



CAR-T CELL THERAPY AND FUNGAL INFECTIONS: ARE WE READY FOR THE INDIAN CHALLENGE?

Parikshit S. Prayag

Department of Infectious Diseases,
Deenanath Mangeshkar Hospital, Pune

Introduction

In 2017, the United States Food and Drug Administration (FDA) approved the first chimeric antigen receptor (CAR)-T cell therapy for pediatric acute lymphoblastic leukemia (ALL). This field has made considerable progress in India, including the availability of indigenously developed CAR-T cell products. However, infections pose a major challenge to the success of CAR-T cell therapy programs in our settings. We will review the burden and risk factors for invasive fungal infections (IFIs) in these patients, with a focus on the prophylactic strategies.

Risk factors for IFIs in these patients

In order to understand the risk of fungal infections, it is important to analyze the net state of immunosuppression in these patients. Usually, CAR-T products target either the CD19 tumor antigen or the B-cell maturation antigen (BCMA). In India, most centers currently use CD19 CAR-T cell therapy. Various factors influence the risk of IFIs in recipients of CAR-T cell therapy. The underlying disease, and the therapies received prior to CAR-T cell therapy can influence the risk of IFIs in these patients. Allogeneic hematopoietic stem cell transplantation (HSCT) is used more commonly in the management of ALL than in Multiple Myeloma or B-cell lymphoma. CD19 CAR-T cell therapy recipients with a history of prior HSCT may have an increased risk of IFIs.¹ In this regard, the time since transplant, post-transplant complications such as graft versus host disease (GVHD) and the therapies used for it may influence the risk of IFIs. Other therapies such as ibrutinib, used prior to the receipt of CAR-T cell therapy can increase the risk of post CAR-T cell IFIs.²

The influence of neutropenia on the risk of IFIs is well known. In this regard, it is important to look at the duration of cytopenias in these patients. CAR-T cell therapy recipients typically receive lymphodepleting regimens prior to receiving immune-effector cells. Strictly speaking, neutropenia is less prolonged in these patients compared to allogeneic HSCT recipients.³ In these patients, the median duration of severe neutropenia has been found to be 9 days.⁴ However these patients can have biphasic neutropenia. The second wave of neutropenia is likely immune mediated. In this regard, the CAR-HEMATOTOX model can be used to predict the duration of cytopenia and hence anticipate the risk of IFIs.⁴ This score looks at two important aspects: the baseline hematopoietic reserve and baseline systemic inflammation. A score ≥ 2 is considered high risk for hematotoxicity.

When analyzing the risk of IFIs in recipients of CAR-T cell therapies, it is imperative to look at three immune effector cell (IEC)-associated complications. These syndromes and their therapies can influence the risk of IFIs in these patients.^{5,6,7,8} These are summarised very briefly in table 1.

Burden of IFIs in this patient population, including our experience

In a review of IFIs in CAR-T cell recipients, there were 71 cases of IFIs reported across 16 studies evaluating 2358 patients.¹ Of these, 66 were identified as proven or probable infections (overall incidence, 2.8%).¹ Of these 66 cases, 45% were invasive yeast infections, 39% invasive mold infections, 14% were due to *Pneumocystis jirovecii*

Message from the Editor

Dear Friends,

A warm welcome to the delegates of the 36th Annual conference of ISOT, 26 from the Fungal Infection Study Forum (FISF). We all know that invasive fungal infections cause substantial morbidity in patients with cancer, hematopoietic stem cell transplant, solid organ transplant and those on CAR-T cell therapy. This issue of the newsletter discusses the challenges in diagnosis and management of IFI in all these immunosuppressed hosts through a review article and two case reports. We hope that these write-ups will help you in your clinical practice.

We encourage you to visit the FISF website www.fisftrust.org to access previous newsletters and other educational resources.

Wishing you an academically enriching time at the conference.

