# Incidence of bacterial bloodstream infections and cytokine release syndrome, and biomarker kinetics to differentiate them after CAR-T cell immunotherapy

**Sai Kit Ng[1,2]; Patrick W Flaherty[2]; Melissa Ancheta[2]; Hu Xie, MS[3]; Wendy M Leisenring, ScD[3]; Jordan Gauthier, MD, MSc[4,5]; Emily C Liang, MD[4,5]; and Joshua A Hill, MD[2,4]**

[1]University of Washington School of Medicine, Seattle, WA; [2]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, WA; [3]Biostatistics, Bioinformatics, and Epidemiology Program, Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA; [4]Department of Medicine, University of Washington, Seattle, WA; [5]Fred Hutchinson Cancer Center, Seattle, WA

## BACKGROUND

Cytokine release syndrome (CRS) is frequent after chimeric antigen receptor-modified (CAR)-T-cell immunotherapy (CTI), often leading to unnecessary antibiotic use due to symptom overlap with bacterial bloodstream infections (BSI).

We aim to describe the incidence and kinetics of CRS and BSI following CTI and hypothesize that plasma biomarkers may distinguish them.

## METHODS

- Retrospective cohort study for patients with lymphoma, leukemia, and myeloma receiving CTI at Fred Hutch from July 2013 to April 2024.
- Assessed six clinically available biomarkers related to inflammation and disease burden:
  1. C-reactive protein (CRP)
  2. Interleukin-6 (IL-6)
  3. Ferritin
  4. Fibrinogen
  5. Lactate Dehydrogenase (LDH)
  6. D-dimer
- Cumulative incidence curves of CRS and BSI within 30 days post-CTI were created, treating death as a competing risk.
- Scatter plots show biomarker kinetics during the time period spanning CRS and BSI onset using LOESS smoothing curves.

