META-ANALYSIS

Risk of infection in patients with hematological malignancies receiving CAR T-cell therapy: systematic review and meta-analysis

Gülçin Telli Dizman a, José María Aguado b,c,d and Mario Fernández-Ruiz b,c,d

aDepartment of Infectious Disease and Clinical Microbiology, Hacettepe University School of Medicine, Ankara, Turkey; bUnit of Infectious Diseases, Hospital Universitario “12 de Octubre”, Instituto de Investigación Sanitaria Hospital “12 de Octubre” (isma12), Madrid, Spain; cCentro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFECC), Instituto de Salud Carlos III (ISCIII), Madrid, Spain; dDepartment of Medicine, School of Medicine, Universidad Complutense, Madrid, Spain

ABSTRACT

Background: Chimeric antigen receptor (CAR) T-cell therapy has emerged as a promising treatment option for relapsed or refractory B-cell malignancies and multiple myeloma. Underlying and treatment-related variables may contribute to the development of infectious complications.

Research design and methods: We conducted a systematic review and meta-analysis on the incidence of overall and severe (grade ≥3) infection in patients with hematological malignancies receiving CAR T-cells. Secondary outcomes included the specific rates of bacterial, viral and invasive fungal infection (IFI), and infection-related mortality. PubMed, Embase and Web of Science databases were searched from inception to 27 May 2022. Sensitivity analysis were performed according to the type of malignancy and study design (randomized clinical trials [RCTs] or observational studies).

Results: Forty-five studies (34 RCTs) comprising 3,591 patients were included. The pooled incidence rates of overall and severe infection were 33.8% (I² = 96.31%) and 16.2% (I² = 74.41%). The respiratory tract was the most common site of infection. Most events were bacterial or viral, whereas the occurrence of IFI was rare. The pooled attributable mortality was 1.8% (I² = 43.44%).

Conclusions: Infection is a frequent adverse event in patients receiving CAR T-cell therapy. Further research should address specific risk factors in this population.

1. Introduction

As cancer incidence and mortality are rapidly increasing worldwide, about 1.2 million of cases of hematological malignancies are diagnosed every year (accounting for ≈7% of newly diagnosed cancers) [1,2]. Developments in oncological treatment over the past few decades, however, have led to a significant improvement in survival rates [3]. Chimeric antigen receptor (CAR) T-cell therapy constitutes an emerging adoptive immunotherapy that has achieved a significant success in hematological cancer patients and, particularly, those with relapsed or refractory (r/r) B-cell malignancies and multiple myeloma (MM) [4].

Autologous T-cells are collected from the peripheral blood by leukapheresis and engineered in vitro to express artificial receptors targeted to specific tumor antigens, such as CD19 or B-cell maturation antigen (BCMA) [5]. Following in vitro expansion and infusion, redirected CAR T-cells target and kill tumor cells with high specificity. CARs are fusion proteins that comprise the extracellular antigen-binding component of a monoclonal antibody, various hinge and transmembrane domains, and the intracellular signaling domains of one or more T-cell receptors [6]. Depending on the structure of this latter component, CAR T-cells are categorized into distinct generations with different antitumor activity [7]. Second- and third-generation CARs contain additional co-stimulatory domains that enhance T-cell activation and proliferation [6,8-10]. Fourth-generation CARs comprise transgenes for cytokine release and co-stimulatory ligands that recruit innate immunity and increase the resistance of CAR T-cells to the immunosuppressive tumor microenvironment [9-11].

Unlike hematological malignancies, solid cancers do not often express one tumor-specific marker, which would markedly increase the risk of on-target off-tumor toxicity. Additional difficulties lie in the difficulty of T-cell trafficking into solid tumor tissues due to the stromal barriers, tumor microenvironment, and tumor-induced T-cell exhaustion. Therefore, the clinical development of CAR T-cell therapy is far more advanced for hematological malignancies – such as large B-cell lymphoma, acute lymphoblastic leukemia (ALL) or MM – than for solid cancers [12-14].

Six CAR T-cell therapies have been approved by the Food and Drug Administration (FDA) since 2017: tisagenlecleucel (Kymriah®), axicabtagene ciloleucel (Yescarta®), brexucabtagene autoleucel (Tecartus®), lisocabtagene maraleucel (Breyanzi®), idecabtagene vicleucel (Abecma®) and ciltaucabtagene autoleucel (Carvykti®). The first four products are directed against CD19 and approved for r/r B-cell malignancies after the failure of previous treatments, such as diffuse
Article highlights

- No previous meta-analyses analyzing the safety of CAR T-cell therapy in patients with hematological malignancies have been specifically focused on the incidence of and risk factors for infection in this at-risk population.
- In the present systematic review and meta-analysis (45 studies with 3,391 patients) the pooled incidence rates for overall and severe infection were high (33.8% and 16.2%, respectively), although moderate-to-high heterogeneity was observed for all outcomes.
- Upper respiratory tract infection, pneumonia and sepsis or bloodstream infection were the most commonly reported sites. The pooled estimate for infection-related mortality was low (1.8%).
- Most of the included studies did not provide granular data regarding the site of infection and causative agent, or whether the patient was receiving or not prophylaxis. The occurrence of IFI, however, was rarely reported.
- Prior HSCT, the number of previous lines of chemotherapy, the presence of baseline neutropenia, the severity of cytokine release syndrome and the requirement of anti-IL-6 agents and corticosteroids were identified in the few studies that assessed the risk factors for infection after CAR T-cell therapy.

large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, primary mediastinal B-cell lymphoma or B-cell precursor ALL. The BCMA-targeted idecabtagene vicleucel and ciltaacabtagene autoleucel are approved for adult patients with r/r MM despite four or more prior lines of therapy [15–21]. Beyond these established indications, CAR T-cell therapies are being evaluated for an increasing number of conditions, such as autoimmune diseases or viral infections [22,23].

The efficacy and safety of CAR T-cell therapies in patients with hematological malignancies have been evaluated in previous meta-analyses [24–29]. These works were mainly focused on clinical response rates and typical adverse events like cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS), which were well defined and reported in randomized clinical trials (RCTs). The occurrence of prolonged cytopenias, infections and different off-tumor effects are other well established complications associated to the use of CAR T-cells [30]. However, no previous systematic reviews or meta-analyses have primarily addressed the incidence and risk factors of infectious complications in hematological patients receiving this therapy.

The risk of infection related to CAR T-cell therapy results from the interplay of a number of factors, such as the immune dysfunction induced by the underlying disease, the cumulative effect of prior lines of therapy, and the lymphodepletion administered before CAR T-cell infusion [31,32]. B-cell aplasia and the resulting hypogammaglobulinemia (HGG) also act as contributing factors [33]. Finally, it should be taken into account the frequent requirement of the anti-interleukin (IL)-6 monoclonal antibody tocilizumab (TCZ) and high-dose corticosteroid boluses for the management of CRS and ICANS [32–34]. A comprehensive assessment of the disease burden posed by infection events in CAR T-cells receptors – including the typically older and heavily treated MM patients – may be useful to refine prevention strategies, including prophylaxis practices, in this specific population.

In the present systematic review and meta-analysis we aimed to offer an updated estimate of the incidence of overall and specific types of infection among patients with hematological malignancies that received CAR T-cell therapy in the setting of RCTs and observational studies. We also assessed the risk factors for the development of infectious complications and the pooled attributable mortality.

2. Materials and methods

2.1. Study methods

This systematic review and meta-analysis was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [35]. The protocol was registered in the international Prospective Register of Systematic Reviews (PROSPERO) database.

2.1.1. Eligibility criteria

We included RCTs and prospective and retrospective observational studies performed in adult patients (≥18 years) diagnosed with hematological malignancies (B-cell and MM) and treated with CAR T-cells that reported absolute and/or relative frequencies of infection. Both comparative and non-comparative studies were included. All the studies had to be published in full-text in English to be considered. Reviews, previous meta-analyses, clinical guidelines, case reports and series, editorials, animal studies and conference abstracts were excluded, as were studies lacking essential data (i.e. the overall number of included patients and the number of participants that developed infection), those conducted in the pediatric population, and those published in languages other than English. In case of partially overlapping publications, only the study with the highest number of patients was included in the analysis.

2.1.2. Search strategy

We searched PubMed (Medline), Embase and Web of Science databases by using the following combination of terms: ‘chimeric antigen receptor’ OR ‘CAR-T’ OR ‘chimeric antigen receptor-T cell therapy’ OR ‘CAR T-cell therapy’ OR ‘receptor, chimeric antigen’ OR ‘chimeric antigen receptor-modified T cell therapy’) AND (‘leukemia’ OR ‘multiple myeloma’ OR ‘lymphoma’ OR ‘hematological malignancies’) AND (‘infection’ OR ‘infectious complications’ OR ‘adverse events’ OR ‘side effects’ OR ‘reactivation’). Electronic databases were searched from inception to 27 May 2022. The references of the resulting articles were reviewed to avoid missing relevant publications. In addition, the references cited in review articles and previous meta-analyses [24–29] were manually screened for any potentially related study.

2.1.3. Data extraction

The following data were extracted from each study by two investigators (G.T.D. and M.F.R.) independently: study characteristics (first author, year of publication, sample size, median follow-up period since CAR T-cell infusion); patient characteristics (median or mean age at study entry, gender, underlying hematological malignancy, disease status, median number of previous lines of chemotherapy, previous hematopoietic stem cell transplantation (HSCT)); treatment characteristics...
(lymphodepletion regimen, CAR T-cell product and dose, use of corticosteroids and TCZ for the management of CRS and ICANS); type of antimicrobial prophylaxis administered; incidence and severity of microbiologically documented infections (overall and severe [grade ≥3] infection, bacterial infection, viral infection, invasive fungal infection [IFI]); and infection-related mortality. Data on the specific type of infection (i.e. clinical syndrome and causative agent), if provided, were also extracted. The severity of infection was established according to the applicable version of the Common Terminology Criteria for Adverse Events (CTCAE). In detail, grade 3 denotes the need of intravenous therapy or any invasive intervention, grade 4 denotes life-threatening consequences or the need of an urgent intervention, and grade 5 denotes death.

