance to other antivirals (67%), confirmed resistance (22%)	480 or 240 mg OD (based on tacrolimus or cyclosporine use)	Decrease in viral load to <200 IU/mL within median 23 days seen in 78%
Ortiz et al. [49] Clin Transplant 2022	4 SOT (3 SPK, 1 kidney)	Intolerance to (val)ganciclovir (50%), confirmed antiviral resistance (50%)	480 or 240 mg OD (based on tacrolimus or cyclosporine use)	Viral clearance reached in 75%, and decrease in viral load to <200 IU/mL in 25%, after 4–9 weeks of treatment
Phoompoung et al. [50] Transplantation 2020	4 SOT (lung), in addition one HSCT included	Refractory infection (50%), intolerance to other antivirals (25%), confirmed antiviral resistance (25%)	480 or 240 mg OD (based on tacrolimus or cyclosporine use)	Decrease in viral load to <200 IU/mL within 3–6 weeks in 75%, treatment failure in 25%
Turner et al. [51] Antimicrob Agents Chemother 2019	4 SOT (2 lung, 2 heart) CMV retinitis in all	confirmed antiviral resistance	720 mg OD, dose titrated up to 960 mg in one patient	All showed clinical improvement, virological treatment failure in 75%
Aryal et al. [52] Transplant Infect Dis 2019	2 SOT (lung, heart) In addition, 7 patient included with LTV prophylaxis	confirmed antiviral resistance	480 or 240 mg OD (based on tacrolimus or cyclosporine use)	viremia clearance in 50%, treatment failure in 50%
Boignard et al. [53] Antiviral Ther 2022	2 SOT (heart)	intolerance to other antiviral (50%), confirmed resistance (50%)	480 mg OD	Viremia clearance in 50%, treatment failure in 50%

Walti CS. New Treatment Options for Refractory/Resistant CMV Infection. Transpl Int. (2023) 36:11785.

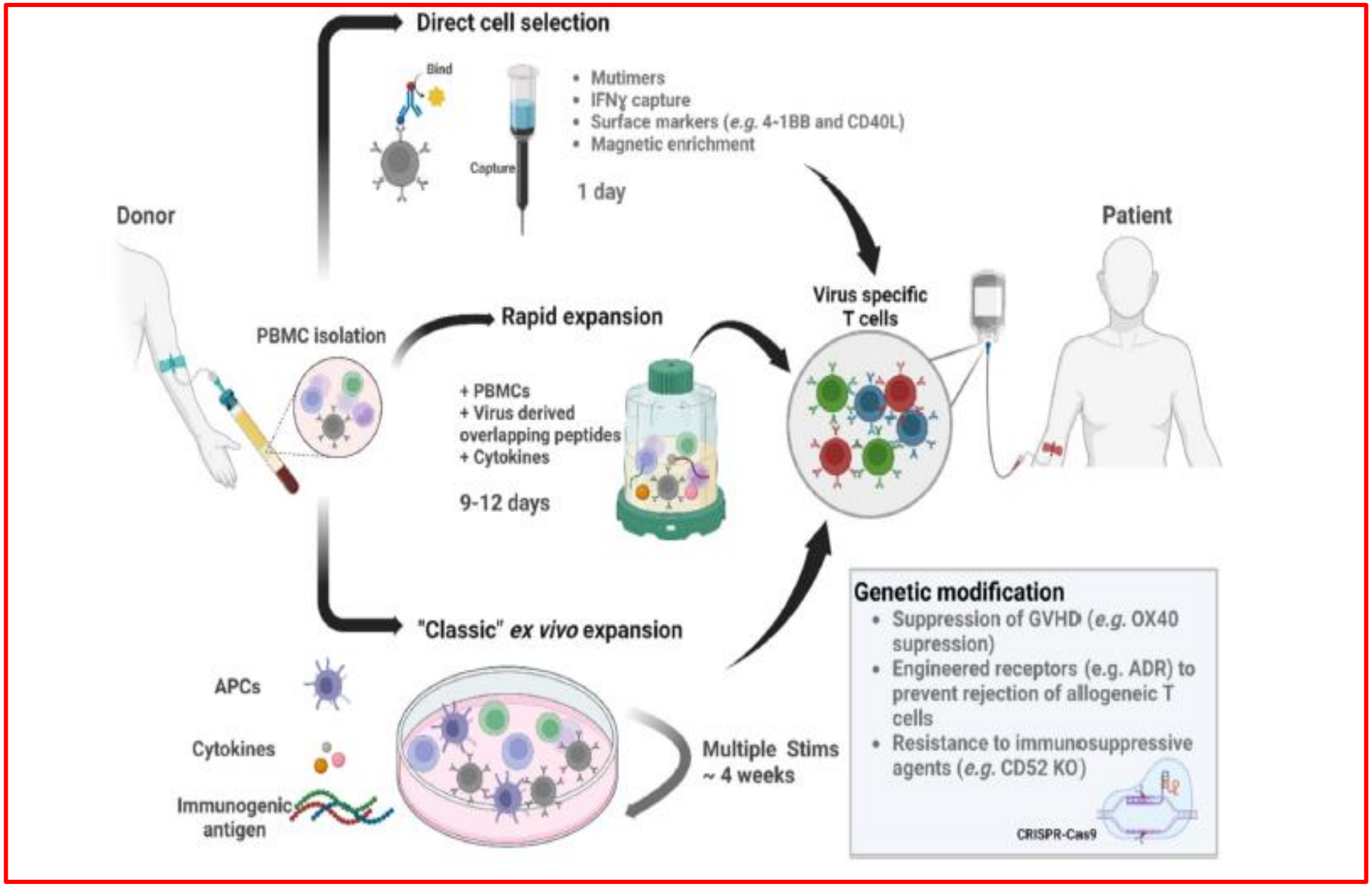
New Treatment Options For R/R CMV
Letermovir

- Letermovir can be considered for treatment of R/R CMV infections
- Favorable results will more likely be reached if treatment is initiated at low-level viremia, but recurrence and development of resistance are remaining concerns
- In cases of poor tolerance to valganciclovir due to leukopenia or neutropenia, the potential to use letermovir as secondary prophylaxis after clearance of viremia could be further explored
- Some concerns about breakthrough infections and emergence of letermovir resistance have been raised in small case series

Walti CS. New Treatment Options for Refractory/Resistant CMV Infection. Transpl Int. (2023) 36:11785.

New Treatment Options For R/R CMV

- **T cell immunity** is essential for CMV control
- In SOT recipients, T cell immunity is weakened by immunosuppressive drugs, making direct restoration of immunity by **infusion of CMV-specific T cells (“adoptive” T cell therapy) attractive**



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Therapeutic Advances in *Pneumocystis jirovecii* Infections

- An increasingly prevalent, opportunistic, and life-threatening fungal infection
- In recent years a rising incidence in immunocompromised patients without HIV infection has been described
- Besides **steroid** therapy, further drugs such as **rituximab**, **cyclophosphamide**, **calcineurin inhibitors**, and **methotrexate** as well as **immunomodulating drugs** pose increased risk

Rhoads, S., Maloney, J., Mantha, A. et al. Curr Fungal Infect Rep (2024)

Therapeutic Advances in *Pneumocystis jirovecii* Infections

- Chronic lung disease,malignancy, both solid tumor and hematopoietic
- Other cell mediated immunocompromised conditions increase the risk of PJP
- Malignancy is present in up to 46% of cases
- Among children, congenital cardiopulmonary disease and severe combined immunodeficiency (SCID) are the disease states most frequently seen with PJP, accounting for 22% and 19% of cases