Dr. Tanu Singhal

Consultant Pediatrics and Infectious Disease

Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute,
Mumbai

Email: tanusinghal@yahoo.com

Welcome All Delegates



9th - 11th October 2026 • HITEX, Hyderabad

Table 1: IEC-associated complications

Complication / Syndrome	Key features	Main pharmacotherapy
Cytokine Release Syndrome (CRS)	Fever, hypotension, hypoxia	Tocilizumab $\pm$ corticosteroids
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Aphasia, confusion, seizures, $\downarrow$ consciousness	Corticosteroids
Immune Effector Cell-Associated Hemophagocytic Syndrome (IEC-HS)	$\uparrow$ Ferritin, new/worsening cytopenias, hypofibrinogenemia, organ dysfunction	Corticosteroids $\pm$ anakinra

pneumonia (PJP), and there was 1 reported case of coccidioidomycosis.¹ In the 328 BCMA CAR-T cell recipients described in this review, there were 8 cases of proven or probable IFIs.¹ We need to generate this kind of data in our settings, where most CAR-T cell therapy programs are just getting started. In our own experience, in our center in Pune, in the 27 recipients of CD19 directed CAR-T cell therapy, there have been 7 cases of proven or probable IFIs (within the first 100 days of receipt of therapy). These include 4 cases of invasive pulmonary aspergillosis, and one each of candidemia, disseminated fusariosis and pulmonary mucormycosis. Interestingly these 7 IFIs developed between day +21 and day +72 after receiving CAR-T cell therapy. This early experience shows that we may have a higher incidence of IFIs (25%) in this patient population; however, larger, multi-center registries are required over time to validate whether this initial observation represents a broader regional trend.

Prophylactic strategies

The optimal prophylactic strategies for CAR-T cell recipients are still being devised.

- ▶ Best Practice Considerations by the American Society of Transplant and Cellular Therapy:

These recommendations, published in 2025 state that centers practicing universal prophylaxis should use fluconazole (or echinocandins when fluconazole is contraindicated) from the initiation of lymphodepleting therapy till the reversal of neutropenia.⁹ These recommendations urge the consideration of mold active prophylaxis in the following situations:

- Persistent neutropenia
- Severe CRS
- Recipients of high-dose corticosteroids
- Centers where Aspergillosis rates are ≥ 6%
- Bruton's tyrosine kinase inhibitors given prior to CART cell therapy

- ▶ European Conference on Infections in Leukemia (ECIL) guidelines:

In the most recent update published in 2025, the expert panel endorsed the use of anti-mold prophylaxis in high-risk patients during pre-infusion and post-infusion, while in low-risk patients, anti-yeast prophylaxis was recommended.¹⁰

A retrospective study of 330 patients published in 2025 divided CAR-T cell therapy recipients into two groups. The first group consisted of patients primarily treated with fluconazole, irrespective of their individual IFI risk profile, while in the second group antifungal prophylaxis was recommended only for high-risk patients.¹¹ The study concluded that individualized prophylaxis was associated with a very low IFI rate, avoiding the risk of unnecessary toxicities, drug-drug interactions, and high costs.¹¹ In our settings we must individualize the need for mold active prophylaxis, also taking into account our in house rates of IFIs in these patients. We need to generate local data with respect to the burden, timeline of IFIs as well as the type of IFIs developing in these patients, to help us formulate local protocols for antifungal prophylaxis.

Conclusions

As CAR-T-cell therapy expands across India, clinicians will face unique local risk factors for IFIs. Rather than adopting universal yeast prophylaxis frameworks designed for azole sensitive yeast and low-mold western environments, Indian centers must generate local data regarding the specific burden, mycological spectrum, and timelines of these infections. This real-world evidence will be foundational to formulating tailored, risk-stratified local protocols for optimal yeast and mold-active antifungal prophylaxis.

References

1. Little JS, Kampouri E, Friedman DZ, et al. The Burden of Invasive Fungal Disease Following Chimeric Antigen Receptor T-Cell Therapy and Strategies for Prevention. *Open Forum Infect Dis*. 2024; 11(6):ofae133.

2. Chamilos G, Lionakis MS, Kontoyiannis DP. Call for action: invasive fungal infections associated with ibrutinib and other small molecule kinase inhibitors targeting immune signaling pathways. *Clin Infect Dis*. 2018; 66(1):140–148.