2.1.4. Methodological quality of the included studies
Cohort studies included in the meta-analysis were evaluated through the Newcastle-Ottawa Quality Assessment Scale, which uses a pre-established star-rating system (from 0 to 9) to assess the quality of non-randomized studies [36]. Studies scoring ≥5 stars were considered to be of moderate to high quality. Discrepancies regarding study eligibility, data extraction or quality assessment were resolved by consensus.

2.2. Primary and secondary outcomes
The primary outcome of this meta-analysis was the incidence rate of overall and severe (grade ≥3) infection in patients with hematological malignancies receiving CAR T-cell therapy. Secondary outcomes included the incidence rates for specific types of infection (bacterial, viral and IFI) and the infection-related mortality rate.

We performed a number of pre-specified sensitivity analyses stratified according to the type of study (RCTs versus observational studies) and the type of the underlying disease (B-cell malignancy [lymphoma and ALL] versus MM).

2.3. Statistical analysis
Statistical analysis and figures were performed with the OpenMeta [Analyst] tool. We performed a meta-analysis of proportions to estimate the pooled rates of study outcomes. Pooled incidence rates were calculated with the corresponding 95% confidence intervals (CIs). Heterogeneity was evaluated by the Cochran’s Q test (which was considered significant at a P-value <0.05) and quantified with the I² statistic. It can take values from 0% (no observed heterogeneity) to 100% (complete heterogeneity), with I² values of <25%, 25% to 75%, and >75% interpreted as representing low, moderate and high heterogeneity levels, respectively [37]. Random-effects model with the Mantel-Haenszel method was used for pooling results from primary studies in the presence of significant heterogeneity; otherwise, a fixed-effects model was applied.

3. Results
3.1. Literature search and study selection
In total, 5,687 potentially relevant citations were retrieved. After deduplication, 3,648 studies were screened. By reviewing titles and abstracts, 2,752 studies excluded and 896 full-text articles were evaluated for eligibility. Finally, after exclusion of studies performed in pediatric or mixed populations, animal studies and articles with irrelevant results, 45 eligible studies [16,18,20,21,38–78] were included. The flowchart of the study selection process is shown in Figure 1.

3.2. Study characteristics
The characteristics of the included studies and demographics and clinical features of the corresponding patient populations are detailed in Table 1. A significant proportion of the studies were RCTs (34 [75.6%]) [16,18,20,21,38–46,48–53,56–59,63,65–68,70,72,74,77], including two post-hoc analysis of RCTs [60,61]. The remaining articles were retrospective (9 [20.0%]) [54,55,64,69,71,73,75,76,78], prospective (one [2.2%]) [62] and ambispective (one [2.2%]) [47] observational cohort studies.

The 45 studies [16,18,20,21,38–78] comprised a total of 3,591 patients. The proportion of male participants ranged between 39% and 84%, their median age ranged from 31 to 73 years, the median number of lines of prior therapy at the time of CAR T-cell infusion was between two and seven, and the prevalence of prior HSCT ranged from 4.6% to 94%. Thirty-five out of 45 studies (77.8%) reported data on patients with B-cell malignancies: B-cell lymphomas in 26 (57.8%) studies [16,18,20,39–42,44,48,52–55,57,62–64,66–71,74–76], ALL in three (6.7%) studies [43,45,65], and both B-cell lymphomas and ALL in 6 (13.3%) studies [46,56,60,61,73,78]. Six (13.3%) further studies included MM patients [21,49,51,59,72,77], whereas the remaining four (8.9%) recruited mixed populations (Hodgkin’s lymphoma [38], MM and B-cell lymphoma [47], AML and MM [50], and Hodgkin’s and non-Hodgkin’s lymphoma [58]). Two (4.4%) studies [60,61] were specifically aimed at analyzing the incidence of hepatitis B virus (HBV) reactivation in patients with chronic or resolved HBV infection.

Out of the 42 evaluable studies that provided individual data on the type of product used, 28 (66.6%) administered anti-CD19 CAR T-cells [16,18,20,39,41–44,46–48,52,53,55,60–62,64–67,69–71,73,74,76,78]. Five (11.9%) studies explored infections following BCMA-targeted CAR T-cells [21,49,59,72,77] (in detail, ciltacabtagene autoleucel [21] and idecabtagene vicleucel [77] in one study each), and one (2.4%) single study reported data following both anti-CD19 and anti-BCMA CAR T-cell therapies [51]. Anti-CD19/20, anti-CD19/22, and anti-CD30 CAR T-cell therapies were used in two (4.8%) [40,68], three (7.1%) [45,57,63] and two (4.8%) studies [38,58], respectively. The product administered was axicabtagene ciloleucel in seven (16.6%) studies [16,39,42,47,53,66,76], tsigagenecleucel in two (4.8%) [20,48], lisocabtagene maraleucel in one (2.4%) [41], and fourth-generation CAR T-cells in one (2.4%) further study [58]. The most commonly used lymphodepletion regimen was the combination of fludarabine and cyclophosphamide (FluCy).
3.3. Antimicrobial prophylaxis

Details on the antimicrobial prophylaxis regimens used, if available, are shown in Table 2. In five (11.1%) studies [18,20,39,42,48] it was only stated that patients received prophylaxis according to national or international guidelines or standard institutional practices. Nine out of the remaining 41 (21.9%) studies [21,46,54,56,64,65,69,71,73] provided information on the antibacterial prophylaxis administered: fluoroquinolones – particularly levofloxacin – was given during the period of neutropenia in 5 (12.2%) studies [21,46,64,69,71] and rifaximin in one (2.4%) [73], whereas the lack of antibacterial prophylaxis was specifically stated in three (7.3%) studies [54,56,65]. Intravenous immunoglobulin (IVig) replacement therapy was administered in case of severe IgG HGG in three (6.7%) studies [66,76,77]. Fifteen (33.3%) studies [21,38,44,46,54,56,60,64,65,69,71,73,75-77] described the regimen of antiviral prophylaxis administered. Patients received no prophylaxis in two (13.3%) of these studies [54,56], whereas acyclovir or valacyclovir was administered from the lymphodepletion to the recovery of CD4 + T-cell counts or for at least 3 to 12 months following CAR T-cell infusion in 10 (66.7%) studies [21,44,46,64,65,69,71,73,75,76]. In addition, prophylaxis for hepatitis B reactivation was given according to the serological status in four (26.7%) studies [38,60,64,77]. Fluconazole was administered as an antifungal prophylaxis during the period of neutropenia in 8 out of 12 studies (66.7%) providing information [21,44,46,64,69,71,73,76], micafungin was preferred in one (8.3%) [65], and no prophylaxis was given in the remaining three (25.0%) evaluable studies [54,56,77]. Finally, *Pneumocystis jirovecii* prophylaxis was given in 10 out of 11 (90.9%) studies providing specific information [21,44,46,64,65,73,75-77], usually based on trimethoprim/sulfamethoxazole for at least 6 months or until the CD4 T-cell count was above 200 cells/µL.

3.4. Infectious complications

The incidence rates of primary (overall and severe infection) and secondary outcomes (bacterial infection, viral infection and IFI) across included studies are shown in Table 2.
Table 1. Characteristics of included studies and patient populations.

| Study, year | Type       | N   | Age, years* | Male gender [n (%)] | Underlying disease | Disease status [n (%)] | Prior lines of therapy [n (%)] | Prior HSCT [n (%)] | LD regimen | CAR T-cell product | CAR T-cell dose | Follow-up* |
|-------------|------------|-----|-------------|---------------------|--------------------|------------------------|-------------------------------|--------------------|------------|---------------------|----------------|------------|
| Neelapu, et al. 2017 [16] | Phase 2 RCT | 101 | 58 (23–76) | 68 (67)             | R/R LCLB             | St. 1–2: 13 (15)       | ≥3 lines: 70 (69)                   | Auto-HSCT: 21 (21) | FluCy     | Axi-cel             | 2 x 10^6 cells/Kg                    | 8.7 mo     |
| Wang, et al. 2020 [18] | Phase 2 RCT | 68  | 65 (38–79)  | 57 (84)             | R/R MCL             | St. 4: 58 (85)          | ≥3 lines: 50 (81)                     | Auto-HSCT: 29 (43) | FluCy     | KTE-X19             | 2 x 10^6 cells/Kg                    | 12.3 mo (7.0–32.3) |
| Schuster, et al. 2019 [20] | Phase 2 RCT | 111 | 56 (22–76)  | NR                  | R/R DLBCL           | St. 1: 8 (7)            | ≥3 lines: 57 (51)                     | Auto-HSCT: 54 (49) | FluCy/Benda | Tisa-cel           | 3 (0.1–6) x 10^8 cells                 | 28.6 mo    |
| Berdeja, et al. 2021 [21] | Phase 1b/2 RCT | 97  | 61 (56–68)  | 57 (59)             | R/R MM              | St. 1: 61 (63)          | 6 (4–8)                          | Auto-HSCT: 87 (90) | FluCy     | Clita-cel          | 0.75 (0.5–1.0) x 10^6 cells/Kg         | 12.4 mo (IQR: 10.6–15.2) |
| Ramos, et al. 2020 [38] | Phase 1/2 RCT | 42  | 35 (17–69)  | 28 (67)             | R/R HL              | St. 1–2: 14 (33)       | 7 (2–23)                         | Auto-HSCT: 32 (76) | FluCy/Benda | Anti-CD30 | 2 x 10^6–2 x 10^8 cells/m^2 | 533 d |
| Locke, et al. 2019 [39] | Phase 1/2 RCT | 108 | <60 y: 59 (IQR: 34–69) | R/R DLBCL          | St. 1–2: 3 (43)      | [phase 1]: 15 (15) [phase 2]: 6 (86) [phase 1]: 8 (85) [phase 2]: 6 (86) | ≥3 lines: 22 (79)                     | Auto-HSCT: 3 (11) | FluCy     | Axi-cel             | Target dose of 2 x 10^6 cells/Kg             | 27.1 mo    |
| Tong, et al. 2020 [40] | Phase 1/2a RCT | 28  | <60 y: 21; ≥60 y: 7 | R/R DLBCL          | St. 1–2: 5 (18)      | [phase 1]: 23 (82)     | ≥3 lines: 139 (52)                    | Auto-HSCT: 9 (33) | FluCy     | Liso-cel          | 50 x 10^6–150 x 10^6 cells               | 18.8 mo (95% CI: 15.0–19.3) |
| Abramson, et al. 2020 [41] | RCT        | 269 | 63 (54–70)  | 174 (65)            | R/R DLBCL           | NR                      | ≥3 lines: 139 (52)                    | Auto-HSCT: 9 (33) | FluCy     | Axi-cel             | 2 x 10^6 cells/Kg                  | 24.9 mo    |
| Locke, et al. 2022 [42] | Phase 3 RCT | 359 | 58 (21–71)  | 237 (66)            | R/R DLBCL           | St. 1–2: 74 (21)       | ≥3 lines: 26 (47)                     | Auto-HSCT: 23 (42) | FluCy     | KTE-X19             | 1 x 10^6 cells/Kg                    | 16.4 mo (IQR: 13.8–19.6) |
| Shah, et al. 2021 [43] | Phase 1/2 RCT | 55  | 40 (IQR: 28–52) | R/R B-ALL          | NR                   | St. 3–4: 285 (79)      | ≥3 lines: 26 (47)                     | Auto-HSCT: 23 (42) | FluCy     | KTE-X19             | 1 x 10^6 cells/Kg                    | 16.4 mo (IQR: 13.8–19.6) |
| Cappell, et al. 2020 [44] | Phase 1 RCT | 43  | 54 (26–68)  | 33 (77)             | R/R DLBCL           | St. 3–4: 33 (77)       | 4 (1–12)                          | Auto-HSCT: 13 (30) | FluCy     | FMC63-28Z            | 2 x 10^6 cells/Kg                    | 27.1 mo    |
| Hu, et al. 2021 [45] | Phase 1 RCT | 6   | 49 (26–56)  | NR                  | R/R B-ALL           | NR                      | 5 (2–8)                           | FluCy/ALE         | FluCy/ALE | CTA101             | 1–3 x 10^6 cells/Kg                  | 4.3 mo |

