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ORIGINAL ARTICLE

Association of time to antibiotics and clinical outcomes in patients with fever and neutropenia during chemotherapy for cancer: a systematic review

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Abstract

Purpose Prompt antibiotic therapy is standard of care for patients with fever and neutropenia (FN) during chemotherapy for cancer. We systematically reviewed the association between time to antibiotics (TTA) and clinical outcomes.

Methods The search covered seven databases; confounding biases and study quality were assessed with the ROBINS-I tool. Safety (death, intensive care unit (ICU) admission, sepsis) and treatment adequacy (relapse of infection, persistence or recurrence of fever) were assessed as primary outcomes.

Results Of 6296 articles identified, 13 observational studies were included. Findings regarding safety were inconsistent. Three studies controlling for triage bias showed a possible association between longer TTA and impaired safety. Meta-analysis for TTA ≤ 60 min versus > 60 min was feasible on four studies, with three studies each reporting on death (OR 0.78, 95%CI 0.16–3.69) and on ICU admission (OR 1.43, 95%CI 0.57–3.60). No study reported data on treatment adequacy. Triage bias, i.e. faster treatment of patients with worse clinical condition, was identified as a relevant confounding factor.

Conclusion There seems to be an association between longer TTA and impaired safety. More knowledge about TTA effects on safety are important to optimise treatment guidelines for FN. Controlling for triage and other biases is necessary to gain further evidence.

Trial registration Registration: PROSPERO [http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018092948].

Keywords Oncology · Fever · Neutropenia · Time to antibiotics · Cancer · Chemotherapy · Systematic review

Background

Fever in chemotherapy-induced neutropenia (FN) is the most frequent potentially lethal complication of chemotherapy for cancer [1]. The risk of life threatening bacterial infection increases when the absolute neutrophil count (ANC) drops below 0.5×10^9/l [2]. Time to antibiotics (TTA) usually refers to the amount of time passed from arrival at the hospital to start of intravenous antibiotic administration [3–5]. Sometimes, different definitions are used, for example, time from the first detection of fever [6].

Current European and American guidelines for treatment of FN in adult patients with cancer, recommend administration of empiric broad-spectrum antibiotics within 1 h from the admission of a patient with FN [7, 8]. International FN guidelines for paediatric patients, developed by an international panel of experts, do not specify a target TTA [9], while the German paediatric guidelines for treatment of FN recommend administration of antibiotics within 60 min without citing specific evidence [10].

Recommendations for the timing of antibiotics are based mainly on studies involving immunocompetent subjects. Delay in antibiotic administration is associated with a decrease

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in survival in patients with severe sepsis [11, 12] and meningitis [13, 14]. In contrast to patients receiving chemotherapy, the patients examined in these sepsis studies were immunocompetent and already significantly ill at presentation. In patients with FN, fever is often the only clinical sign. The impact of chemotherapy, e.g. damage to the gastrointestinal mucosa, therapy-induced thrombopenia, anaemia or liver dysfunction, complicate detection of infections and potentially their outcomes in patients with cancer. Therefore, direct comparisons may be inaccurate.

Some organizations have defined TTA < 60 min as a measure of quality of care [3], and several centres have used considerable resources to reduce in hospital TTA [4, 15, 16]. To make recommendations for targeted TTA, it is important to know whether the chosen timespan is safe and whether earlier antibiotic treatment can reduce complications of infections. If TTA is of low value, focus on a more rigorous diagnostic could improve quality of treatment and clinical outcome. Other influences than TTA, e.g. travel time to the hospital, illiteracy and poverty, have been identified to be associated with sepsis and infectious death [17].

In summary, there is a lack of evidence for the impact of TTA on clinical outcomes. Therefore, we performed a systematic review to synthesise the available data on the association between TTA and clinical outcomes in patients with FN being treated with chemotherapy for cancer. We also aimed to explore the effect of important covariates on modifying outcomes.