3. Fried S, Avigdor A, Bielora B, et al. Early and late hematologic toxicity following CD19 CAR-T cells. *Bone Marrow Transplant*. 2019;54 (10):1643–1650.

4. Rejeski K, Perez A, Sesques P, et al. CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma. *Blood*. 2021; 138(24):2499–2513.

5. Park JH, Romero FA, Taur Y, et al. Cytokine release syndrome grade as a predictive marker for infections in patients with relapsed or refractory B-cell acute lymphoblastic leukemia treated with chimeric antigen receptor T cells. *Clin Infect Dis*. 2018; 67(3):533–540.

6. Santomasso BD, Nastoupil LJ, Adkins S, et al. Management of immune-related adverse events in patients treated with chimeric antigen receptor T-cell therapy: ASCO guideline. *J Clin Oncol*. 2021; 39(35):3978–3992.

7. Sterner RC, Sterner RM. Immune effector cell associated neurotoxicity syndrome in chimeric antigen receptor-T cell therapy. *Front Immunol*. 2022; 13:879608.

8. Hines MR, Knight TE, McNeerney KO, et al. Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome. *Transplant Cell Ther*. 2023; 29(7):438.e1–438.e16.

9. Shahid Z, Jain T, Dioverti V, et al. Best Practice Considerations by the American Society of Transplant and Cellular Therapy: Infection Prevention and Management After Chimeric Antigen Receptor T Cell Therapy for Hematological Malignancies. *Transplant Cell Ther*. 2024; 30(10):955–969.

10. Pagano L, Maschmeyer G, Lamoth F, et al. Primary antifungal prophylaxis in hematological malignancies. Updated clinical practice guidelines by the European Conference on Infections in Leukemia (ECIL). *Leukemia*. 2025; 39(7):1547–1557.

11. Melica G, Luna de Abia A, Shah GL, et al. Shift from Widespread to Tailored Antifungal Prophylaxis in Lymphoma Patients Treated with CD19 CAR T Cell Therapy: Results from a Large Retrospective Cohort. *Transplant Cell Ther*. 2025; 31(1):36–44.

PULMONARY COINFECTION IN A RENAL TRANSPLANT RECIPIENT: NAVIGATING A NARROW AND TREACHEROUS STRAIT

Sharvari Kondpalle, Sayali Makne, Geethu Joe, Rajeev Soman
Jupiter Hospital, Pune

Introduction

Invasive pulmonary fungal infections post formidable diagnostic and treatment challenges in the solid organ transplant recipient. Having another coinfection compounds these challenges. We discuss here a challenging case of dual infection in a renal transplant recipient.

Case report

A 47 years female patient underwent an ABO incompatible living donor renal transplant in October 2025. Her early post operative period was marked by graft dysfunction and TMA (Thrombotic Microangiopathy), for which she had received high dose methyl prednisolone (MPS) and Antilymphocyte globulin. Later she was on triple immunosuppression – MMF, Everolimus and oral Prednisolone with TMP-SMX prophylaxis for 1 month.

In May 2026, she developed dry cough, for which she received antibiotics for 14 days elsewhere. There were similar signs and symptoms in family members. The cough persisted on and off since then and her respiratory symptoms worsened in June along with fever.

The HRCT done on 21.07.2026 revealed subsegmental consolidation with air bronchogram in both upper lobe, right middle lobe, lingula and superior segment of right lower lobe of lung (Figure 1).

Adjacent tree in bud opacities were also noted in these regions.

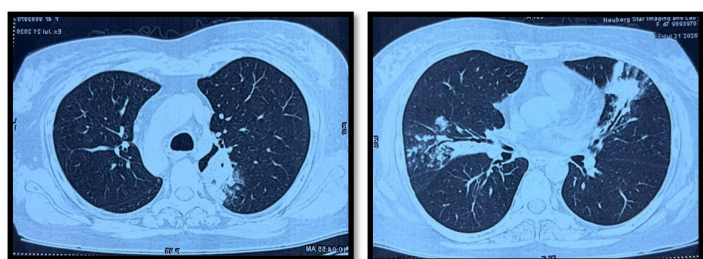


Figure 1: HRCT chest of index patient

With above HRCT and respiratory complaints, the patient got admitted and ID reference was asked for.