(Continued)
| Study, year          | Type               | N    | Age, years (n [%]) | Male gender [n (%)] | Underlying disease | Disease status [n (%)] | Prior lines of therapy [n (%)] | Prior HSCT [n (%)] | LD regimen | CAR T-cell product | CAR T-cell dose | Follow-up [d (total)] |
|---------------------|--------------------|------|-------------------|---------------------|--------------------|------------------------|-------------------------------|-------------------|------------|---------------------|-----------------|---------------------|
| Hill, et al. 2018   | Phase 1/2 RCT      | 133  | 54 (20–73)        | 93 (69.9)           | R/R ALL, CLL or NHL | NR                     | 4 (1–11)                      | Auto-HSCT: 25 (18.8) | FluCy: 104 (78) | Anti-CD19           | 2 x 10^5–2 x 10^7 cells/Kg | 90 d (total)      |
| Azoulay, et al. 2021| Observational in patients requiring ICU admission | 241  | 58 (43–66)        | 97 (40)             | B-lymphoma, FL, ALL, MM | NR                     | 3 (2–4)                      | Auto-HSCT: 42 (17) | FluCy: 231 (96) | NR                  | NR              | 95 d (IQR: 93–97)   |
| Schuster, et al. 2021| Phase 2 RCT       | 115  | 56 (46–64)        | NR                  | R/R LBCL            | St: 1: 9 (8)           | St: 2: 13 (69)                | Auto-HSCT: 56 (49) | FluCy/Benda: 107 (93) | Tisa-cel           | 0.1 x 10^6–6 x 10^6 cells/Kg | 40.3 mo (IQR: 37.8–43.8) |
| Wang, et al. 2021   | Phase 1 RCT        | 18   | 53.5 (38–66)      | 10 (55.6)           | R/R MM              | St: 1: 10 (55.6)       | St: 2: 8 (44.4)               | Auto-HSCT: 6 (33.3) | FluCy     | CT103A (anti-BCMA) | 1, 3 and 6 x 10^6 cells/Kg | NR                |
| Baumeister, et al. 2019 | Phase 1 RCT      | 12   | 70 (44–79)        | 9 (75)              | AML/MDS R/R MM      | NR                     | AML: 1 (0–4) MM: all ≥5 lines | MM: 5 (100) | NR                  | NKG2D-CAR T-cells | 1 x 10^6–3 x 10^7 cells/Kg | 3 mo (total)     |
| Yan, et al. 2019    | Phase 2 RCT       | 21   | 58 (49.5–61)      | 10 (48)             | R/R MM              | St: 2: 13 (69) St: 3: 4 (19) Missing: 4 (19) | 6 (5–8)                      | Auto-HSCT: 3 (14) | FluCy     | Humanized anti-CD19 and anti-BCMA | 1 x 10^6 cells/Kg | 179 d (IQR: 72–295) |
| Zhou, et al. 2020   | Phase 1 RCT       | 21   | <60 y: 11; ≥60 y: 10 | 13 (62)             | R/R B-cell NHL      | St: 2: 1 (5) St: 3: 3 (24) St: 4: 15 (71) | 1–5 lines: 16 (76) 6–10 lines: 5 (24) | Auto-HSCT: 5 (23.8) | FluCy     | 4SCAR19 (anti-CD19) | 8.9 x 10^5 cells/kg | 13.7 mo (0.7–23.8) |
| Jacobson, et al. 2022 | Phase 2 RCT      | 148  | 61 (53–68)        | 84 (57)             | Indolent NHL (FL or MZL) | St: 1–2: 20 (14) St: 2: 48 (32) St: 4: 80 (54) | 3 (2–4)                      | Auto-HSCT: 33 (22) | FluCy     | Axi-cel            | 2 x 10^6 cells/Kg | 17.5 mo (IQR: 14.1–22.6) |
| Gaut, et al. 2021   | Observational     | 22   | 65 (57–68)        | 12 (54.6)           | R/R DBCL            | NR                     | ≥3 lines: 13 (59.1)            | Auto-HSCT: 1 (4.6) | FluCy     | NR                | NR              | 30 d (total)        |
| Zettler, et al. 2021| Observational     | 804  | 62 (18–90)        | 476 (59)            | LCBL                | NR                     | NR                            | NR                | NR                  | Axi-cel and Tisa-cel | NR                |
| Wittmann et al. 2021| Phase 1b/2 RCT    | 52   | 45.9 (25.9–70.6)  | 34 (65.4)           | R/R B-cell (NHL, ALL) | NR                     | ≥3 lines: 39 (75)             | Auto-HSCT: 11 (21.2) | FluCy     | NR                | NR              | 30 d for early events/60 d for late events |
| Wu, et al. 2021     | RCT               | 13   | 42 (23–65)        | 6 (46.2)            | CNSL                | NR                     | NR                            | FluCy/THIO, BEAM | Tandem anti-CD19/22 | Median: 4.1 (2.6–8.4) and 4.3 (2.0–9.2) x 10^6 cells/Kg | 14.2 mo (1.4–24.2) |

(Continued)
| Study, year | Type | N | Age, years* | Male gender [n (%)] | Underlying disease | Disease status [n (%)] | Prior lines of therapy [n (%)]b | Prior HSCT [n (%)] | LD regimen | CAR T-cell product | CAR T-cell dose | Follow-up* |
|------------|------|---|-------------|---------------------|------------------|-----------------------|------------------------|----------------|------------|-----------------|----------------|----------|
| Ramos, et al. 2017 [58] | Phase 1 RCT | 9 | 31 (20–65) | 6 (66.7) | EBV-CD30+ lymphoid malignancy | NR | ≥3 lines: 9 (100) | NR | NR | Anti-CD30 | 0.2 x 10^6–2 x 10^6 cells/m² | 12 (total) |
| Li, et al. 2021 [59] | Phase 1 RCT | 30 | 55 (34–65) | 17 (56.7) | R/R MM and PCL | St. 1: 10 (35.7) St. 2: 10 (35.7) St. 3: 8 (28.6) | 4 (3.11) | Auto-HSCT: 11 (36.7) | FluCy | Anti-BCMA | 11.2 x 10⁶ cells/Kg | 385 d |
| Cui, et al. 2021 [60] | Post-hoc analysis of RCT in patients with chronic HBV infection | 20 | 51 (25–75) | 12 (60) | R/R DLCBL or B-ALL | NR | NR | NR | FluCy | Humanized anti-CD19 B-ALL: 1.5 x 10⁶ cells/Kg DLCBL: 4 x 10⁶ cells/Kg | 10 mo |
| Li, et al. 2021 [61] | Post-hoc analysis of phase 1/2 RCT with resolved HBV infection | 30 | 59 (14–81) | 17 (57) | R/R B-cell malignancy | NR | NR | Auto-HSCT: 3 (10) | FluCy | Anti-CD19 | 1–3 x 10⁶ cells/Kg | 12 mo (2–37) |
| Li, et al. 2019 [62] | Observational (comparative group of auto-HSCT recipients) | 56 | 62 (27–70) | 17 (58.6) | R/R B-NHL | St. 3: 5 (17.2) St. 4: 24 (82.8) | ≥3 lines: 17 (58.6) | Auto-HSCT: 4 (13.8) | FluCy | Anti-CD19 | 5 x 10⁶–10 x 10⁶ cells/Kg | 5.2 mo (0–12) |
| Zeng, et al. 2020 [63] | RCT | 14 | 47.5 (28–66) | 9 (64.3) | R/R B-cell NHL | St. 3–4: 14 (100) | 4.5 (2–6) | ≥3 lines: 12 (85.7) | Auto-HSCT: 3 (21.4) | FluCy | Sequential anti-CD22 and anti-CD19 | NR | 10.7 mo (0.7–21.6) |
| Wudhikarn, et al. 2020 [64] | Observational | 60 | 63 (19.5–85.9) | 42 (70) | R/R DLCBL | St. 1–2: 14 (23.3) St. 3–4: 38 (63.3) | 3 (2–9) | Auto-HSCT: 5 (8.3) | FluCy, FluCy/Benda | Axi-cel: 43 (71.7), tisa- cel: 17 (28.3) | NR | NR |
| Park, et al. 2018 [65] | Phase 1 RCT | 53 | 45 (30–74) | 39 (74) | R/R B-ALL | NR | 3 (2–7) | FluCy | Axi-cel | 1 x 10⁶ and 3 x 10⁶ cells/Kg | 180 d (total) |
| Kochenderfer, et al. 2017 [66] | RCT | 7 | 43 (38–64) | 3 (42.9) | R/R DLCBL | NR | ≥3 lines: 6 (85.7) | Auto-HSCT: 1 (14.3) | FluCy | Anti-CD19 | 1 x 10⁶–5 x 10⁶ cells/Kg | NR |
| Zhang, et al. 2022 [67] | RCT | 31 | 73 (65–86) | 16 (51.6) | R/R DLCBL | St. 1–2: 5 (16.1) St. 3–4: 26 (83.9) | ≥5 lines: 24 (77.4) | NR | FluCy | Anti-CD19 | 2 x 10⁶ cells/Kg | NR |
| Zhang, et al. 2022 [68] | Phase 1/2 RCT | 87 | <60 y: 71; ≥60 y: 16 | 41 (47.1) | R/R DLCBL | St. 1–2: 13 (15) St. 3–4: 74 (85.2) | ≥3 lines: 51 (58.6) | Auto-HSCT: 12 (14) | FluCy | TanCAR7 (tandem anti-CD19 /CD20) | 0.5–8 x 10⁶ cells/Kg | 27.7 mo |
| Beyar-Katz, et al. 2022 [69] | Observational | 60 | 69.3 (19.8–85.2) | 31 (52) | R/R DLCBL | NR | 2 (2–8) | Auto-HSCT: 13 (22) | FluCy | Axi-cel and tisa-cel | NR | NR |