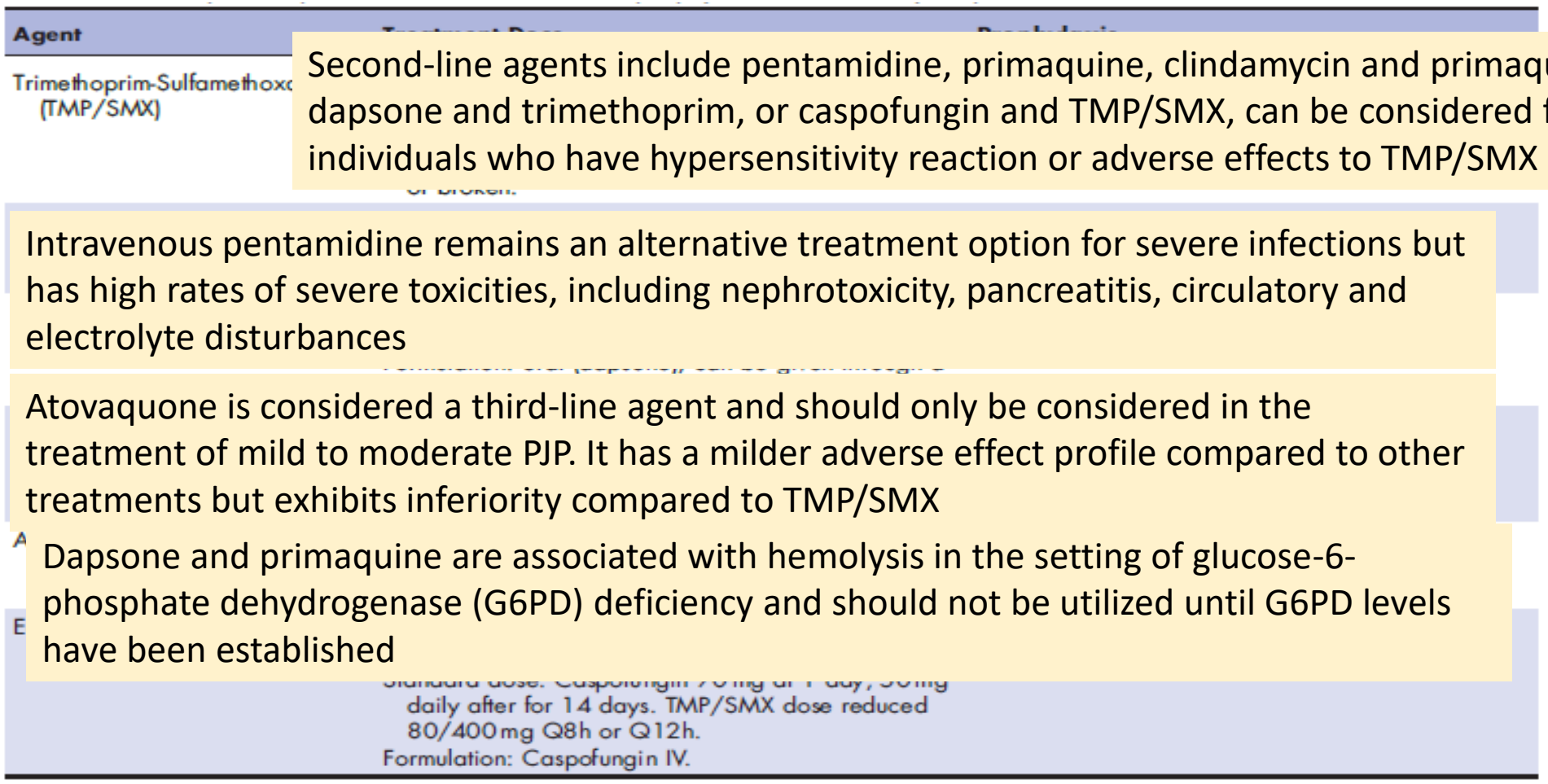
Rhoads, S., Maloney, J., Mantha, A. et al. Curr Fungal Infect Rep (2024)

Table 1. Risk factors for *Pneumocystis jirovecii* pneumonia in solid organ transplant recipients

Agent or condition	Description
Immunosuppressive agents	
Lymphocyte-depleting agents	
Antithymocyte globulin	Increases risk of PJP in first 6 months [12], and, historically, one of the highest risk factors for PJP.
Alemtuzumab	High risk of PJP in recipients of kidney transplant [12].
Rituximab	Used as an agent for desensitization and treatment of rejection and PTLD, rituximab is an independent risk factor for PJP [18,67].
Maintenance immunosuppressive agents	
Calcineurin inhibitors (tacrolimus and cyclosporine A)	Retrospective study showed higher incidence of PJP among renal transplant recipients receiving tacrolimus-based regimen compared to cyclosporine [68]. However, more recent studies suggest CIs may be protective [12,69].
Mycophenolate and mycophenolic acid	In-vitro animal models indicate possible anti-*Pneumocystis* effect; however, recent retrospective case-control studies suggest increased PJP risk in MPA treated patients [70,71].
mTOR inhibitors (sirolimus and everolimus)	Increased risk of PJP with sirolimus [69,72,73].
Corticosteroids	Prednisone dose $\geq$ 20 mg/day $\geq$ 1 month or high pulse dose during episodes of acute rejection. Steroids: monthly average dose of $\geq$ 13.7 mg/day of prednisolone was independent risk factor for PJP [74] but this was in immunosuppressed population without HIV and not specifically SOTr.
Other factor or condition	
CMV viremia	Due to immunomodulating effects of the virus [12,63].
Allograft rejection	As an independent factor and as a result of treatment for rejection [63].
Lymphopenia	In a retrospective case-control study, ALC $\leq$500 associated with PJP [2].
Neutropenia	Enhances risk of PJP because of impaired host immunity [27].
Globulin	Gamma globulin concentration as a risk factor [27] reflect body's defense ability.
Prior respiratory viral infection	COVID-19 and increased prevalence of PJP in non-HIV patients without HIV [75]; postrenal transplant [76,77].

Saadatzadeh T, Angarone M, Stosor V. Pneumocystis jirovecii in solid organ transplant recipients: updates in epidemiology, diagnosis, treatment, and prevention. Curr Opin Infect Dis. 2024 Jan 18

Therapeutic Advances in Pneumocystis jirovecii Infections



Second-line agents include pentamidine, primaquine, clindamycin and primaquine, dapsone and trimethoprim, or caspofungin and TMP/SMX, can be considered for individuals who have hypersensitivity reaction or adverse effects to TMP/SMX