Differential diagnosis taking into consideration above radiological findings such as multiple dense nodules, tree in bud appearance and airway abnormality are explained in Table 1.

On physical examination, phlycten near the limbus was noted. The discovery of an ocular phlycten in an immunosuppressed renal transplant recipient presenting with respiratory symptoms is a clue pointing towards active TB.

Pulmonary TB, Invasive Aspergillosis, Nocardiosis, PTLD (post-transplant lymphoproliferative disorder and *pneumocystis jirovecii* pneumonia (PCP) were thought of as differentials at this point, with points in support and against them.

Table 1: Differential diagnosis in the index case

Clinical Imaging Features	Pulmonary TB	Invasive Aspergillosis	Nocardiosis	PTLD	PCP
Large nodules	+	++	++	++	—
Tree in Bud	++	+	—	—	—
Ocular phlycten	++	—	—	—	—
Prior TMP-SMX prophylaxis	NA	NA	++	NA	++

++ = strongly associated; + = present/associated; — = absent/not characteristic; NA = not applicable / not relevant

Diagnostic bronchoscopy was performed and BAL fluid sample showed AFB on smear, GeneXpert MTB ultra was positive (load high). RIF resistance was not detected. The diagnosis of pulmonary TB was thus confirmed. The MTB XDR showed no isoniazid and fluoroquinolone resistance.

BAL Galactomannan turned out to be positive with value of 2.1. Galactomannan is a heat stable polysaccharide component released from cell wall of *Aspergillus* species during active hyphal growth and tissue invasion. Thus, it serves as an antigen based mycological evidence of tissue invasion. The possibility of a false positive GM was also considered in this patient but no factors such as receipt of antibiotics, dextrose containing fluids, contaminated collecting device etc were apparent. Radiologic evidence of halo may not be seen in non-neutropenic patients. Taking into consideration the high pretest probability of an IFI and compatible clinic radiologic factors and a positive biomarker a diagnosis of probable invasive aspergillosis was made.

Discussion

The management plan had to address infection while preventing allograft rejection and drug-drug interaction. The primary therapeutic challenge lies in the simultaneous administration of ATT, targeted antifungal therapy and maintenance immunosuppression. These 3 drug classes exert opposing and highly overlapping effects on hepatic Cytochrome 450 (specifically CYP3A4) enzyme system and P-glycoprotein drug efflux transporter.

1. Rifampicin is a strong inducer of hepatic CYP3A4, CYP2C9, CYP2C19 and P-glycoprotein causing increase in clearance of Voriconazole thereby reducing its levels by 90-95%. and a potent competitive inhibitor of CYP3A4.
2. Voriconazole is primarily metabolized by CYP2C19, CYP2C9, and CYP3A4 and it is also a potent competitive inhibitor of CYP3A4. If Rifampicin is omitted, the administration of Voriconazole alone acts as a potent inhibitor of CYP3A4. This

blocks the metabolism of Everolimus, causing its serum levels to increase 3 to 4 folds causing everolimus toxicity.

3. Both everolimus and Prednisolone are narrow therapeutic index substrates that rely entirely on CYP3A4 and P-gp for their metabolism and clearance. Rifampicin's induction of CYP3A4 and P-gp accelerates the clearance of Everolimus and Prednisolone, reducing their serum concentrations by upto 80%.

The patient was treated with non-rifampicin based treatment including Levofloxacin, Isoniazid, pyrazinamide, and ethambutol. Isavuconazole, that has less interaction as compared to voriconazole was chosen and the dose of Everolimus was reduced.

In severely immunocompromised patients, simultaneous infections may coexist, demanding careful assessment and management as clinicians navigate a narrow and treacherous strait described by the Hickman dictum.