(Continued)
| Study, year | Type      | N  | Age, years* | Male gender [n [%]] | Underlying disease | Disease status [n [%]] | Prior lines of therapy [%] | Prior HSCT [%] | LD regimen | CAR T-cell product | CAR T-cell dose | Follow-up [mo] |
|------------|-----------|----|-------------|---------------------|--------------------|------------------------|---------------------------|----------------|------------|---------------------|----------------|---------------|
| Ortiz-     | RCT      | 9  | 58 (47–74)  | 5 (56)              | CLL<sup>a</sup>    | NR                    | 4 (3–6)                   | FluCy          | St: 56     | ARI-0001            | 0.4–0.5 × 10<sup>6</sup>, 1 x 10<sup>6</sup>, 5 × 10<sup>6</sup> cells/Kg | NR            |
| McKndonado, et al. 2022 | [70] |     |            |                     |                    |                        |                           |                |            | CART19 (anti-CD19) |                |               |
| Thakkar, et al. 2021 | [71] | 19 | 61 (49–84)  | 10 (53)             | R/R DLCBL          | NR                    | 3 (1–9)                   | Auto-HSCT     | St: 1–2 | Anti-CD19          | NR             | 30 d –2 y (total) |
| Cornell, et al. 2021 | [72] | 14 | 56 (47–71)  | 10 (59)             | R/R MM              | St: 1–2: 7 (41)       | ≥3 lines: 7/14 (50)      | FluCy          | St: 3: 4 | KITE-585 (anti-BCMA) | 3 × 10<sup>7</sup> cells/Kg | 12.0 mo (total) |
| Korell, et al. 2021 | [73] | 60 | 56 [20–74]  | 40 (66.6)           | R/R ALL or B-NHL   | NR                    | 5 (2–10)                  | FluCy          |              | Axi-cel, tisacel and HD-CAR-1 | Axi-cel: 0.4–2 × 10<sup>6</sup> cells/Kg | NR            |
| Huang, et al. 2020 | [74] | 11 | 49 (29–69)  | 8 (72.7)            | R/R LCBL, MCL      | St: 3–4: 9 (81.8)    | 3 (2–6)                   | FluCy          |              | Anti-CD19          | 1.8–3 × 10<sup>6</sup> cells/Kg | 253 d (130–1,017) |
| Logue, et al. 2021 | [75] | 85/70 | 64 (28–79) / 63 (28–79) | 51 (60)/61.4 (70) | R/R B-cell lymphoma | St: 1–2: 18 (21.2)/17 (24.3) | 3 (1–8)/3 (1–7) | Auto-HSCT | St: 3–4: 67 (78.8)/53 (75.7) | FluCy | Anti-cel | 12.8 mo (0.8–42.4) |
| Baird, et al. 2021 | [76] | 41 | 56 [21–76]  | 24 (58.5)           | R/R LCBL           | St: 1–2: 9 (22)       | 3 (2–4)                   | Auto-HSCT | St: 3–4: 32 (78) | FluCy | Axi-cel | 2 x 10<sup>6</sup> cells/Kg | 19.8 mo (at least 12 mo) |
| Munshi, et al. 2021 | [77] | 128 | 61 (33–78)  | 76 (59)             | R/R MM              | NR                    | 6 (3–16)                  | FluCy          |              | Auto-HSCT          | 1.5 x 10<sup>6</sup>, 300 × 10<sup>6</sup> or 450 × 10<sup>6</sup> cells/Kg | At least 24 mo |
| Cordeiro, et al. 2020 | [78] | 86 | 57 (23–75)  | 63 (73)             | R/R ALL, NHL or CLL | NR                    | 4 (1–8)                   | FluCy          |              | Anti-CD19          | 2 x 10<sup>5</sup>–2 × 10<sup>7</sup> cells/Kg | 28.1 mo (12.5–62.6) |

A: All; ALL: acute lymphoblastic leukemia; allo-HSCT: autologous hematopoietic stem cell transplantation; auto-HSCT: autologous hematopoietic stem cell transplantation; axi-cel: axicabtagene ciloleucel; BCMA: B-cell maturation antigen; BEAM: carmustine, etoposide, cytarabine and melphalan; benda: bendamustine; CAR T-cell: chimeric antigen receptor T-cell; CLL: chronic lymphocytic leukemia; CNSL: central nervous system lymphoma; d: day; DLCBL: diffuse large B-cell lymphoma; EBV: Epstein-Barr virus; FL: follicular lymphoma; FluCy: fludarabine and cyclophosphamide; HBV: hepatitis B virus; ICU: intensive care unit; ide-cel: idecabtagene vicugene; IQR: interquartile range; LD: lymphodepletion; MCL: mantle-cell lymphoma; MDS: myelodysplastic syndrome; MM: multiple myeloma; mo: month; MZL: marginal zone lymphoma; NHL: non-Hodgkin lymphoma; NR: not reported; RCT: randomized clinical trial; R/R: relapsed or refractory; St: stage; tisacel: tisagenlecleucel; THIO: thiopeta.

<sup>a</sup>Median and range are shown, unless otherwise noted.
<sup>×</sup>Median and range values or absolute and relative frequencies [n [%]] are shown, unless otherwise noted.
<sup>b</sup>If the patient weighed ≥100 Kg, a fixed dose of 2 × 10<sup>6</sup> CAR T-cells was administered.
<sup>c</sup>Phase 3 trial, with 180 patients assigned to receive axicabtagene ciloleucel and 179 to receive standard care.
<sup>d</sup>Six patients developed concomitant Richter's syndrome.
<sup>e</sup>Analysis up to 30 days/after 30 days from CAR T-cell infusion.
Table 2. Details on antibacterial prophylaxis regimens used.

| Study, year | Antibacterial prophylaxis | Antiviral prophylaxis | Antifungal prophylaxis | Anti-PCP prophylaxis |
|-------------|---------------------------|-----------------------|------------------------|---------------------|
| Neelapu, et al. 2017 [16] | NR | NR | NR | NR |
| Wang, et al. 2020 [18] | Not mandatory as per study protocol | As per NCCN guidelines or standard institutional practice | NCCN guidelines or standard institutional practice | NCCN guidelines or standard institutional practice |
| Schuster, et al. 2019 [20] | As per local guidelines dictated by the preceding lymphodepletion | As per local guidelines dictated by the preceding lymphodepletion | As per local guidelines dictated by the preceding lymphodepletion | As per local guidelines dictated by the preceding lymphodepletion |
| Berdeja, et al. 2021 [21] | Levofloxacin (500 mg PO or IV daily) or equivalent from neutropenia onset to resolution/cefpodoxime (200 mg PO twice a day) | Acyclovir (400–800 mg PO twice a day) or valacyclovir (500 mg PO twice a day) from day 1, for at least 12 months after CAR T-cell infusion | Fluconazole (400 mg PO or IV daily) from neutropenia onset to resolution/alternatives: caspofungin or micafungin | TMP-SMX (1 DS tablet PO daily) from day 1 to 6 months after infusion or until CD4 T-cell count recovered to ≥200 cells/µL/alternatives: aerosolized pentamidine, dapsone or atovaquone |
| Ramos, et al. 2020 [38] | Anti-HBc-positive, DNA-negative patients must receive prophylaxis against HBV initiated prior to lymphodepletion | NR | NR | NR |
| Locke, et al. 2019 [39] | NR | NR | NR | NR |
| Tong, et al. 2020 [40] | NR | NR | NR | NR |
| Abramson, et al. 2020 [41] | NR | NR | NR | NR |
| Locke, et al. 2022 [42] | Prophylactic broad-spectrum antibiotics in case of prolonged neutropenia as per institutional practice | As per NCCN guidelines or standard institutional practice | NCCN guidelines or standard institutional practice | NCCN guidelines or standard institutional practice |
| Shah, et al. 2021 [43] | NR | NR | NR | NR |
| Cappell, et al. 2020 [44] | Not mandatory as per study protocol | Valacyclovir (500 mg PO daily) or acyclovir (250 mg/m² IV twice a day), for at least 6 months after CAR T-cell infusion | Fluconazole (400 mg PO or IV daily) from the end of lymphodepletion until ANC recovered ≥1,000 cells/µL | TMP-SMX (1 DS tablet PO three times a week) starting between days −5 to −8, for at least 6 months after infusion or until CD4 T-cell count recovered to ≥200 cells/µL/alternatives: aerosolized pentamidine if sulfam allergy |
| Hu, et al. 2021 [45] | NR | NR | NR | NR |
| Hill, et al. 2018 [46] | Levofloxacin (750 mg PO daily) if ANC <500 cells/µL | Acyclovir or valacyclovir for HSV- or VZV-seropositive patients starting on the day of lymphodepletion, for at least 3 months after CAR T-cell infusion | Fluconazole (400 mg PO or IV daily) if ANC <500 cells/µL | TMP-SMX starting after ANC recovery, for at least 3 months after CAR T-cell infusion |
| Azoulay, et al. 2021 [47] | NR (observational multicenter study) | NR (observational multicenter study) | NR (observational multicenter study) | NR (observational multicenter study) |
| Schuster, et al. 2021 [48] | As per local guidelines dictated by the preceding lymphodepletion | As per local guidelines dictated by the preceding lymphodepletion | As per local guidelines dictated by the preceding lymphodepletion | As per local guidelines dictated by the preceding lymphodepletion |
| Wang, et al. 2021 [49] | NR | NR | NR | NR |
| Baumeister, et al. 2019 [50] | NR | NR | NR | NR |
| Yan, et al. 2019 [51] | NR | NR | NR | NR |
| Zhou, et al. 2020 [52] | NR | NR | NR | NR |
| Jacobson, et al. 2022 [53] | NR | NR | NR | NR |
| Gaut, et al. 2021 [54] | No antibacterial prophylaxis was given | No antiviral prophylaxis was given | No antifungal prophylaxis was given | No anti-PCP prophylaxis was given |