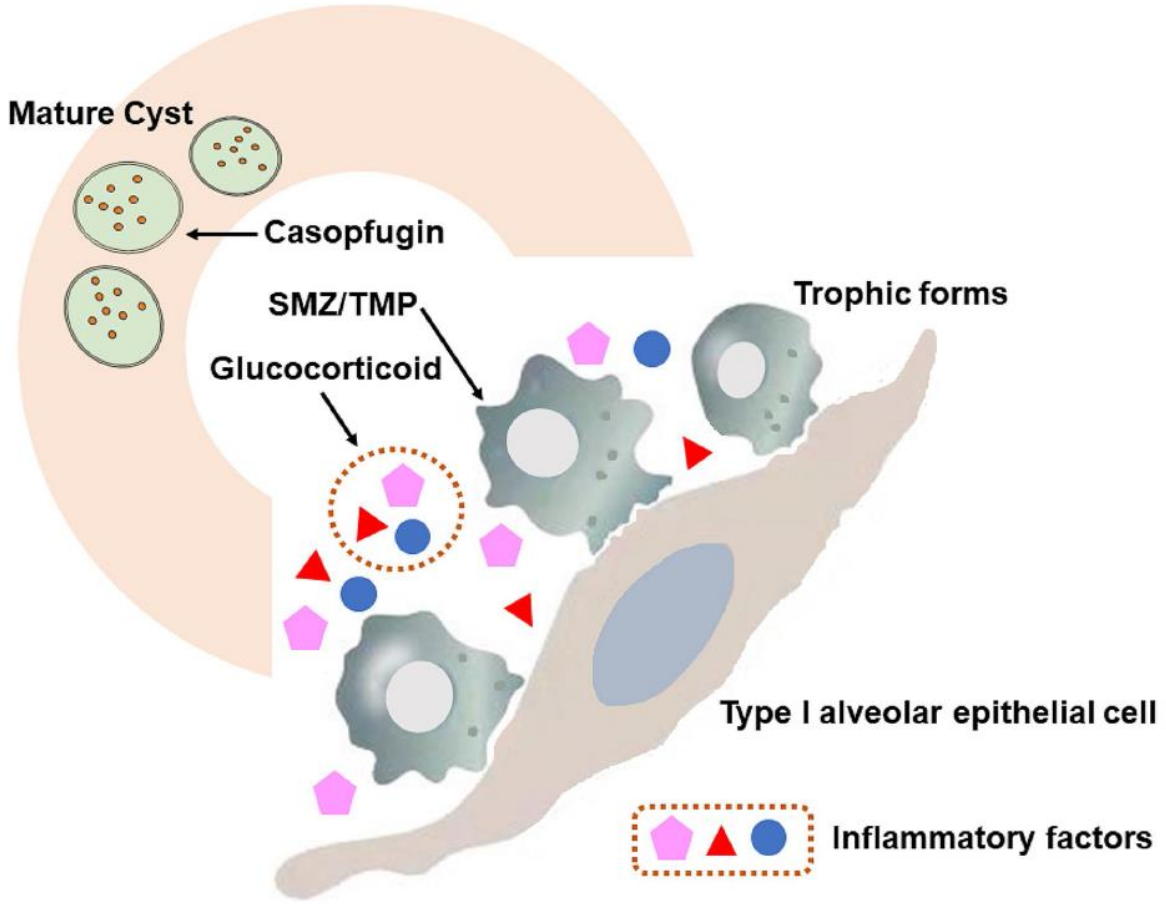
Intravenous pentamidine remains an alternative treatment option for severe infections but has high rates of severe toxicities, including nephrotoxicity, pancreatitis, circulatory and electrolyte disturbances

Atovaquone is considered a third-line agent and should only be considered in the treatment of mild to moderate PJP. It has a milder adverse effect profile compared to other treatments but exhibits inferiority compared to TMP/SMX

Dapsone and primaquine are associated with hemolysis in the setting of glucose-6-phosphate dehydrogenase (G6PD) deficiency and should not be utilized until G6PD levels have been established

Saadatzadeh T et al. Pneumocystis jirovecii in solid organ transplant recipients: updates in epidemiology, diagnosis, treatment, and prevention. Curr Opin Infect Dis. 2024 Jan 18

- Echinocandins target the synthesis of BDG present in the cell walls of cystic forms
- In animal models, caspofungin was found to target the cystic forms, while anidulafungin and rezafungin appear effective against both the cyst and trophozoite stages
- The efficacy of combination caspofungin with low-dose TMP/SMX has been evaluated in case reports



Li et al. BMC Infectious Diseases (2024) 24:152
https://doi.org/10.1186/s12879-024-09031-7

BMC Infectious Diseases

RESEARCH Open Access

A regimen based on the combination of trimethoprim/sulfamethoxazole with caspofungin and corticosteroids as a first-line therapy for patients with severe non-HIV-related pneumocystis jirovecii pneumonia: a retrospective study in a tertiary hospital

Abstract

Background Pneumocystis jirovecii pneumonia (PJP) is a life-threatening and severe disease in immunocompromised hosts. A synergistic regimen based on the combination of sulfamethoxazole-trimethoprim (S

Aim: Exploring the efficacy and safety of synergistic therapy in non-HIV-PJP patients

is important to explore the efficacy and safety of this synergistic therapy for treating non-HIV-related PJP patients.

Methods t the First Affiliated Hospital of Xi'an Jia y group (ST group, $n=20$) and the m diagnosed with severe PJP. In the ST g bined with caspofungin (70 mg as prednisolone 40–80 mg/ day). Patie ay). The clinical response, adverse events and mortality were compared between the two groups.

Method: Retrospective

38 patients

Synergistic group: n=20 Monoteraphy group: n=18

Outcome: Clinical Response, advers events and mortality

Results The percentage of patients with a positive clinical response in the ST group was significantly greater than that in the MT group (100.00% vs. 66.70%, $P=0.005$). The incidence of adverse events in the MT group was greater than that in the ST group (50.00% vs. 15.00%, $P=0.022$). Furthermore, the dose of TMP and duration of fever in the ST group were markedly lower than those in the MT group (15.71 mg/kg/day vs. 18.35 mg/kg/day ($P=0.001$) and 7.00

Li et al. BMC Infectious Diseases (2024) 24:152
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BMC Infectious Diseases

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A regimen based on the combination of trimethoprim/sulfamethoxazole with caspofungin and corticosteroids as a first-line therapy for patients with severe non-HIV-related pneumocystis jirovecii pneumonia: a retrospective study in a tertiary hospital

	Total, *n* = 38	ST group, *n* = 20	MT group, *n* = 18	*P*
Positive of clinical response [%, no.]	84.21(32/38)	100.00(20/20)	66.70(12/18)	0.026*
Duration of hospital stay	20.50(10.75–31.25)	30.00(10.50–42.50)	15.00(9.00-22.25)	0.059
Duration of fever	8.00(6.00-10.25)	7.00(5.00-8.75)	11.50(8.00-16.25)	0.029*
Dose of TMP, mg/kg/day	16.55(15.69–18.67)	15.71(14.23–16.43)	18.35(16.48–19.40)	0.001*
All-cause mortality,%	21.05(8/38)	25.00(5/20)	16.67(3/18)	0.277
All adverse effects [%, no.]	31.58(12/38)	15.00(3/20)	50.00(9/18)	0.022*
Nausea/Vomiting [%, no.]	10.53(4/38)	5.00(1/20)	16.67(3/18)	
Hyperkaliemia [%, no.]	7.89(3/38)	5.00(1/20)	11.11(2/18)	
Diarrhea [%, no.]	7.89(3/38)	0.00(0/20)	16.67(3/18)	
Thrombocytopenia [%, no.]	2.63(1/38)	5.00(1/20)	0.00(0/18)	
Drug eruption [%, no.]	2.63(1/38)	0.00(0/20)	5.56(1/18)	

ST group, synergic therapy group; MT group, monotherapy group;

JOURNAL OF CHEMOTHERAPY
2023, VOL. 35, NO. 3, 181–187
https://doi.org/10.1080/1120009X.2022.2095155

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Meta-analysis of echinocandins combined with trimethoprim-sulfamethoxazole for treatment of Pneumocystis pneumonia

Jiayu Guo*, Zhongbao Chen*, Chenyang Kong, Bo Yu, Tianyu Wang, Yalong Zhang, Yiting Liu, Jiangqiao Zhou and Tao Qiu