References

1. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010;50(8):1101-1111. doi:10.1086/651262
2. Brüggemann RJ, Alffenaar JW, Blijlevens NM, et al. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. Clin Infect Dis. 2009;48(10):1441-1458. doi:10.1086/598327
3. Azanza Perea JR. Pharmacological interactions of isavuconazole. Rev Iberoam Micol. 2025;42(1):45-50. doi:10.1016/j.riam.2025.04.001

CASE REPORT: ETHANOL LOCK THERAPY FOR CATHETER SALVAGE IN CATHETER RELATED CANDIDEMIA

Subramanian S, Raj Kumar J, Niveditha N, Mohamed Sulaiman G

Department of Infectious Diseases, Gleneagles Hospital| Fortis Network, Chennai, India

Background

Central venous catheter (CVC) are an important component in the care of high risk patients to ensure long term vascular access. These are prone to catheter related bloodstream infections (CRBSIs). In such cases, the best option is often to remove the catheter. However, for high risk patients, catheter removal may not be feasible due to difficulty in venous access. Ethanol lock therapy (ELT) has emerged as a promising option to eradicate microbial biofilms inside catheters and to salvage infected lines. ELT is a process to install ethanol solution into catheter lumen with a dwell time to sterilize and disrupt biofilms in conjunction with systemic antimicrobial therapy to address the bloodstream infections. Studies have shown that ELT is effective in treating and preventing CRBSI with tolerability safety profiles, although protocols for its use vary widely.

Case Presentation

A 54-year-old female known case of relapsed ovarian carcinoma, diabetes, hypertension, post angioplasty was being treated with therapy through a Chemo port.

During the prior admission, she was diagnosed with *Candida parapsilosis* catheter related blood stream infections (CRBSI) (azole susceptible). She was initially treated with Intravenous IV anidulafungin which was transitioned over to IV fluconazole based on culture and susceptibility reports. Once blood culture clearance was confirmed with paired samples she was discharged with oral fluconazole.

One week later, she came to Emergency department with complaints of abdominal distension, constipation, multiple episodes of vomiting and fever (T- 101°F). She was empirically started on IV piperacillin-tazobactam and IV fluconazole 800mg OD, after

paired blood cultures were sent. Blood c/s eventually grew *Candida parapsilosis* with an identical susceptibility pattern; Paired culture showed a differential time to positivity of >120 minutes (with a line culture flagging earlier than the peripheral culture), concerning for the possibility of catheter-related source. IV fluconazole was continued and primary team was advised to change the catheter. After 5 days of IV fluconazole therapy repeat blood cultures were sent to check for clearance unfortunately they continued to remain positive for *Candida parapsilosis*. The primary team felt that securing new IV access would be very difficult in this patient and they requested to try and salvage the port. On day 6 of admission Ethanol lock therapy (ELT) as described below, was started for 3 consecutive days, following this blood cultures returned negative and the patient clinical fever and symptoms improved was discharged home on Day 14. On last follow up, 47 days later, the patient has not had further recurrence of candidemia and the chemo port continues to be in use.

Ethanol Lock Therapy Protocol

A 70% ethanol solution was used for the lock therapy.

Lock Volume Calculation

The lock volume was calculated based on the catheter's manufacturer-specified priming volume (Usually marketed on the catheter hub), adjusted for cut length if trimmed at insertion typically 1.5-3mL per lumen. For this patient, a 2mL lock was used, prepared as follows:

- ▶ Ethanol 70%: 1.43mL
- ▶ Sterile water for injection (SWI), quantity sufficient to make 2mL.

Lock Procedure

1. Withdraw the existing contents of the lumen and discard.
2. Flush the catheter with normal saline
3. Instill the calculated volume of ethanol lock solution to fill the catheter lumen.
4. At the conclusion of the dwell period, aspirate the ethanol lock solution before using the line to administer medications.
5. Heparin should not be used concomitantly with ELT as it forms precipitate with ethanol.

ELT was administered daily with a dwell time of 2-4 hours for 3 consecutive days. Concurrent systemic IV fluconazole was continued throughout the course of therapy. Follow-up blood cultures turn to be negative, confirming clearance of infection, and the catheter was salvaged successfully.

