VACCIREVIEW

Early, deadly infection burden after CAR-T – with product-specific risk patterns

Bibliography

Zha C, Yang Z, Li L, et al. Infections post-CAR-T therapy: a real-world pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database. Clin Ther. 2026; Published online April 7, 2026.

Summary

Using FAERS data from Q1 2017–Q4 2024, this pharmacovigilance study identified 50,386 CAR-T–related adverse event reports, of which 3,467 (7%) were infection-related in 2,238 individuals, representing 15.7% of reported CAR-T recipients. The case-fatality proportion among infection reports was high at 41%. Disproportionality analysis demonstrated a significant overall association between CAR-T and infections (ROR 1.42, 95% CI 1.36–1.49; IC025 0.38), with infection signals for 5 of 6 products (all except ide-cel); tisa-cel showed the strongest signal (ROR 1.76; IC025 0.58). Pneumonia, sepsis, “infection” NOS, COVID-19, septic shock, and bacteremia were the most frequently reported preferred terms, and strong signals emerged for opportunistic pathogens including C. difficile, Candida, Aspergillus, mucormycosis, BK virus, CMV pneumonia, fungaemia, and HHV-6 encephalitis. Time-to-onset analysis showed 74.7% of infections occurring within 30 days post-infusion (median 5 days), with viral infections significantly later than bacterial infections and particularly delayed with cilta-cel (median 40 days). Multivariable models implicated tisa-cel, cilta-cel, neutropenia, and hypogammaglobulinemia as independent risk factors.

Comment

In summary, this FAERS-based CAR-T infection analysis reiterates that infections after CAR-T are frequent and often fatal, but it misuses spontaneous reporting data in ways that make its conclusions of limited value for clinicians: it conflates true clinical infections with syndromic diagnoses and mere pathogen detections, something FAERS cannot reliably distinguish; it treats disproportionality signals and crude logistic models—built on highly incomplete, confounded, and denominator-free data—as if they reflected comparative infection risk, time-dependent hazards, and product-specific differences; and it quotes striking figures such as a 41% “fatality rate among infection cases” without adjudication of cause of death or severity grading, which is more alarming than actionable. There is no need for you to read the full paper.

In detail, this FAERS analysis reiterates that infections are frequent and often fatal after CAR-T, but it adds very little of practical value for clinicians and in several respects is methodologically misleading and potentially confusing.

Misuse of the term "infection" as a clinical concept

- The paper promises to characterize "infections" after CAR-T, yet the outcome is an undifferentiated mix of pathogen detections (for example CMV or BK viraemia) and organ diagnoses such as "pneumonia" or "sepsis", all treated as equivalent "infection-related AEs". Not to mention that there is no definition of these terms or specified methods of pathogen detection. AE reporting has different goals.
- Asymptomatic colonization or viraemia cannot be captured reliably in a spontaneous reporting system, and FAERS has no systematic way to distinguish colonization, subclinical reactivation, and clinically relevant infection; nonetheless the authors interpret safety signals as if they reflected true infectious disease burden.
- Some of the strongest signals are for extremely rare entities (for example HHV-6 encephalitis, mucormycosis) based on very small numbers of reports, but they are presented side-by-side with common entities such as pneumonia, which risks gross misperception of relative risk in routine practice.

Fundamental limitations of FAERS ignored in the headline claims

- The database has no denominator, no exposure time, and no systematic capture of events, so the paper cannot estimate incidence, comparative risks between products, or time-dependent hazards, yet the narrative repeatedly lapses into incidence-like language ("higher risk", "later onset") that clinicians will naturally read as epidemiologic facts.
- Confounding by indication, baseline disease status, prior lines and intensity of therapy, and center practices (prophylaxis, diagnostics, ICU thresholds) is entirely unmeasured; nevertheless, product-specific "risk factors" are inferred from simple logistic models that adjust for only a few FAERS variables.
- The time-to-onset analysis uses EVENT_DT and START_DT fields that are notoriously incomplete and inaccurate in spontaneous reports; extensive exclusions for missing or implausible dates are acknowledged, but the authors still model TTO with log-rank and Mann-Whitney tests as if the underlying time scale and censoring were reliable.

Outcomes and severity: apparent precision without clinical granularity

- The reported 41% "fatality rate among infection cases" is based on the death outcome flag in FAERS, not on adjudicated infection-attributable mortality, and no attempt is made to separate deaths from progressive malignancy, CAR-T toxicity, or underlying comorbidities; quoting such a number without context is more alarming than informative.
- Severity grading of infections (for example grade 3–4 vs mild) is not available, but the discussion frequently implies severe, life-threatening disease based purely on preferred terms like "sepsis" and "septic shock", although these labels are themselves subject to reporting bias and local coding practices.

Signal detection overinterpretation

- The authors use multiple disproportionality algorithms (ROR, PRR, BCPNN, MGPS) and then restrict attention to PTs positive in all four, which may look statistically rigorous but does not solve the core problem: FAERS disproportionality can only generate hypotheses of disproportionate reporting, not comparative clinical risk between CAR-T products.
- Product-specific "differences" in infection profile are almost certainly driven by different approval dates, indications, geographic uptake, and differential awareness/reporting, yet they are translated into product-level risk statements (for example "tisa-cel and cilta-cel associated with increased risk") that go far beyond what a spontaneous reporting signal can support.

Limited clinical usefulness

- I would have some key clinical questions—Which patients truly need enhanced prophylaxis? What is the absolute risk of serious bacterial vs viral infection over time? How do CAR-T products compare after proper adjustment? —cannot be answered from FAERS in principle due to the nature of AE reporting, and the authors acknowledge many of these limitations in the discussion but still present their findings as a "comprehensive overview" and propose product-tailored prophylactic strategies on this basis.
- No practical, evidence-based recommendations for antimicrobial choice, duration, monitoring schedules, or IVIG strategies can be derived from this dataset beyond what is already stated in recent consensus guidance and prospective cohort work; for most busy clinicians, the lengthy catalogue of

> PT-level signals risks obscuring, rather than clarifying, the already well-recognized need for early bacterial coverage and later viral surveillance after CAR-T.

In summary, this FAERS-based CAR-T infection analysis reiterates that infections after CAR-T are frequent and often fatal, but it misuses spontaneous reporting data in ways that make its conclusions of limited value for clinicians: it conflates true clinical infections with syndromic diagnoses and mere pathogen detections, something FAERS cannot reliably distinguish; it treats disproportionality signals and crude logistic models—built on highly incomplete, confounded, and denominator-free data—as if they reflected comparative infection risk, time-dependent hazards, and product-specific differences; and it quotes striking figures such as a 41% “fatality rate among infection cases” without adjudication of cause of death or severity grading, which is more alarming than actionable. There is no need for you to read the full paper.

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