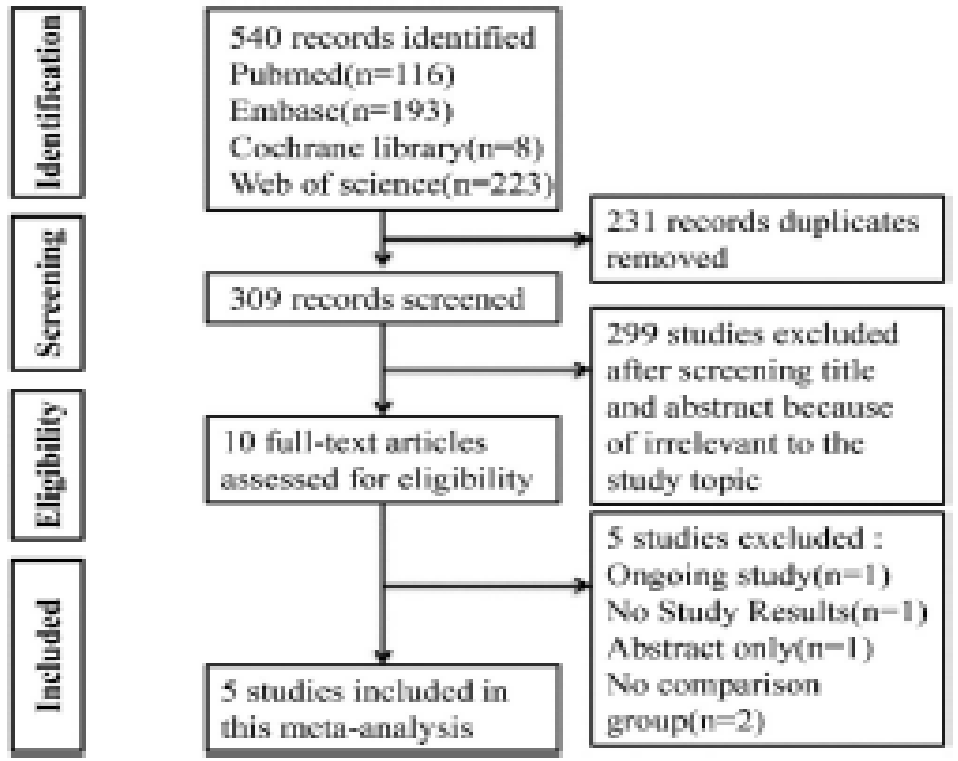
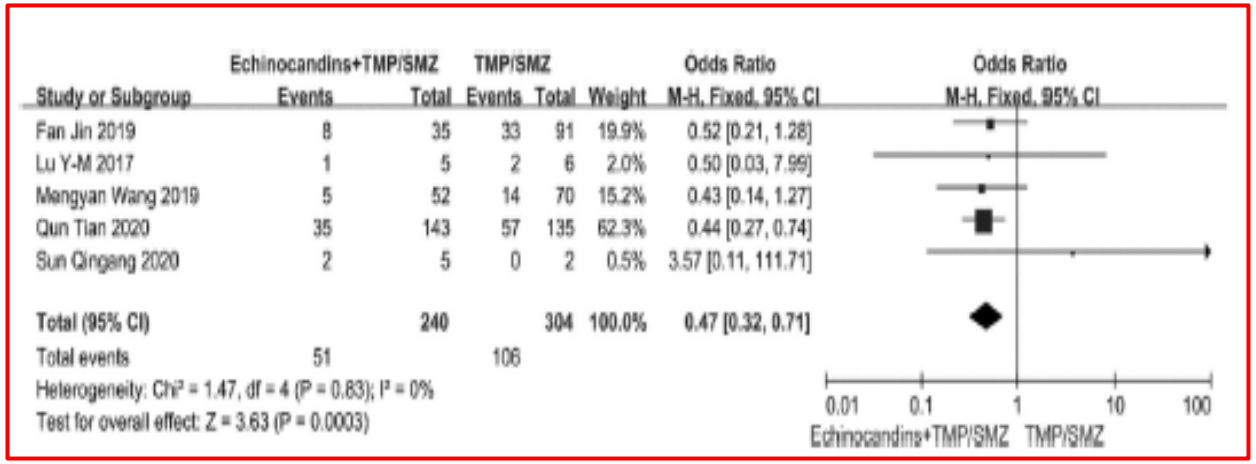
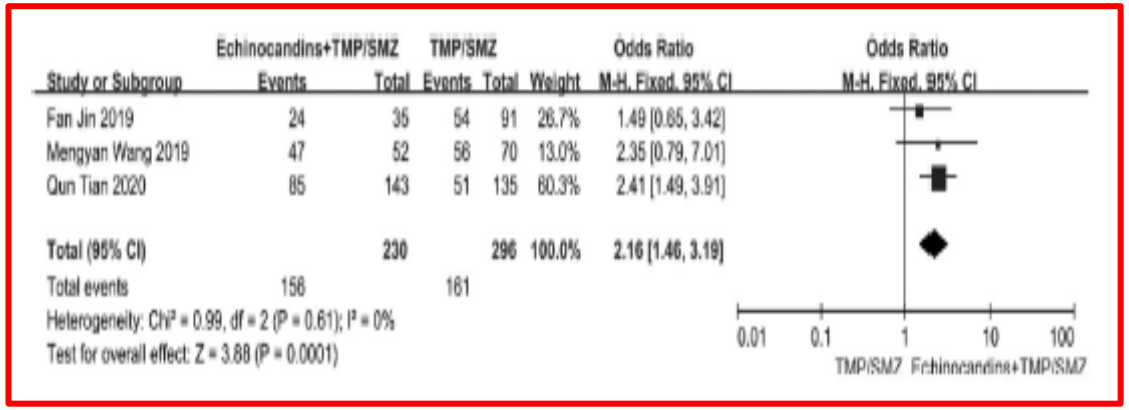


Figure 1. Flow diagram of the literature search.





AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

SUSCEPTIBILITY

The Antifungal and Anti-*Pneumocystis* Activities of the Novel Compound A3IS (Mycosinate)

Nathan P. Wiederhold,[a] Thomas F. Patterson,[b,c] Sandra Rebholz,[d,e] Connell W. C. Boal,[f] Monika Ehrensberger,[f] Ryan Boyle,[f] Melanie T. Cushion[d,e]

TABLE 2 Activity scale of 72-h IC_{50} values

Activity rank	Concentration
Highly active	<0.010 μg/mL
Very marked	0.011 to 0.099 μg/mL
Marked	0.10 to 0.99 μg/mL
Moderate	1.0 to 9.99 μg/mL
Slight	10.0 to 49.9 μg/mL
None	≥50 μg/mL

- Pneumocystis murina, from mice, and Pneumocystis carinii, from rats
- These 2 species are considered suitable surrogate models for the species which infects humans, Pneumocystis jirovecii
- No species of this genus of fungi can be grown outside the mammalian lung, and short-term cultures of rodent-derived Pneumocystis spp. have been used to predict activity for preclinical drug development
- The IC50 of mycosinate for P. carinii was 0.6415 mg/mL and 4.155 mg/mL for P. murina, which are ranked as having “Marked” and “Moderate” activity
- Similar in-vitro activity of pentamidine

Adjunctive corticosteroids in Pneumocystis jirovecii Infections

- The use of adjunctive corticosteroids in treatment does not play a role in treating mild or moderate disease
- The potential benefit of corticosteroids is perhaps mediated by diminished immune-mediated lysis of Pneumocystis organism, decreasing surfactant inactivation
- While the optimal dose has yet to be determined, prednisone of at least 60 mg/day or 1 mg/kg/day has been utilized
- The most widely utilized recommendation for prednisone duration suggests 5 days of high-dose therapy, followed by 5 days of prednisone 40 mg daily and 20 mg prednisone daily for pneumocystis treatment based on studies in HIV patients

Therapeutic Advances in *Clostridioides Difficile* Infections

- Incidence rate is 110.2 cases per 100,000 in USA
- CDI occurs when there is a shift in the colonic microbial flora allowing toxin-producing strains of the Gram-positive, spore-forming, anaerobic bacillus to over proliferate
- Antibiotic exposure, the most important risk factor
- This leads to a decrease in competition for space and resources for *C. difficile* allowing it to replicate unchecked
- An ineffective host immune response contributes to this disease process
- Clinical manifestations: Fever, leukocytosis, abdominal pain and profuse watery diarrhea
- Severe complications: dehydration, electrolyte imbalances, AKI and pseudomembranous colitis
- The presence of toxic megacolon, ileus or shock indicates fulminant (severely complicated) disease which requires aggressive medical therapy

Markantonis, J.E et al. Pathogens 2024, 13, 118.