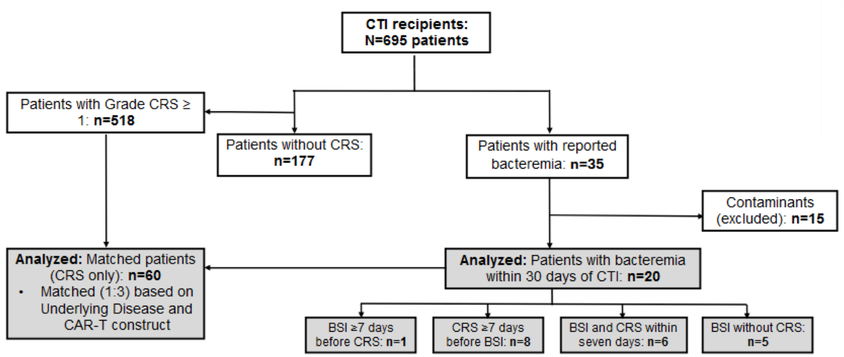


**Figure 1. Study Cohort.**

## RESULTS

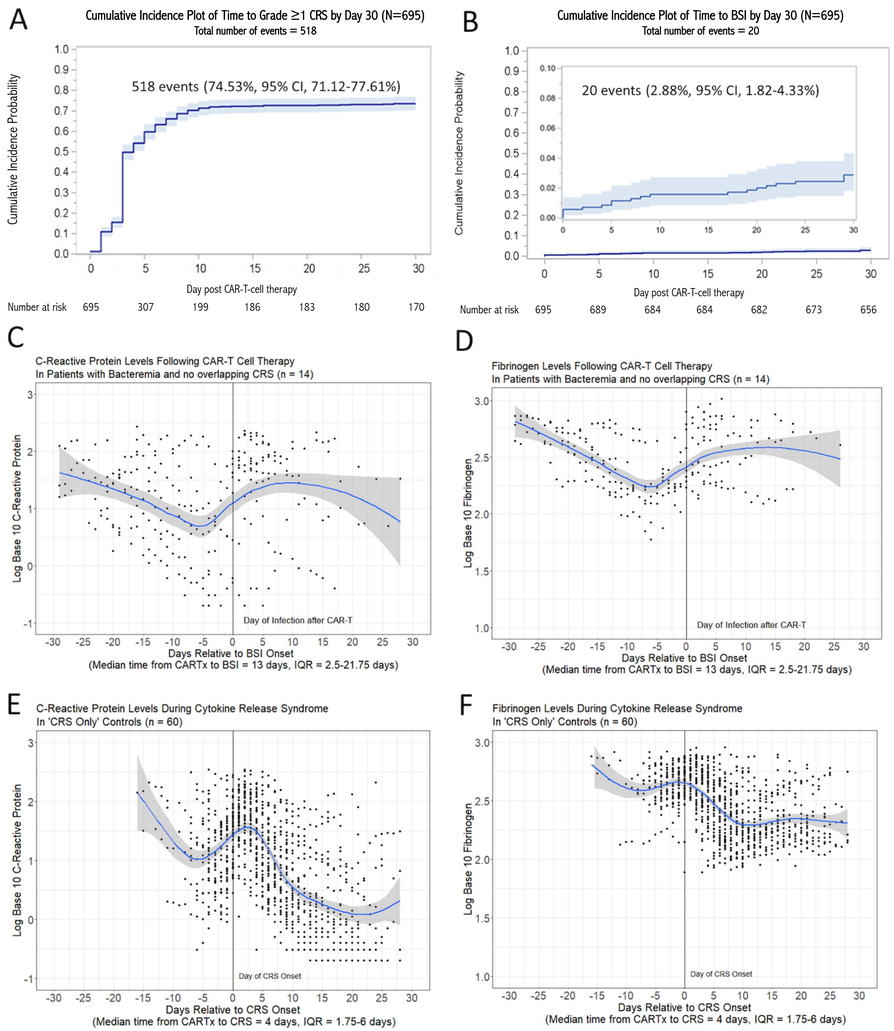


**Figure 2. Cumulative incidence of CRS and BSI; and CRP and fibrinogen kinetics in the BSI and CRS only cohorts.**
**A-B.** Cumulative incidence estimates of time to CRS and BSI by day 30 post-CTI, respectively, treating death as a competing risk. **C-D.** LOESS curves of CRP (mg/L, $\log_{10}$ transformed) and fibrinogen levels (mg/dL, $\log_{10}$ transformed) over time relative to BSI onset. **E-F.** LOESS curves of CRP (mg/L, $\log_{10}$ transformed) and fibrinogen levels (mg/dL, $\log_{10}$ transformed) over time relative to CRS onset.

## DISCUSSION

- Among 695 CTI recipients, 518 (75%; 95% CI, 71-78%; **Fig. 2A**) developed CRS within 30 days of CTI.
- Twenty patients (2.9%; 95% CI, 1.8-4.3%; **Fig. 2B**) developed BSI, 15 of whom also had CRS.
- All 60 matched controls with CRS but no BSI were admitted to the hospital with fever related to CRS, and 92% received empiric antibiotics for a median of seven days (IQR, 5-9; range, 3-20).
- In biomarker analyses of BSI events occurring ≥7 days from CRS (n=1 pre-CRS, n=8 post-CRS) or without CRS (n=5), we observed increases in CRP and fibrinogen levels beginning up to 5 days prior to infection diagnosis (**Fig. 2C, 2D**).
- Controls showed elevation of CRP associated with CRS without subsequent elevation and decreasing fibrinogen levels (**Fig. 2E, 2F**).

**Future Directions**

- Synthesize and further analyze biomarker kinetic data.
- Determine absolute biomarker levels and statistical analyses of bacterial BSI patients vs CRS controls.

## CONCLUSIONS

- Most CTI recipients develop CRS prompting empiric antibiotics for a median of 7 days, but BSI is rare.
- Recurrent elevation of CRP levels after CRS suggests BSI and should be further investigated prospectively for its utility in early diagnosis and targeted therapy.
- Increasing fibrinogen levels may also identify patients with BSI and no CRS.
- Clinical monitoring of stable patients without empiric antibiotics or earlier antibiotic discontinuation, in conjunction with fibrinogen and CRP monitoring, may reduce antibiotic overutilization after CTI to improve outcomes.

## ACKNOWLEDGEMENTS

My thanks to the Hill Group at the Fred Hutch Cancer Center for their mentorship and guidance.