(Continued)
Table 2. (Continued).

| Study, year | Antibacterial prophylaxis | Antiviral prophylaxis | Antifungal prophylaxis | Anti-PCP prophylaxis |
|-------------|---------------------------|-----------------------|------------------------|-----------------------|
| Zettler, et al. 2021 [55] | NR | NR | NR | NR |
| Wittmann et al. 2021 [56] | No antibacterial prophylaxis was given | No antiviral prophylaxis was given | No antifungal prophylaxis was given | TMP-SMX for the duration of CAR T-cell therapy |
| Wu, et al. 2021 [57] | NR | NR | NR | NR |
| Ramos, et al. 2017 [58] | NR | NR | NR | NR |
| Li, et al. 2021 [59] | NR | NR | NR | NR |
| Cui, et al. 2021 [60] | NR | TDF (300 mg PO daily) or ETV (0.5 mg PO daily) in HBsAg-positive or anti-HBc-positive patients | No antiviral prophylaxis was given | NR |
| Li, et al. 2021 [61] | NR | No antibacterial prophylaxis was given | NR | NR |
| Li, et al. 2019 [62] | NR | NR | NR | NR |
| Zeng, et al. 2020 [63] | Fluoroquinolone or beta-lactam in 31 patients (51.7%) | Acyclovir (400 mg PO twice daily) for at least 6 months after CAR T-cell infusion, ETV in anti-HBc-positive patients | Fluconazole (200 mg PO daily) until ANC recovery | TMP-SMX (1 DS tablet PO three times a week) or aerosolized pentamidine (300 mg monthly) for at least 3 months after CAR T-cell infusion; 55 patients (91.7%) received prophylaxis Atovaquone, dapsone, pentamidine, TMP-SMX; 46 (86.8%) patients received prophylaxis |
| Wudhikurn, et al. 2020 [64] | No antibacterial prophylaxis was given | Acyclovir, famciclovir or valacyclovir; 52 patients (98.1%) received prophylaxis | Micafungin, fluconazole, posaconazole or voriconazole; 42 (79.2%) patients received prophylaxis | |
| Park, et al. 2018 [65] | Intravenous immunoglobulins in patients with serum IgG <500 mg/dL; 3 (42.8%) patients received prophylactic immunoglobulin replacement | Acyclovir starting from lymphodepletion regimen | Fluconazole upon the development of aplasia | NR |
| Kochenderfer, et al. 2017 [66] | NR | NR | NR | NR |
| Zhang, et al. 2022 [67] | NR | NR | NR | NR |
| Zhang, et al. 2022 [68] | NR | NR | NR | NR |
| Beyar-Katz, et al. 2022 [69] | Ciprofloxacin upon the development of aplasia | Acyclovir starting from lymphodepletion regimen | Fluconazole upon the development of aplasia | NR |
| Ortiz-Maldonado, et al. 2022 [70] | NR | NR | NR | NR |
| Thakkar, et al. 2021 [71] | Levofoxacin until ANC >500 cells/µL | Valacyclovir until ANC >500 cells/µL | Fluconazole until ANC >500 cells/µL | NR |
| Cornell, et al. 2021 [72] | NR | NR | NR | NR |
| Korell, et al. 2021 [73] | Rifaximin (200 mg PO twice a day) until ANC recovery | Acyclovir (400 mg PO twice a day or 5 mg/Kg daily) until CD4 T-cell count recovery | Fluconazole (200 mg PO or IV daily) until ANC recovery, posaconazole (300 mg PO daily) if previous IFI | TMP-SMX (1 DS tablet PO three times a week) from day 0 until regeneration |
| Huang, et al. 2020 [74] | NR | NR | NR | NR |
| Study, year | Antibacterial prophylaxis | Antiviral prophylaxis | Antifungal prophylaxis | Anti-PCP prophylaxis |
|-------------|---------------------------|----------------------|------------------------|---------------------|
| Logue, et al. 2021 [75] | Fluoroquinolone starting on the day of CAR T-cell infusion (or earlier if the patient was neutropenic) until ANC recovery | Mostly acyclovir for at least 12 months after CAR T-cell infusion | Fluconazole starting on the day of CAR T-cell infusion (or earlier if the patient was neutropenic) until ANC recovery | TMP-SMX starting on day 30 after CAR T-cell infusion, for at least 6–12 months or until CD4 T-cell count recovered to ≥200 cells/µL/alternative: inhaled pentamidine, dapsone or atovaquone |
| Baird, et al. 2021 [76] | Intravenous immunoglobulins in patients with sino-pulmonary infection and serum IgG < 400 mg/dL | Acyclovir (400 mg PO three times a day) or valacyclovir (500 mg twice a day) starting with the lymphodepletion regimen, for at least 12 months after CAR-T infusion | Fluconazole (400 mg PO daily) if the patient has severe mucositis, until ANC recovery > 1,000 cells/µL | TMP-SMX (400 mg PO once daily) starting on day 28 after CAR T-cell infusion, for at least 6 months after CAR-T infusion or until CD4 T-cell count recovered to ≥200 cells/µL/alternative: atovaquone (1,500 mg PO once daily if ongoing cytopenias were present) |
| Munshi, et al. 2021 [77] | Intravenous immunoglobulins in patients with serum IgG < 400 mg/dL to maintain the IgG level > 400 mg/dL | LMV, ETV or TDF in HBsAg-positive or anti-HBc-positive patients | No antifungal prophylaxis was given | TMP-SMX (1 DS tablet PO three times a week) if CD4 T-cell count < 200 cells/µL |
| Cordeiro, et al. 2020 [78] | NR | NR | NR | NR |

ANC: absolute neutrophil count; CAR T-cell: chimeric antigen receptor T-cell; DS: double strength; ETV: etravirine; HSV: herpes simplex virus; IFI: invasive fungal infection; IV: intravenous; NCCN: National Comprehensive Cancer Network; LMV: lamivudine; NR: not reported; PCP: *Pneumocystis jirovecii* pneumonia; PO: per os; SS: single strength; TDF: tenofovir; TMP-SMX: trimethoprim-sulfamethoxazole; VZV: varicella-zoster virus.
3.4.1. Overall infection

Thirty-four (75.6%) studies \([18,20,29,42,44,46,48,49,51–59,62–67,69,71–78]\), that comprised a total of 2,767 patients, reported data for the analysis of overall infection (primary study outcome). The pooled incidence rate was 33.8% (95% CI: 25.9–41.6) with high heterogeneity \(\left(\chi^2 = 96.31\%; P\text{-value} < 0.001\right)\) (Figure 2). When the studies from Yan et al. \([51]\) and Ramos et al. \([58]\) were removed due to the very low occurrence of infection (4.8% and 5.0%, respectively), the pooled incidence rate was 39.8% (95% CI: 33.7–45.9) with a slight decrease of heterogeneity \(\left(\chi^2 = 83.73\%; P\text{-value} < 0.001\right)\).

Details on microbiologically documented episodes of infection were provided in only 28 (62.2%) studies (Table S1 in Supplementary Material).

In the sensitivity analysis according to the type of underlying disease, the pooled incidence rates of overall infection among patients with B-cell malignancies (27 studies with 2,450 patients) and MM (6 studies with 308 patients) were 34.4% (95% CI: 25.7–43.2; \(\chi^2 = 96.45\%; P\text{-value} < 0.001\)) and 35.5% (95% CI: 15.5–55.5; \(\chi^2 = 93.47\%; P\text{-value} < 0.001\)), respectively (Figure S1). In addition, pooled incidence rates were lower for RCTs (31.8%; 95% CI: 24.1–39.4; \(\chi^2 = 91.46\%; P\text{-value} < 0.001\)) than for observational studies (38.5%; 95% CI: 20.3–56.6; \(\chi^2 = 97.23\%; P\text{-value} < 0.001\)) (Figure S2).

3.4.2. Severe (grade ≥3) infection

Twenty-six (57.8%) studies \([16,18,20,21,38–43,45,48–53,56,58,66,68,70,72,75,78]\) that overall comprised 1,745 patients provided information regarding the occurrence of severe (grade ≥3) infection. The pooled incidence rate was 16.2% (95% CI: 12.7–19.6) with moderate heterogeneity \(\left(\chi^2 = 74.41\%; P\text{-value} < 0.001\right)\) (Figure 3). When the two studies reporting the lowest rates of severe infection \([38,58]\) were removed, the pooled incidence rate increased to 20.4% (95% CI: 16.3–24.5) and the heterogeneity decreased \(\left(\chi^2 = 65.93\%; P\text{-value} < 0.001\right)\). Among patients diagnosed with B-cell malignancies (20 studies, 1,574 patients) \([16,18,20,38–43,45,48,52,53,56,62,66,70,75,78]\) and MM (4 studies, 150 patients) \([21,49,51,72]\) the pooled incidence rates were 17.0% (95% CI: 13.2–20.9; \(\chi^2 = 76.16\%; P\text{-value} < 0.001\)).
**Figure 3.** Forest plot of the meta-analysis for the pooled incidence rate of severe (grade ≥3) infection.