Determination of Risk Factors for Infectious Diarrhea in Patients with Hematological Malignancy

Şükran Şahinkaya [1], Zeynep Ture [2], Ali Unal [3], Gamze Kalın Ünüvar [2], and Ayşegül Ulu Kılıç [2]

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ic Infection & Chemotherapy

Aim

The study aimed to determine the risk factors for infectious diarrhea in patients receiving chemotherapy or hematopoietic stem cell transplantation due to hematological malignancy.

Methods

Patients with diarrhea were categorized as infectious and unidentified and compared regarding demographic data, treatments, risk factors, laboratory findings, and prognosis.

Result

In the study, 838 patients were hospitalized, and 105 of those who met the definition criteria were included (12.5%).

Highest organism: *Clostridioides difficile* (12.4%)

	Unidentified diarrhea (n = 67, 63.8%)	Infectious diarrhea (n = 38, 36.2%)
Duration of diarrhea	5 days	9 days
Corticosteroid use	7.5%	39.5%
G-CSF use	67.2%	42.1%

Risk factors of diarrhea

Corticosteroid use	G-CSF treatment
Risk increase (OR, 4.75)	Risk reducing (OR, 2 [illegible])

Conclusion

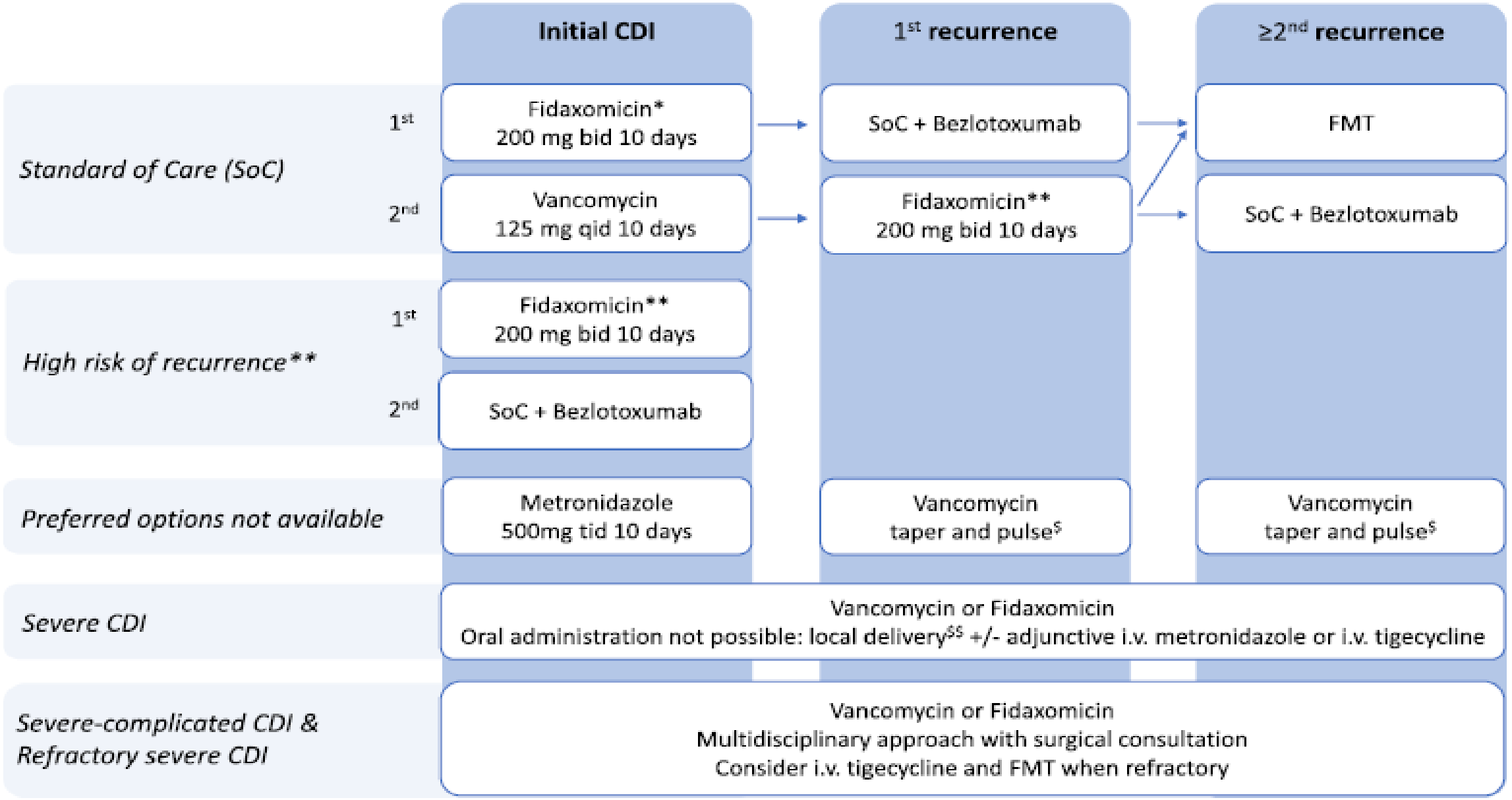
Infectious diarrhea lasts longer in patients with hematological malignancies. While corticosteroid use is a risk factor for developing infectious diarrhea, GCSF use has a protective effect.

Infect Chemother. 2024 ;56(2):e1 https://doi.org/10.3947/ic.2023.0102

Therapeutic Advances in *Clostridioides Difficile* Infections

Clinical Presentation	Recommended and Alternative Treatments	Comments
Initial CDI episode	Preferred: Fidaxomicin 200 mg given twice daily for 10 days	Implementation depends upon available resources
	Alternative: Vancomycin 125 mg given 4 times daily by mouth for 10 days	Vancomycin remains an acceptable alternative
	Alternative for nonsevere CDI, if above agents are unavailable: Metronidazole, 500 mg 3 times daily by mouth for 10–14 days	Definition of nonsevere CDI is supported by the following laboratory parameters: White blood cell count of 15 000 cells/μL or lower and a serum creatinine level <1.5 mg/dL
First CDI recurrence	Preferred: Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for 5 days followed by once every other day for 20 days	…
	Alternative: Vancomycin by mouth in a tapered and pulsed regimen	Tapered/pulsed vancomycin regimen example: 125 mg 4 times daily for 10–14 days, 2 times daily for 7 days, once daily for 7 days, and then every 2 to 3 days for 2 to 8 weeks
	Alternative: Vancomycin 125 mg given 4 times daily by mouth for 10 days	Consider a standard course of vancomycin if metronidazole was used for treatment of the first episode
	Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics[a]	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure[b]
Second or subsequent CDI recurrence	Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for 5 days followed by once every other day for 20 days	…
	Vancomycin by mouth in a tapered and pulsed regimen	…
	Vancomycin 125 mg 4 times daily by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days	…
	Fecal microbiota transplantation	The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation
	Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics[a]	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure[a]
Fulminant CDI	Vancomycin 500 mg 4 times daily by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal vancomycin, particularly if ileus is present	Definition of fulminant CDI is supported by: Hypotension or shock, ileus, megacolon