Methods

The protocol for this review was registered on PROSPERO (CRD42018092948) prior to commencing the work and published in Systematic Reviews [6]. Simultaneously with this review, we collected information on interventions performed to reduce TTA, their effect and the potential benefits of these approaches. This will be reported elsewhere.

Electronic searches of MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, CINAHL, CDSR, CENTRAL and LILACS were performed on May 9, 2018. The search was updated on April 9th, 2019. The search strategy included the Medical Subject Heading terms and text words to identify fever and neutropenia and the intervention of treatment with antibiotics. Antibiotics were also searched by groups and names of antibiotic drugs (e.g. penicillins, beta-lactams, quinolones).

In EMBASE search, 'time' was added as a required search factor to narrow the results. Studies from 1997 onward were eligible; no language restrictions were applied. Pilot searching took place before the actual search and found all five previously identified studies [4, 5, 18–20]. The search strategy is provided with the protocol publication [6]. Manual searches of references and forward citation searching of included articles were conducted. Authors of relevant studies and experts within the field were contacted to seek further studies.

Study selection

Inclusion and exclusion criteria were defined a priori. Inclusion criteria were the following:

Patients:

- Patients (adults and children) with fever and neutropenia during chemotherapy for cancer or after haematopoietic stem cell transplantation

Intervention:

- Measured time to antibiotics (mostly defined as arrival at the hospital to first dose of antibiotics administration)

Predefined
Outcomes (any of primary or secondary outcomes)
Primary outcomes:

- Safety–death, admission to ICU, severe sepsis, including septic shock
- Treatment adequacy–relapse of primary infection, persistence of fever or recurrence of fever without a new infection

Secondary outcomes:

- Control outcomes: microbiologically defined infections, new infections, modification of antibiotics
- Duration of illness: length of fever, length of hospital stay

Study design:

- All kinds of study designs, except case reports.

The study-specific composite outcome was recorded and analysed if predefined outcomes were implemented. Time point of outcome assessment was not predefined; they could be assessed during FN episode or later.

Studies were excluded if (1) they were not specific to cancer or did not report on this subgroup separately, (mixed populations were permitted if > 50% population were diagnosed with cancer or had haematopoietic stem cell transplantation (HSCT)), (2) they did not report any of the predefined primary or secondary outcomes in association with TTA or (3) they were only abstract or posters.

One reviewer (CK) screened title and abstract of all studies for inclusion. A second reviewer (CS) independently screened 60% of the titles and abstracts. The kappa statistic for

agreement was calculated and showed good agreement between reviewers ($k = 0.91$, 95% confidence interval (CI) 0.87 to 0.94). Full text was obtained for all potential articles of interest. All full texts were assessed for eligibility by two reviewers (CK and CS; $k = 0.79$, 95%CI 0.69 to 0.89). Fourteen studies were referred to a third reviewer (RSP), where 11 were excluded.

Data extraction and risk of bias assessment

Data extraction and risk of bias assessment were done by one reviewer (CK) and independently checked by a second (RAA). Discrepancies were resolved by consensus. Risk of bias was assessed using the Risk Of Bias In Non-randomised Studies—of interventions (ROBINS-I) tool [21] at the level of the individual study and includes all assessed outcomes from that study. All articles were included in the review irrespective of the risk of bias.

Statistical methods

Where appropriate, meta-analysis was undertaken with a random-effects model using DerSimonian and Laird estimator using the metafor library [22] within the R programming environment [23]. Statistical heterogeneity was quantified using χ^2 tests, the I^2 and tau^2 statistic. Where heterogeneity of outcomes and definitions did not permit meta-analysis, narrative synthesis was undertaken. Subgroup analysis was planned for adult versus paediatric patients, different risk status, localisation of presentation, admission time, severe neutropenia versus non-severe neutropenia, patients with versus without comorbidities, antibiotic prophylaxis versus no prophylaxis, inpatient versus outpatient and income level of countries.

Results

Overview

Titles and abstracts from 6296 studies were assessed and 177 full-text articles retrieved. A flow diagram of study selection is provided in Fig. 1.