**Figure 4.** Forest plot of the meta-analysis for the pooled incidence rate of bacterial infection (secondary study outcome).
value <0.001) and 13.8% (95% CI: 2.1–25.5; I² = 79.89%; P-value = 0.002) respectively (Figure S3).

3.4.3. Late infection
The timeframe for defining late infection varied across studies (from 28 to 90 days after infusion of CAR T-cells). One outlier study that defined late infection beyond month 6 was not included in the present subanalysis. The pooled incidence rate (8 studies, 554 patients) [20,46,49,56,65,75,77,78] was 36.0% (95% CI: 21.0–50.9), with high heterogeneity (I² = 94.21%; P-value <0.001). In half of these studies [46,56,65,75] the late infection developed beyond day 28–30.

3.4.4. Bacterial infection
Twenty-four (53.3%) studies including with 1,623 patients [39–41,44–47,50,54,58,59,63–69,71,73,76–78] reported data on the occurrence of bacterial infection (secondary outcome) with a pooled incidence of 16.3% (95% CI: 11.8–20.7) and a high degree of heterogeneity (I² = 89.23%; P-value <0.001) (Figure 4).

3.4.5. Viral infection
The pooled incidence rate of viral infection (secondary outcome) was 12.5% (95% CI: 9.2–15.8) with high heterogeneity (I² = 88.46%; P-value <0.001), according to the 32 (71.1%) evaluable studies including 1,884 patients [18,40,41,44–46,48–50,53,54,56–58,60,62,63,65–67,69,71–73,75–78] (Figure 5).

3.4.6. Invasive fungal infection
Twenty-seven (60.0%) studies comprising 1,565 patients [18,39,43–46,48,53,56,58,59,62–73,75–77] reported incidence rates of IFI (secondary outcome). The pooled incidence rate was 2.0% (95% CI: 1.1–3.0) with moderate heterogeneity (I² = 43.48%; P-value = 0.009) (Figure 6).

3.5. Risk factors for infection
The occurrence of CRS was one of the most common side effect associated to CAR T-cell therapy and it was reported in 42 (93.3%) studies [16,18,20,21,38–43,45–55,57–65,67–78]. In addition, the use of corticosteroids and TCZ use for the treatment of CRS was documented in 35 (77.8%) [16,18,20,21,38,40–43,45–54,58–65,68–71,75–77] and 36 (80.0%) studies [16,18,20,21,38,40–43,45–54,58–65,68–71,75–78], respectively (Table 3). The nature of the data available in the individual studies did not allow the meta-analysis. Prior HSCT (either autologous or allogeneic), the number of prior
lines of chemotherapy and the presence of neutropenia (absolute neutrophil count <500 cells/μL) were established as baseline risk factors (i.e. before the initiation of the lymphodepletion regimen) in two (4.4%) [46,65], three (6.7%) [46,65,76] and one (2.2%) [46] study, respectively. On the other hand, the grade of CRS and the requirement of TCZ and corticosteroids were reported as risk factors following CAR T-cell infusion in seven (15.6%) [46,64,65,69,71,75,76], four (8.9%) [46,64,75,76] and six (13.3%) studies [46,64,69,73,75,76], respectively (Table S2).

### 3.6. Site of infection

Thirty-seven studies (82.2%) provided data on the specific type of infection (clinical syndrome). In detail, rates of upper respiratory tract infection (URTI) and pneumonia were reported in 16 (35.6%) [16,18,20,21,38,39,41,46,48,50,52,53,57,59,72,75,78] and 29 (62.2%) studies [16,18,21,38–41,44–46,48,49,51–55,59,62,64,66,68,69,71,73–76,78]. The occurrence of sepsis, urinary tract infection, skin and soft tissue infection and bloodstream infection (BSI) was separately reported in 12 (26.7%) [16,18,21,39,45,48–50,55,63,69,75], 10 (22.2%) [39,46,48,52,53,64,70,71,75,76], seven (15.6%) [46,49,52,64,69,75,76] and six (13.3%) [63,65,69,71,75,76] studies, respectively (Table S3). The respiratory tract was the most common site of infection, either in form of URTI (incidence rates ranging from 0.9% to 20.0%) or pneumonia (incidence rates ranging from 2.3% to 17.6%). The development of sepsis or BSI was also common (incidence rates ranging from 0.9% to 16.7%).

### 3.7. Infection-related mortality

Thirty (66.7%) studies comprising 2,113 patients [18,21,40–43,46,47,50–53,58,60–65,67–77] provided infection-related mortality. No deaths attributable to infection were reported in nine (30.0%) of these studies [47,50–52,58,61,62,67,70]. The pooled infection-related mortality rate was 1.8% (95% CI: 1.0–2.5) with moderate heterogeneity (I² = 43.44%; P-value = 0.005) (Figure S4).

### 3.8. Study quality

Table 4 shows the quality assessment according to the Newcastle-Ottawa Scale of the 11 observational cohort studies included [47,54,55,62,64,69,71,73,75,76,78]. All studies were categorized as moderate quality with 5 or 6 stars.

### 4. Discussion

Infection constitutes a relevant adverse event related to CAR-T cell therapies, with multiple factors contributing to this complication. The present systematic review and meta-analysis comprising 3,591 patients with hematological malignancies from 45 studies revealed a pooled incidence rate for overall
Table 3. Incidence rates across included studies of primary (overall and severe infection) and secondary outcomes (bacterial infection, viral infection and IFI), CRS and use of immunosuppressive therapy.

| Study, year | Overall infection [n (%)] | Severe infection [n (%)] | Bacterial infection [n (%)] | Viral infection [n (%)] | IFI [n (%)] | CRS [n (%)] | TCZ use [n (%)] | Steroids use [n (%)] |
|-------------|---------------------------|--------------------------|-----------------------------|------------------------|------------|------------|---------------|-------------------|
| Neelapu, et al. 2017 [16] | 8 (7.9) | 8 (7.9) | 4 (3.9) | 3 (2.9) | 0 (0.0) | 94 (93) | 43 (43) | 27 (27) |
| Wang, et al. 2020 [18] | 38 (55.9) | 22 (32.4) | NR | 8 (11.8) | 0 (0.0) | 62 (91) | 40 (59) | 15 (22) |
| Schuster, et al. 2019 [20] | First 8 wks: 38/111 (54) | NR | NR | NR | NR | 64 (58) | 16 (14) | 11 (10) |
| | Beyond 8 wks: 37/96 (39) | NR | NR | NR | NR | 92 (53) | 67 (69) | 21 (22) |
| Berdeja, et al. 2021 [21] | 56 (58) | 19 (20) | NR | NR | NR | NR | NR | NR |
| Ramos, et al. 2020 [38] | NR | 2 (5) | NR | NR | NR | NR | 10 (24) | NR |
| Locke, et al. 2019 [39] | 48 (44.4) | 30 (27.8) | 25 (23.1) | 18 (16.7) | 0 (0.0) | 100 (92.6) | NR | NR |
| Tong, et al. 2020 [40] | NR | 3 (10.7) | 6 (21.4) | 18 (64.2) | NR | 14 (50.0) | 5 (17.9) | 1 (3.6) |
| Abramson, et al. 2020 | NR | 33 (12.3) | 4 (1.5) | 2 (0.7) | NR | 127 (47) | 48 (17.8) | 26 (9.7) |
| Locke, et al. 2022 [42] | Axi-cel: 74 (41) | Axi-cel: 25 (14) | NR | NR | NR | 157 (92) | 117 (65) | 43 (24) |
| Shah, et al. 2021 [43] | NR | 14 (25.1) | NR | NR | 1 (1.8) | 49 (89) | 44 (80) | 41 (75) |
| Cappell, et al. 2020 [44] | 4 (9.3) | NR | 3 (6.9) | 2 (4.7) | 0 (0.0) | NR | NR | NR |
| Hu, et al. 2021 [45] | NR | 3 (50.0) | 1 (16.7) | 5 (83.3) | 1 (16.7) | 6 (100) | 1 (17) | 1 (17) |
| Hill, et al. 2018 [46] | First 28 d: 30/133 (23) | NR | First 28 d: 22/133 (17) | First 28 d: 11/133 (8) | First 28 d: 4/133 (3) | 93 (69.9) | 21 (16) | 27 (20) |
| | Beyond 28 d: 171/119 (14) | Beyond 28 d: 7/119 (7) | | | | | | |
| Azoulay, et al. 2021 | NR | NR | 30 (12.4) | NR | NR | 200 (83) | 166 (68.9) | 155 (64.3) |
| Schuster, et al. 2021 | 43 (37.4) | 22 (19.1) | NR | 20 (17.4) | 5 (4.3) | 66 (57.4) | 18 (15.6) | 12 (10.4) |
| Wang, et al. 2021 [49] | First 8 wks: 2/18 (11.1) | NR | NR | 2 (11.1) | NR | 17 (94.4) | 11 (61.1) | 12 (66.6) |
| | Beyond 8 wks: 7/18 (38.9) | | | | | | | |
| Baumeister, et al. 2019 [50] | NR | 3 (25) | 1 (8) | 2 (17) | NR | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Yan, et al. 2019 [51] | 1 (4.8) | 1 (4.8) | NR | NR | NR | 90 (53.3) | 1 (4.8) | 5 (23.8) |
| Zhou, et al. 2020 [52] | 7 (33.3) | 3 (14.3) | NR | NR | NR | 3 (14.3) | 0 (0.0) | 0 (0.0) |
| Jacobson, et al. 2022 [53] | 79 (53.4) | 26 (17.6) | NR | 9 (6.0) | 3 (2.0) | 121 (81.8) | 74 (50.0) | 27 (18.2) |
| Gaut, et al. 2021 [54] | 5 (22.7) | NR | 2 (9) | 2 (9) | NR | 14 (63.6) | 12 (54.6) | 13 (59.1) |
| Zettler, et al. 2021 [55] | 35 (43.3) | NR | NR | NR | NR | 499 (82) | NR | NR |
| Wittmann Dayagi, et al. 2021 [56] | First 30 d: 5/52 (29) | First 30 d: 11/52 | First 30 d: 11/52 | First 30 d: 5/52 (9.6) | 0 (0.0) | NR | NR | NR |
| | 30 to 61 d: 13/47 (21) | 30 to 61 d: 24/43 (7) | 30 to 61 d: 24/43 (7) | 30 to 61 d: 0 episodes | | | | |
| Wu, et al. 2021 [57] | 4 (30.8) | NR | NR | 4 (30.8) | NA | 11 (84.6) | NR | NR |
| Ramos, et al. 2017 [58] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Li, et al. 2021 [59] | 9 (30.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 29 (96.7) | 0 (0.0) | 12 (40) |
| Cul, et al. 2021 [60] | Not applicablea | Not applicablea | Not applicablea | 1 (5.0) | Not applicablea | 20 (100) | 3 (15) | 2 (10) |
| Li, et al. 2021 [61] | Not applicablea | Not applicabla | Not applicabla | 2 (6.7) | Not applicabla | 16 (53.3) | 8 (27) | 6 (20) |
| Li, et al. 2019 [62] | 4 (13.8) | 4 (13.8) | NR | 0 (0.0) | 0 (0.0) | 23 (79.3) | 7 (24.1) | 3 (10.3) |
| Zeng, et al. 2020 [63] | 2 (14.3) | NR | 2 (14.3) | 0 (0.0) | 0 (0.0) | 13 (92.9) | 0 (0.0) | 1 (7.1) |