Clinical Practice Guidelines for C. difficile Infection • cid 2021:73 (1 September) • e1029



J. van Prehn et al. / Clinical Microbiology and Infection 27 (2021) S1eS21

Digestive Diseases and Sciences (2020) 65:1761–1766
https://doi.org/10.1007/s10620-019-05900-3

ORIGINAL ARTICLE

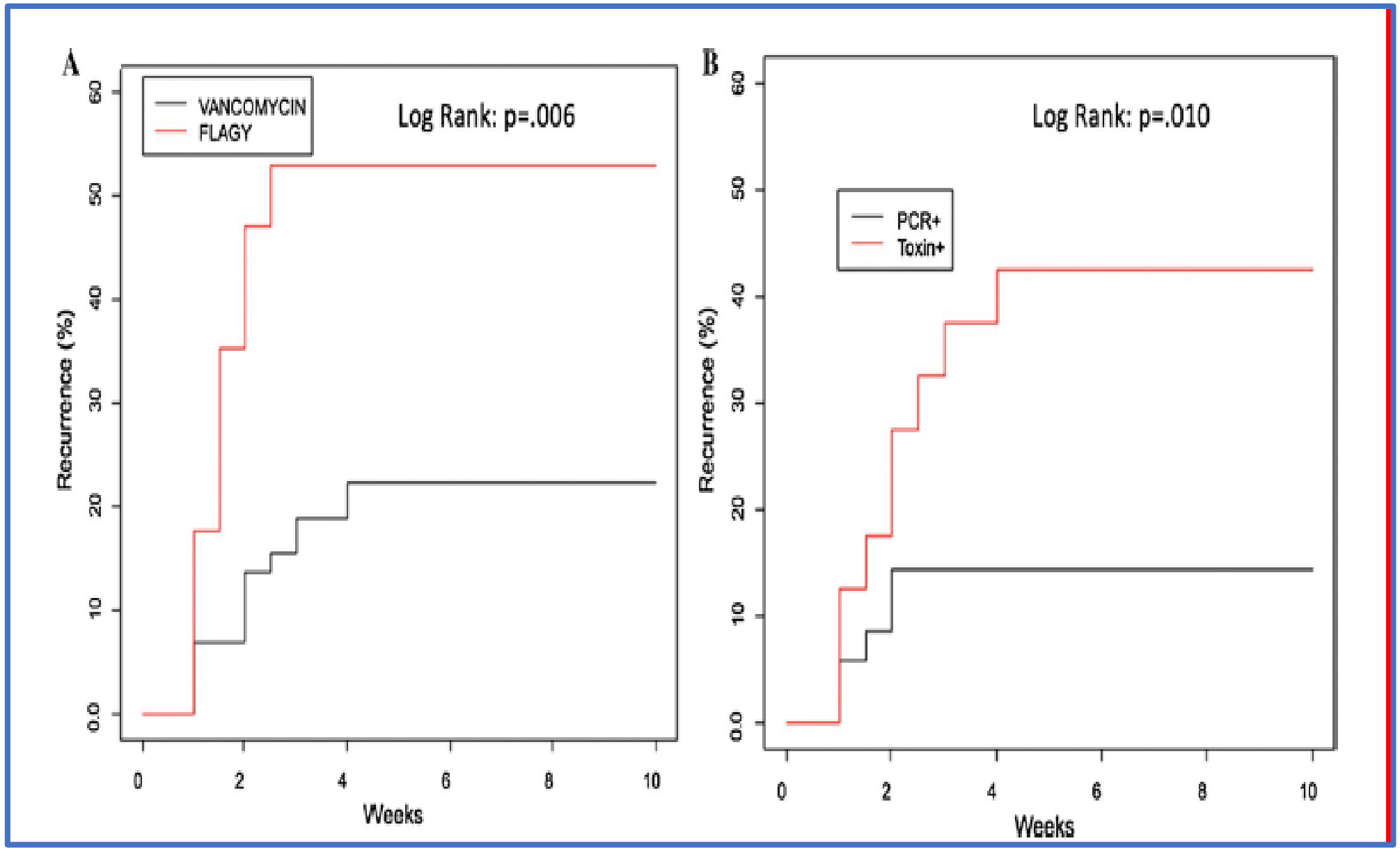
Clinical Predictors of Recurrence After Primary *Clostridioides difficile* Infection: A Prospective Cohort Study

Jessica R. Allegretti[1,2] · Jenna Marcus[1] · Margaret Storm[1] · Jessica Sitko[1] · Kevin Kennedy[3] · Georg K. Gerber[2,4] Lynn Bry[2,4]

- A prospective longitudinal study of patients experiencing their first episode of uncomplicated CDI
- Patients were followed from diagnosis through 8 weeks post-completion of their anti-CDI therapy to assess recurrence
- Stool was collected at diagnosis and weekly for 8 weeks following treatment
- Recurrence was defined as diarrhea as well as a positive stool test by toxin EIA (EIA) for *C. difficile*

Allegretti et al.Digestive Diseases and Sciences (2020) 65:1761–1766

	CDI recurrence		*P* value
	Yes *N* = 22	No *N* = 53	
Mean age (±SD)			
Female (*N*, %)			
Race (*N*, %)			
Black			
White			
Mean BMI (±SD)			
Received antibiotics prior to c			
Antibiotic type			
Beta-lactam			
Fluoroquinolone			
Lincosamide			
Macrolide			
Metronidazole			
Nitrofurantoin			
Peptide antibiotic			
Rifamycin			
Sulfa drug			
None			
Prior PPI use (*N*, %)			
History of cirrhosis (*N*, %)			
Dietary restrictions			
N, %			
No			
Vegan			
Vegetarian			
Gluten free			
Lactose free			
Smoking status (*N*, %)			
Never	15 (68.2%)	24 (46.2%)	0.220
Former	6 (27.3%)	25 (48.1%)	
Current	1 (4.5%)	3 (5.8%)	
Diagnosis of irritable bowel syndrome (*N*, %)	0 (0.0%)	8 (16.3%)	0.051
Baseline diarrhea or constipation (*N*, %)			
No	18 (81.8%)	36 (70.6%)	0.575
Diarrhea	1 (4.5%)	7 (13.7%)	
Constipation	2 (9.1%)	7 (13.7%)	
Both	1 (4.5%)	1 (2.0%)	
Baseline Bristol score (±SD)	2.7 ± 1.2	3.3 ± 1.2	0.084
Ursodiol use (*N*, %)	0 (0.0%)	0 (0.0%)	0.0
Cholestyramine use (*N*, %)	2 (9.1%)	0 (0.0%)	0.085
Colestipol use (*N*, %)	0 (0.0%)	1 (1.9%)	1.0
CDI treatment regimen (*N*, %)			
Metronidazole	9 (40.9%)	8 (15.1%)	**0.030**
Vancomycin	13(59.1%)	45 (84.9%)	
Test used for diagnosis (*N*, %)			
PCR	5 (22.7%)	30 (56.6%)	**0.007**
EIA toxin	17 (77.3%)	23 (43.4%)	
Mean white blood cell count (±SD)	8.2 ± 3.3	14.8 ± 18	0.147
Mean platelet count (±SD)	206.3 ± 72.	270.9 ± 114.8	**0.030**