Thirteen studies were included, nine in adult [18, 24–31] and four in paediatric [5, 17, 19, 20] patients with cancer, including a total of 5186 and 2461 FN episodes, respectively. The authors of two additional studies were contacted, because of insufficient primary data. Due lack of response, neither of these studies was included in this review. The included studies were conducted in eight different countries. One paediatric study [19] included five centres; all others were single-centre studies. No randomised or quasi-randomised trials were identified. All studies were observational, either prospective ($n = 4$), retrospective ($n = 8$) or mixed ($n = 1$). Characteristics of included studies are given in Table 1. Fever was defined within a temperature range of ≥ 38.0 to ≥ 38.5 °C. Eleven studies defined neutropenia as an absolute neutrophil count (ANC) < 0.5×10^9/l; in seven studies, patients with an ANC expected to decrease to < 0.5×10^9/l were included. Two studies defined neutropenia as ANC < 1.0×10^9/l. One study [17] also included non-neutropenic patients, but 51% of the included patients had an ANC < 0.5×10^9/l. TTA was measured from triage or arrival at the hospital to first dose of antibiotics in seven studies [5, 17, 19, 27, 28, 30, 31], two studies started measurement at time of fever detection [18, 24] and three studies started time measurement either at the check-in for outpatients or at time of first fever for clinic patients [20, 25, 26]. One study gave no definition for TTA [29]. These different definitions should be kept in mind when comparing the included studies. The study-specific definitions are available as Online Resource 1.

Risk of bias

Study quality and risk of bias assessment identified a moderate or serious risk for bias in all but two of the included studies (Table 2). Baseline confounding was the major domain for bias; the other domains were never judged more than at moderate risk for bias, keeping in mind that sometimes, judgement was impossible due to lack of reporting [28].

Risk status of patients, initial illness severity and time of presentation were identified as possible confounders in almost all studies. Further identified covariates potentially influencing clinical outcomes were as follows: type of infection and antibiotic prophylaxis before FN. The duration of fever before arrival at the hospital was identified as limitation of the assessment of TTA and outcome by one study [27].

Intervention

TTA was analysed as a continuous variable in nine studies [5, 17, 18, 24, 26, 28–31]. The time intervals compared and outcomes assessed varied; they are shown in Table 3. Primary outcomes defined in the protocol were reported inconsistently:

Primary outcomes: safety

The number of deaths was reported by all 13 studies. Its prevalence was 0.7 [5] to 3.4% [20] in paediatric patients and 2.3 [27] to 13.6% [29] in adult patients. In one study [31] ($n = 32$), no deaths occurred. Two studies [18, 25] found a direct, statistically significant association between TTA and death in adult patients. Rosa et al. [18] found that all-cause mortality 28 days after FN onset was lower in patients with a TTA ≤ 30 min (3.0%) compared to patients with a TTA 31-60 min (18.1%) and TTA was longer (median 1.66 h; IQR 5.17) in patients who died, compared to patient who survived (median