(Continued)
| Study, year          | Overall infection [n (%)] | Severe infection [n (%)] | Bacterial infection [n (%)] | Viral infection [n (%)] | IFL [n (%)] | CRS [n (%)] | TCZ use [n (%)] | Steroids use [n (%)] |
|----------------------|---------------------------|--------------------------|----------------------------|-------------------------|------------|------------|----------------|-----------------|
| Wudihikam, et al. 2020 [64] | 40 (66.7) First 30 d: 37 episodes Beyond 30 d: 64 episodes | First 30 d: 11 episodes Beyond 30 d: 16 episodes | First 30 d: 10 episodes Beyond 30 d: 28 episodes | First 30 d: 1 episode Beyond 30 d: 1 episode | 48 (80.0) | 0 (0.0) | 0 (0.0) |
| Park, et al. 2018 [65] | First 30 d: 22/53 (42) Beyond 30 d: 10/32 (31) | NR | First 30 d: 16/53 (32) Beyond 30 d: 5/32 (16) | First 30 d: 5/53 (9.4) Beyond 30 d: 9/32 (28) | 45 (84.9) | 19 (35.8) | 17 (32.1) |
| Kochenderfer, et al. 2017 [66] | 3 (42.8) | 1 (14.2) | 1 (14.2) | 0 (0.0) | 0 (0.0) | 7 (14.2) | 0 (0.0) | 0 (0.0) |
| Zhang, et al. 2022 [67] | 7 (22.6) | NR | 7 (22.6) | 0 (0.0) | 0 (0.0) | 16 (51.6) | NR | NR |
| Zhang, et al. 2022 [68] | NR | 4 (4.6) | 16 (18.4) | 34 (39.1) | 0 (0.0) | 61 (70.1) | 15 (17.2) | 15 (17.2) |
| Beyar-Katz, et al. 2022 [69] | 27 (45) | NR | 16 (27) | 14 (23) | 0 (0.0) | 44 (73.3) | 28 (47) | 32 (53) |
| Ortiz-Maldonado, et al. 2022 [70] | NR | 4 (44.4) | NR | NR | 0 (0.0) | 7 (87.5) | 3 (37.5) | 0 (0.0) |
| Thakkar, et al. 2021 [71] | 9 (47) | NR | 5 (26) | 7 (37) | 3 (16) | 12 (63.2) | 6 (31.6) | 3 (15.8) |
| Cornell, et al. 2021 [72] | 3 (21) | 0 (0.0) | NR | 0 (0.0) | 0 (0.0) | 3 (21) | NR | NR |
| Korel, et al. 2021 [73] | 16 (26.7) | NR | 8 (13.3) | 3 (5.0) | 5 (8.3) | 33 (55.0) | 0 (0.0) | 0 (0.0) |
| Huang, et al. 2020 [74] | 3 (27.3) | NR | NR | NR | 0 (0.0) | 10 (90.9) | 0 (0.0) | 0 (0.0) |
| Logue, et al. 2021 [75] | First 30 d: 31/85 (36.5) Beyond 30 d: 31/70 (44.3) | First 30 d: 13/85 (15.3) Beyond 30 d: 7/70 (10.0) | First 30 d: 10/85 (11.8) [rhinovirus (7), RSV (1), influenza (2)] Beyond 30 d: 19/70 (27.1) [rhinovirus (4), RSV (2), influenza (2), parainfluenza (2)] | 2 (2.3) | 79 (92.9) | 17 (24.3) | 39 (45.9) | 28 (39.0) |
| Baird, et al. 2021 [76] | 27 (65.9) | NR | NR | 17 (41.5) | 18 (43.9) | 13 (31.7) | 37 (80.2) | 34 (82.9) | 31 (75.6) |
| Munshi, et al. 2021 [77] | First 8 wks: 63/128 (49.2) 8 wks to 6 mo: 67/122 (54.9) 6 to 24 mo: 27/101 (26.7) | NR | NR | First 8 wks: 16/128 (13) 8 wks to 6 mo: 6/122 (2) 6 to 24 mo: 4/101 (4) | First 8 wks: 15/128 (12) 8 wks to 6 mo: 21/122 (17) 6 to 24 mo: 5/101 (5) | First 8 wks: 7/128 (5) 8 wks to 6 mo: 3/122 (2) 6 to 24 mo: 5/101: 1/101 (1) | 107 (84) | 67 (52) | 19 (15) |
| Cordeiro, et al. 2020 [78] | 33/54 (61) | 18/54 (33.3) | 11/54 (20.3) | 7/54 (12.9) | 4/54 (7.4) | 7 (8.1) | 21 (24.4) | NR |

Axi-cel: axicabtagene ciloleucel; CRS: cytokine release syndrome; d: day; IFL: invasive fungal infection; mo: months; NR: not reported; RSV: respiratory syncytial virus; SoC: standard of care; TCZ: tocilizumab; wks: weeks.

*Only late infections occurring ≥6 months after CAR T-cell infusion were reported.

*Study restricted to critically ill CAR T-cell recipients admitted to the intensive care unit.

The study only assessed the rate of HBV reactivation.
infection of 33.8%. The majority of the studies (75.6%) were RCTs, and all but one [42] were in phase 1 or 2. In the sensitivity analysis stratified by the type of design, the incidence of overall infection was even higher in observational studies (38.5%), suggesting that patients receiving CAR T-cell in real-life practice are more prone to develop infection than the highly selected population recruited in early phase trials.

In a recent pharmacovigilance study and meta-analysis of safety data, the pooled incidence rate of infection of any grade was 27.7% (11 studies with high heterogeneity) [29]. The lower rate compared to our results may be explained by the inclusion of pediatric patients. In another meta-analysis restricted to ALL patients with consolidative HSCT following anti-CD19 CAR T-cell therapy, only three out of 11 studies reported data related to infections and yielded a pooled incidence of 39%, also with high heterogeneity [27]. Therefore, the present systematic review and meta-analysis provides the most comprehensive synthesis to date in terms of number of summarized studies, and the only one specifically devoted to assess the occurrence of infectious complications after CAR T-cell therapy.

The pooled estimate for severe infection — on the basis of 26 studies with 1,745 patients — was nearly half that for overall infection (16.2%). All but two [75,78] of these studies were RCTs, which may explain the lower degree of heterogeneity observed ($I^2 = 74.41\%$). In a meta-analysis comprising 15 studies on $t/r$ ALL patients receiving CD19-specific CAR T-cells, the pooled cumulative incidence rate of infection events graded $\geq 3$ was higher (29%) than that found in our study [28]. A direct comparison, however, should be taken with caution. Unlike our patient population, all participants in the meta-analysis by Aamir et al. had a diagnosis of ALL as underlying disease, and their age range (0 to 30 years) was also different. Since we specifically excluded pediatric or mixed studies, only three RCTs restricted to ALL patients [43,45,65] and six further studies comprising both ALL and B-cell lymphomas [46,56,60,61,73,78] were included. Finally, the differential impact of specific disease biology and previous lines of chemotherapy according to the type of B-cell malignancy (i.e. the common use of purine analogues in ALL) cannot be ruled out.

Two CAR T-cell therapies targeted against different tumor-associated antigens are currently used in clinical practice. Since BCMA is selectively induced during plasma cell differentiation [79,80], anti-BCMA CAR T-cells are being increasingly used in MM patients, with two FDA-approved products (ide-cabtagene vicleucel and ciltacabtagene autoleucel). Anti-CD19 CAR T-cells are preferred for B-cell malignancies, as CD19 is specifically expressed on the surface of normal and neoplastic B-cells and follicular dendritic cells [81]. In accordance with its more advanced clinical development, two thirds of the pooled studies were related to anti-CD19 CAR T-cells, in contrast to only five studies on anti-BCMA therapies. Heavily treated MM patients have a high risk of infection that result from B-cell dysfunction and associated HGG, immune defects involving T-cells and NK cells, older age and frequent comorbidities [82]. Therefore, it may be expected that infection events would be more common with anti-BCMA than with anti-CD19 CAR T-cell therapies. The pooled estimates for overall infection, however, were very similar between both patient populations (35.5% and 34.4%, respectively), whereas the incidence rate of severe infection was actually higher in patients with B-cell malignancies.

The pooled incidence rate of late infection was estimated at 36% based on data provided by 8 studies, again with high heterogeneity ($I^2 = 94.21\%$). Of note, the definition of late infection and the follow-up period were not homogeneous across studies. For instance, Cappell et al. reported 6 episodes of infection requiring hospital admission (including one case of disseminated herpes zoster [HZ]) that were diagnosed up to 3 years after CAR T-cell infusion [44]. In another study that defined late infection as any event occurring beyond 90 days, the cumulative incidence was as high as 61%, which accounted for an incidence density of 0.55 per 100 days at risk (2.08 per patient-year). Although upper (48%) and lower respiratory infections (23%) were the most common syndromes, 20% and 5% of the episodes required hospital and intensive care unit admission, respectively [78]. Long-term B-cell depletion and HGG with delayed T-cell recovery have been well described following CD19-targeted CAR T-cell therapy, with some studies showing low serum immunoglobulin levels for up to 5 years after infusion [44].