A
VANCOMYCIN
FLAGY
Log Rank: p=.006
Recurrence (%)
0.0
10
20
30
40
50
60
0
2
4
6
8
10
Weeks
B
PCR+
Toxin+
Log Rank: p=.010
Recurrence (%)
0.0
10
20
30
40
50
60
0
2
4
6
8
10
Weeks

Bezlotoxumab

- A monoclonal antibody directed against *C. difficile* toxin B
- Bezlotoxumab has a10% reduced risk of recurrences in the placebo controlled **MODIFY-I and II trials**
- Be careful in patients with a history of congestive heart failure

European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-024-04762-6

ORIGINAL ARTICLE

Bezlotoxumab during the first episode of *Clostridioides difficile* infection in patients at high risk of recurrence

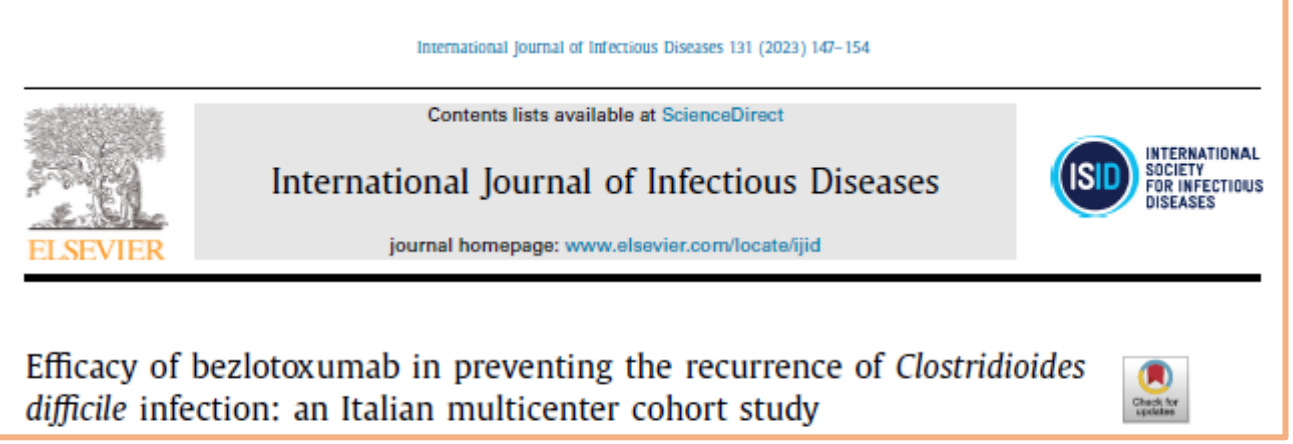
Rosa Escudero-Sanchez[1,2,3] · Antonio Ramos-Martínez[4] · Antonio F. Caballero-Bermejo[5] · Beatriz Díaz-Pollán[3,6,7] · Guillermo Ruiz-Carrascoso[7,8] · María Olmedo Samperio[9] · Patricia Muñoz García[9] · Paloma Merino Amador[10] · Fernando González Romo[10] · Oriol Martín Segarra[11] · Gema Navarro Jiménez[11] · Laura del Campo Albendea[12,13] · Alfonso Muriel García[12,13,14] · Javier Cobo[1,2,3]

- A prospective and multicentre study of patients with a high risk of recurrence
- Patients were treated with bezlotoxumab during their first episode of CDI was conducted

- Sixty patients (mean age:72 years) were prospectively treated with bezlotoxumab plus anti-Clostridioides antibiotic therapy
- Vancomycin (48) and fidaxomicin (12) were prescribed for CDI treatment, and bezlotoxumab was administered at a mean of 4.2 (SD:2.1) days
- Recurrence rates at 12 weeks were 15.0% (6/40) in bezlotoxumab-treated patients vs. 23.2% (16/69) in non-bezlotoxumab treated patients
- No adverse effects

- patients treated with bezlotoxumab in a real-world setting during a first episode, presented low rate of recurrence
- A significant difference in recurrence could not be proved

Eur J Clin Microbiol Infect Dis. 2024;43(3):533-540



- A real-world setting, the MODIFY trials in a cohort of participants with multiple risk factors for rCDI treated with BEZ in addition to the standard of care (SoC) versus SoC alone.
- ***Methods:*** A multicenter cohort study
- Including 442 patients with *Clostridioides difficile* infection from 2018 to 2022
- 18 Italian centers
- The main outcome: 30-day occurrence of Rcdi
- The secondary outcomes: all-cause mortality at 30 days

Meschiari et al. International Journal of Infectious Diseases, 2023-06-01, Volume 131, Pages 147-154

International Journal of Infectious Diseases 131 (2023) 147–154

Contents lists available at ScienceDirect

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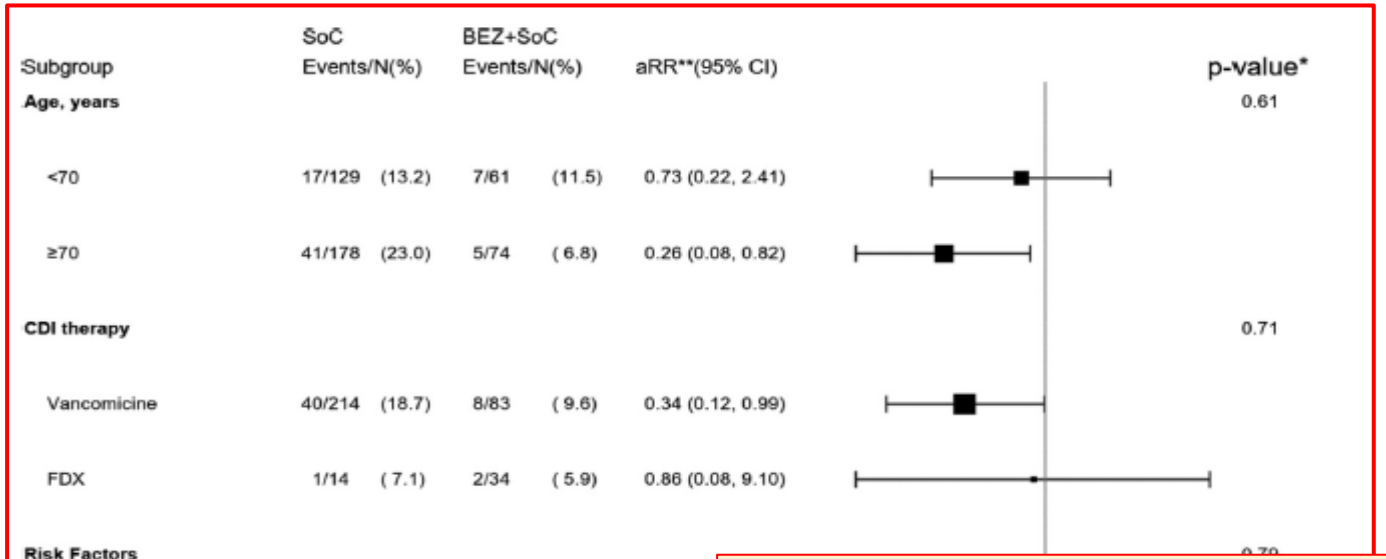
journal homepage: www.elsevier.com/locate/ijid

Efficacy of bezlotoxumab in preventing the recurrence of *Clostridioides difficile* infection: an Italian multicenter cohort study



- Bezlotoxumab is more effective than standard of care alone in preventing the rCDI
- BEZ reduces the risk of rCDI by 60% in a selected population with multiple risk factors)
- BEZ is effective regardless of age, type of standard of care, number of risk factors, and previous *Clostridioides difficile* infection.
- In patients aged <70 years and treated with fidaxomicin, the benefit of BEZ is attenuated

What is the best treatment for severe and severe complicated CDI?