Discussion

Antimicrobial lock therapy has been used for treatment and prevention of catheter related blood stream infections. Experience with Ethanol lock therapy have included therapeutic interventions with variable results.

This case highlights ELT's utility catheter salvage strategy in patient with CRBSI who have difficulty in line removal. ELT disrupts microbial biofilms, enhancing systemic antifungal efficacy and reduce the risk of relapse. Literature reports ELT success rates of nearly 48-88% for salvage in catheter infections, some adverse effects such as transient catheter occlusion or flushing. The use of ELT in adults is still limited. We wish to show that this should be considered as one of the options in such situations.

ELT may not be a universal solution. It is important to assess the material compatibility for ethanol use, and the clinical team should be aware of potential adverse effects that may occasionally occur. Areas of the research includes optimal alcohol or ethanol concentration and required dwell time. At this point the common practice is 70% Ethanol with a 2-4-hour dwell time. Overall, the decision to use ELT should be based on a multidisciplinary approach, which includes both systemic therapy and careful selection of patient, treatment of pathogens for which meaningful antimicrobial therapy is available and combined with good systemic therapy.

Conclusions

We may consider ethanol lock therapy in patients with line-related infections when catheter removal is not feasible and other salvage options have failed. In combination with systemic antifungal treatment, ELT may be a viable option for catheter salvage in

patients with candidemia where catheter removal is challenging. This case adds to the accumulating evidence validating ELT's role in antimicrobial stewardship for complex vascular access infections.

References

1. Rane HS, Bernardo SM, Walraven CJ, Lee SA. In Vitro Analyses of Ethanol Activity against *Candida albicans* Biofilms. *Antimicrobial Agents and Chemotherapy*. 2012 May 21;56(8):4487-9.
2. Iwade T, Sumida W, Watanabe Y. A case of ethanol-lock therapy for candida parapsilosis in catheter-related blood stream infection. *Nihon Rinsho Geka Gakkai Zasshi (J Jpn Surg Assoc)* [Internet]. 2011;72(6):1374-7. Available from: https://www.jstage.jst.go.jp/article/jjsa/72/6/72_6_1374/_article/-char/en.
3. Chiba M, Yonekura T, Kaji T, Amae S, Tazuke Y, Oowari M, et al. Ethanol lock therapy in pediatric patients: A multicenter prospective study. *Pediatr Int* [Internet]. 2020;62(3):379-85. Available from: <http://dx.doi.org/10.1111/ped.14096>.
4. Ethanol Lock Therapy (E-Lock) in the Prevention of Catheter-Related Bloodstream Infection in adult patients. *PLoS One*. 2014; 9(3):e91838.
5. Ethanol Lock Technique: Review of the Literature. *Infection Control & Hospital Epidemiology*. 2009;30(11):1096-1108. doi:10.1086/606162

About FISF

The purpose of the Fungal Infections Study Forum is to conduct educational activities, undertake epidemiological and clinical studies and to promote research activities on invasive fungal infections. The results of such research would benefit clinicians, mycologists and the general public. The trust was formed in view of emergence of Invasive fungal infections (IFIs) in India which is posing a serious challenge to haematologists, critical care providers, ID specialists, pulmonologists, neurologists, medical mycologists and many other clinicians handling serious and immunocompromised patients. The trust consists of clinicians and mycologists and was instituted on 3rd March 2012 at Mumbai, India



Fungal Infection Study Forum

www.fisftrust.org

Members of FISF

Dr Arunaloake Chakrabarti	Dr Suneetha Narreddy
Dr Rajeev Soman	Dr Subramanian Swaminathan
Dr Atul Patel	Dr V Ramasubramanian
Dr Ram Gopalkrishnan	Dr Ritesh Agarwal
Dr Subhash Todi	Dr Parikshit Prayag
Dr MR Shivaprakash	Dr Sachin Jadhav
Dr Subhash Varma	Dr Tanu Singhal
Dr Pradeep Kumar Bhattacharya	Dr Nitin Bansal
Dr Prakash Shastri	

Advisors

Dr OC Abraham	Dr Arvind Baronia
Dr Shirish Prayag	Dr Randeep Guleria