The pooled incidence rate of bacterial infection was 16.3% ($I^2 = 89.23\%$), although details on microbiologically documented episodes were lacking in the majority of the studies. A similar limitation also applies for viral infection (pooled estimate of 12.5%), although the occurrence of HZ was separately reported in a number of studies [39,40,44,49,53,66,76]. In addition, limited data was available on the incidence of coronavirus disease 2019 (COVID-19) since the onset of the pandemic [39,41,42,69,71], with rates ranging from 0.3% to 15.8%. Similarly to patients receiving anti-CD20 monoclonal

Table 4. Quality of included cohort studies according to the Newcastle-Ottawa Scale.

| Study, year | Quality indicators |
|-------------|--------------------|
|             | Selection | Comparability | Outcome | Total |
| Azoulay, et al. 2021 [47] | *** | Not applicable$^a$ | *** | ***** (6) |
| Gaut, et al. 2021 [54] | *** | Not applicable$^a$ | ** | ***** (5) |
| Zettler, et al. 2021 [55] | *** | Not applicable$^a$ | - | ***** (5) |
| Li, et al. 2019 [62] | *** | Not applicable$^a$ | *** | ***** (6) |
| Wudhikam, et al. 2020 [64] | *** | Not applicable$^a$ | *** | ***** (6) |
| Beyar-Katz, et al. 2022 [69] | *** | Not applicable$^a$ | ** | ***** (5) |
| Thakkar, et al. 2021 [71] | *** | Not applicable$^a$ | *** | ***** (6) |
| Korell, et al. 2021 [73] | *** | Not applicable$^a$ | ** | ***** (5) |
| Logue, et al. 2021 [75] | *** | Not applicable$^a$ | ** | ***** (5) |
| Baird, et al. 2021 [76] | *** | Not applicable$^a$ | *** | ***** (6) |
| Cordeiro, et al. 2020 [78] | *** | Not applicable$^a$ | *** | ***** (6) |

$^a$Cohort study with no comparator group (i.e. patients not receiving CAR T-cell therapy).
antibodies, it has been shown that CD19-targeted CAR T-cell therapy negatively impacts the capacity to mount humoral responses following mRNA vaccination, although the amount of specific T-cell responses seems to be similar (or even higher) than healthy controls [83, 84].

Less than two thirds of the analyzed studies provided data on the occurrence of IFI, which resulted in a pooled incidence of 2.0% with moderate heterogeneity ($I^2 = 43.48\%$). Once again, the scarcity of specific information limits the risk assessment of this life-threatening complication. The development of invasive aspergillosis was anecdotally reported in seven studies (incidence rates: 0.9% to 3.8%) [39, 46, 48, 56, 65, 76, 78]. The timing of diagnosis and antimould prophylaxis status, however, were not given in most of them. The occurrence of PCP was overall uncommon [46, 48, 76], likely reflecting the widespread use of anti-Pneumocystis prophylaxis for at least 3–6 months or with the duration guided by the recovery of CD4 T-cell counts. Interestingly, in the study reporting the highest cumulative incidence of PCP (7.3%), all the three cases occurred within 3 months of completing the prespecified course of trimethoprim-sulfamethoxazole prophylaxis despite the persistence of CD4 T-cell counts below 200 cells/µL [76].

Previous meta-analysis focused on efficacy and safety outcomes reported no separate rates for specific types of infection or causative agents. Only five out of 19 studies included in the meta-analysis by Xu et al. detailed the microbiological characteristics of the episodes of infection, reporting 36 cases of cytomegalovirus (CMV) infection [27]. The incidence of CMV infection in our meta-analysis largely varied from 0.3% [41] to 33.3% [45], although the type of event (i.e. asymptomatic viremia or clinical disease) is not usually provided. In addition, the cumulative incidence depends to some extent on the frequency of monitoring for CMV DNAemia, which was not homogeneous across studies. Baseline neutropenia was identified in the study by Hill et al. as a risk factor for infection after CAR T-cell therapy, although the association lost its statistical significance after multivariate adjustment [46]. Monocytopenia and lymphopenia – in particular low CD4 T-cell levels – have been additionally explored as risk factors for viral and fungal infection [46, 65, 75, 85–87]. Due to the insufficiency of the data extracted these variables could not be examined in our meta-analysis. Various studies [46, 64, 65, 69, 71, 75, 76] have analyzed the development (and severity) of CRS as a potential risk factor, since it has been suggested that the associated endothelial damage would initiate or facilitate the infection process [85, 88]. Nevertheless, only the study by Park et al. showed an independent association between grade ≥3 CRS and overall infection (adjusted hazard ratio [aHR]: 2.67; $P$-value = 0.05) and BSI (aHR: 19.97; $P$-value <0.001) [65]. After adjusting for clinical covariates in multivariate models, the number of prior lines of chemotherapy [46, 76] and the use of corticosteroids for the management of CRS or ICANS [64] were ultimately identified as independent risk factors in the few studies that have specifically assessed this issue, most of them retrospective cohorts.

Whereas all-cause mortality rates are detailed in the majority of studies as a key safety outcome (with progression of the underlying disease as the most common cause of death), mortality attributable to adverse events was assessed in a limited number of papers only. One third of them reported a no infection-related deaths. The resulting pooled rate was 1.8% with moderate heterogeneity, in line with a previous meta-analysis that included a much lower number of studies (1.3% ($I^2 = 0\%$) based on three studies) [29].

Our systematic review and meta-analysis have some limitations. Since most of the articles were phase 1/2 RCTs, the number of patients per study was relatively low (20 trials had sample sizes <50 patients). Excess of small-sample studies can explain the wide variation observed in infection rates, which led to high heterogeneity for most of the estimates. Additional reasons of heterogeneity are the disparity in follow-up periods and the lack of consensus definitions for infection events. With a few exceptions – typically observational studies rather than RCTs [73, 75, 76, 78] – most of the studies simply reported absolute and relative frequencies for overall and/or severe infection. Therefore, details on microbiologically documented episodes and sites of infection were limited. In addition, some trials only contained data for specific types (i.e. pneumonia) or specific pathogens (i.e. HZ). Definitions for early and late infection differed across studies. The timing of diagnosis or whether they occurred while the patient was under antimicrobial prophylaxis or following its discontinuation was not always discernible. Most of the studies that specifically investigated the risk factors for infection were retrospective in design [46, 64, 65, 69, 71, 73, 75, 76]. In addition, the paucity and variability of available data across studies prevented us to perform a meta-analysis. Finally, some studies only reported the absolute number of infection events during the follow-up period, making difficult the estimation of cumulative incidence rates.

In conclusion, this systematic review and meta-analysis offer a comprehensive assessment on the incidence of infectious complications in patients receiving CAR T-cells for the treatment of different types of hematological malignancies. Infection revealed as a frequent adverse event associated with this emerging therapy. The occurrence of severe opportunistic infections such as invasive aspergillosis or PCP, however, was uncommon, and the attributable mortality was low. In addition, we have detected a need for prospective data evaluating the risk factors for this complication, as well as for a more detailed description of microbiologically documented infection events in RCTs.

5. Expert opinion

The advent of CAR T-cell therapy has revolutionized the approach to hematological malignancies, and major advances are to be expected in the coming years, with a growing number of approved products and indications. As revealed by the present systematic review and meta-analysis, infection remains a major complication following CAR T-cell therapy, since one in three patients will develop any-grade episode and one in six will suffer a severe event. Unfortunately, the implementation of effective risk minimization strategies may be problematic due to a number of reasons. First, the specific attribution of causality to CAR T-cell therapy in the
pathogenesis of infection may be confounded by the impact of baseline immunodeficiency that usually develops among heavily pretreated patients with r/r ALL or MM, with a meaningful proportion of previous HSCT recipients. Second, in addition to the lymphodepletion regimen administered (FluCy in most of the studies), the variable occurrence of CRS and its therapeutic management – based on an anti-IL-6 agent with or without high-dose corticosteroids – represents a further source of patient heterogeneity. Third, a notable variation was also found across studies in terms of antimicrobial prophylaxis. In the absence of dedicated RCTs, prophylaxis practices following CAR T-cells have been mostly modelled upon regimens used in other at-risk groups such as neutropenic patients or allo-HSCT recipients. Nevertheless, CAR T-cell therapy entails some specific risks, such as long-term lymphopenia and HGG. This notion is supported by the high incidence rate of late infection observed in our meta-analysis (pooled estimate of 36.0%), even by considering the inconsistent definition of this outcome in the literature. Therefore, it is likely that the optimal timing for the discontinuation of prophylaxis must be established on an individualized basis and informed by the kinetics of CD4 + T-cells (i.e. PCP prophylaxis) or serum immunoglobulin levels. In addition, IVlg replacement therapy should be routinely implemented in patients with severe HGG (IgG <400 mg/dL), in line with the common practice in MM [89]. Lastly, the present research reveals that the majority of RCTs lack granularity in the reporting of infectious complications in study populations, which often was incomplete and unstructured. Although this drawback has been also noted in RCTs assessing other treatments for hematological malignancies [90], further efforts are urgently needed to standardize the report of infectious events after CAR T-cell with accepted definitions and classified by both type of pathogen and source of infection. Keeping in mind this limitation, the burden of IFI and other opportunistic infections (i.e. CMV disease) following CAR T-cell therapy seems to be relatively low. In fact, only a few studies required as per protocol the use of antiviral or mould-active antifungal prophylaxis. Thus, the main disease burden in patients receiving CAR T-cell therapy actually lies on the development of bacterial infection in form of pneumonia or bacteremia, which should prompt the assessment of the role of antibiotic prophylaxis and IVlg replacement in future RCTs.

Declaration of interest
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or material discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or mending, or royalties.

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ORCID
Gülçin Telli Dizman ♦ http://orcid.org/0000-0001-8195-3345

José María Aguado ♦ http://orcid.org/0000-0002-9520-8255
Mario Fernández-Ruiz ♦ http://orcid.org/0000-0002-0315-8001

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