- When a patient is deteriorating or progressing to severe complicated CDI while on anti-CDI antibiotic therapy, addition of iv **tigecycline** may be considered on a case-by-case basis
- **Consult a surgeon** for any severe-complicated case
- **Total abdominal colectomy** might be prevented by partial colectomy or loop ileostomy

Clinical Practice Guidelines for C. difficile Infection • cid 2021:73 (1 September) • e1029

Fecal Microbiata Transplantation

- Fecal microbiota transplantation has emerged as a safe and effective treatment option for rCDI
- Recent IDSA 2021 guidelines with moderate-quality evidence strongly recommend the initiation of FMT in patients with multiple recurrences of CDI not responding to appropriate antibiotic regimens
- The American College of Gastroenterology 2021 guidelines concur with this recommendation and strongly recommend moderate-quality evidence initiation of **FMT after a second CDI recurrence**
- Repeat FMT in case there is recurrence within 8 weeks of the initial FMT
- Several modes of delivery including capsules, an enema, colonoscopy, and a nasogastric tube are available
- A colonoscopy and the oral route have been shown to be more efficacious than an enema

Berry P. Recurrent Clostridioides difficile Infection: Current Clinical Management and Microbiome-Based Therapies. BioDrugs. 2023 Nov;37(6):757-773.

Adverse Events After FMT

- The most frequent side effects associated with FMT are **abdominal pain, transient diarrhea, and post-infection IBS**
- There have also been isolated cases of **aspiration** when performing FMT via the upper gastrointestinal route
- One report from FMT clinical trials for **hepatic encephalopathy** and **graft-versus-host disease** prevention revealed two events
- **Transmission of extended-spectrum beta-lactamase-producing E. coli** from a donor to a recipient

Berry P. Recurrent Clostridioides difficile Infection: Current Clinical Management and Microbiome-Based Therapies. BioDrugs. 2023 Nov;37(6):757-773.

Therapy [trial registration number]	Study design	Key inclusion criteria	Key exclusion criteria	Endpoints	Overall resolution
			BS, immunocompro-d	Lack of CDI recurrence at 8 and 24 weeks Adverse events	74.5% vs 61.5% at 8 weeks 73.5% vs 59.4% at 24 weeks
			Factorial diarrhea	Absence of CDI recurrence on day 40 Mortality or hospitalization because of CDI	79% resolution after the first treatment and 75% resolution in those needing a second treatment
			BS, immunocompro-	8-week recurrence	55.6 % resolution after two
	2. Placebo				
	Phase III, randomized double-blinded, two-armed in a 1:1 ratio Active or placebo	Thre wi Diag ca		participation, major gastro-intestinal surgery within the past 3 months	

Open Forum Infectious Diseases

MAJOR ARTICLE

Effect of Fecal Microbiota, Live-Jslm (REBYOTA [RBL]) on Health-Related Quality of Life in Patients With Recurrent *Clostridioides difficile* Infection: Results From the PUNCH CD3 Clinical Trial

Kevin W. Garey,[1,*] Erik R. Dubberke,[2] Amy Guo,[3] Adam Harvey,[4] Min Yang,[5] Viviana Garcia-Horton,[6] Mir[illegible] Lindy L. Bancke,[4] and Paul Feuerstadt[8,9]

[1]University of Houston, Houston, Texas, USA, [2]Washington University, St Louis, Missouri, USA, [3]Ferring Pharmaceuticals, Parsippa[illegible] Minnesota, USA, [5]Analysis Group Inc., Boston, Massachusetts, USA, [6]Analysis Group, Inc., New York, New York, USA, [7]GST Micro, [illegible] Haven, Connecticut, USA, and [8]PACT-Gastroenterology Center, New Haven, Connecticut, USA

Background. Recurrence of *Clostridioides difficile* infection (rCDI) is common, pro[illegible] poor quality of life. We evaluated disease-specific health-related quality of life (HRQL[illegible] microbiota, live-jslm (REBYOTA [RBL]; Rebiotix) versus placebo.

Methods. This was a secondary analysis of a randomized, double-blind, placebo-con[illegible] disease-specific *Clostridioides difficile* Quality of Life Survey (Cdiff32) was administered a[illegible] in Cdiff32 total and domain (physical, mental, social) scores from baseline to week 8 were[illegible] for responders and nonresponders.

Results. Findings were analyzed in a total of 185 patients (RBL, n = 128 [69.2%]; place[illegible] data. Patients from both arms showed significant improvements in Cdiff32 scores relativ[illegible] time points (all $P < .001$); RBL-treated patients showed significantly greater improvemen[illegible] placebo. In adjusted analyses, RBL-treated patients showed greater improvements than[illegible] mental domains (all $P < .05$). Similar improvement in mental domain was observed[illegible] showed numerical improvements with RBL but not placebo.

Conclusions. In a phase 3 double-blinded clinical trial, RBL-treated patients reporte[illegible] specific HRQL improvements than placebo-treated patients.

Clinical Trials Registration. ClinicalTrials.gov NCT03244644 (https://clinicaltrials[illegible]

Keywords. fecal microbiota; health-related quality of life; live-jslm; randomized cli[illegible]

Prevalence of Comorbid Factors in Patients with Recurrent *Clostridioides difficile* Infection in ECOSPOR III, a Randomized Trial of an Oral Microbiota-based Therapeutic

Study Population

73 men, 109 women

Adults with ≥3 episodes of rCDI), inclusive of qualifying episode

Mean age, 65.5 years

73.1% had a Charlson Comorbidity Index score ≥3

Study Design

182 patients randomized

Double-blind design

VOS (VOWST™ Oral Spores) (n=89)
4 oral capsules (~3x10^7 spore colony-forming units) once daily over 3 consecutive days

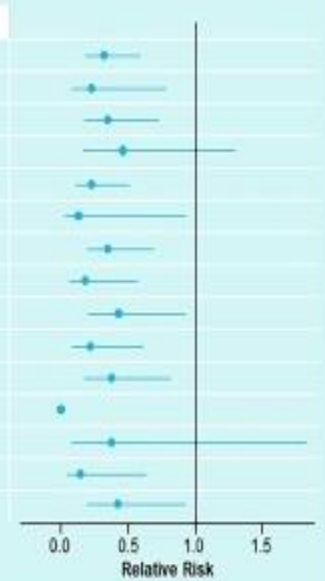
Placebo (n=93)
4 oral capsules once daily over three consecutive days

Primary Outcome

Post-hoc exploratory analysis of the rate of CDI recurrence at 8 weeks among VOS-treated patients compared to placebo in certain subgroups by:

- Number of prior CDI episodes
- Exposure to non-CDI targeted antibiotics after dosing
- Charlson Comorbidity Index score category (0, 1-2, 3-4, ≥5).
- Age (≥ 65 and <65 years) and sex
- Use of acid-suppressing medications (ASMs)

Results



Limitations: Small size of subgroups precluded evaluation of whether treatment effect varied across subgroups.

Conclusions: In this post-hoc analysis, VOS was observed to reduce CDI recurrence compared to placebo, regardless of baseline characteristics, comorbidities or use of ASMs.

Conclusion

- Opportunistic infections pose a risk for morbidity and mortality in immunosuppressed patients
- Recurrent infections and treatment failure are common
- Prophylaxis reduces the risk of infection in appropriate patients
- Current treatments are especially successful in recurrent infections


Thank
you