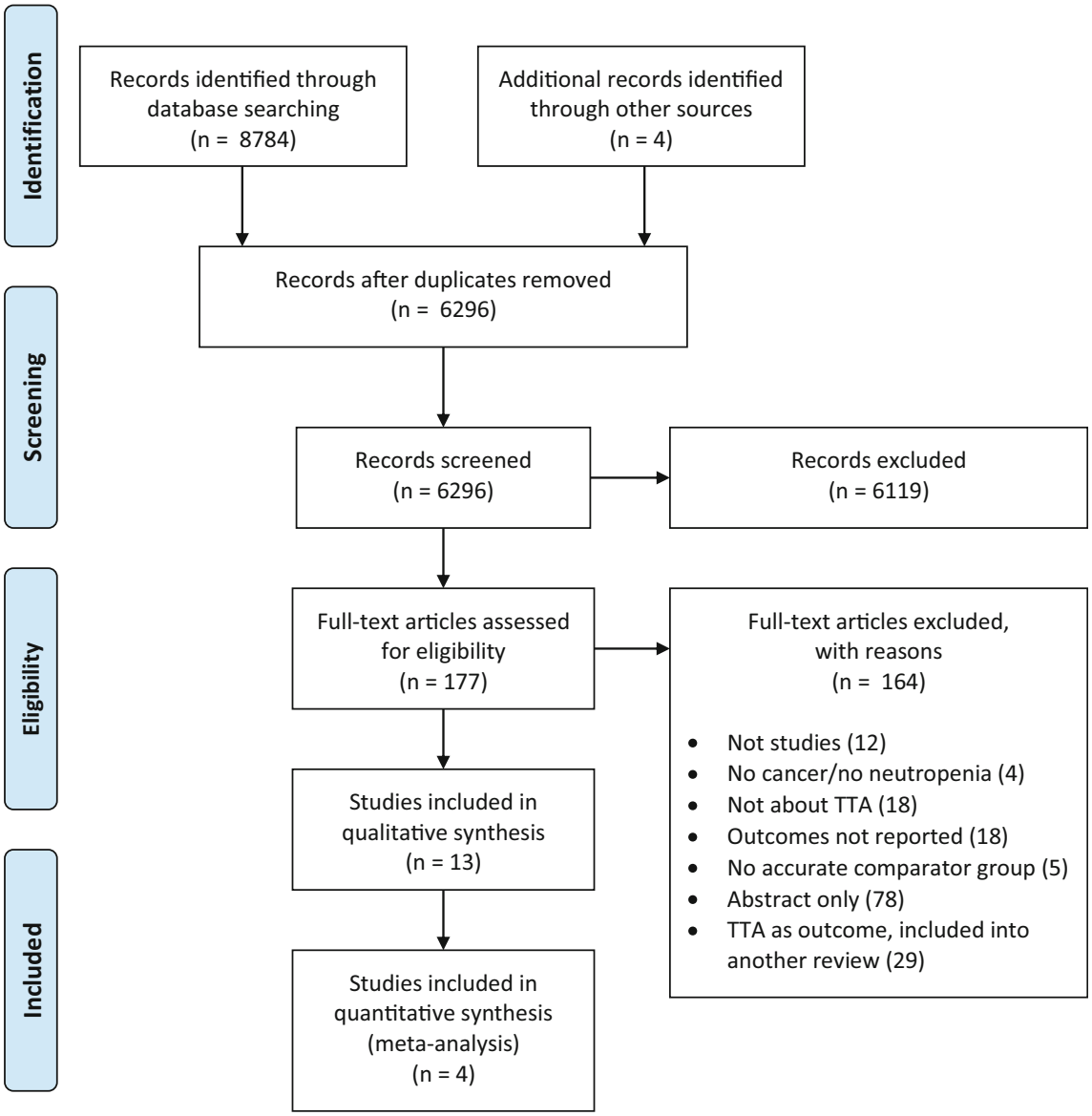

Fig. 1 PRISMA flow diagram of identification and selection of eligible studies

0.33 h; IQR 1.0) (HR, 1.18; 95% CI, 1.10 to 1.26). Each increase of 1 h in TTA raised the risk for death by 18%. Daniels et al. [25] found a higher 30-day mortality in patients with TTA of 3 to 6 h (OR 1.57) and 24 to 48 h (OR 2.08, mortality 13%) when compared to TTA 0 to 2 h (mortality 5%). This effect was not seen when TTA was only moderately delayed (2 to 3 h; OR 0.87) and not statistically significant for the group treated from 6 to 24 h (OR 1.37).

Three studies reported death in patients with TTA ≤ 60 min versus > 60 min [19, 20, 27], including a total of 675 FN episodes. The pooled odds ratio for death was 0.78 (95% CI 0.1 to 3.69), with substantial statistical heterogeneity (I^2 = 56.1%, tau^2 = 1.05; Fig. 2a). Ko et al. [27] only reported deaths within patients with severe sepsis/septic shock and patients with bacteraemia. Only one other study [17] reported death as single outcome. This study found no association of death and TTA in the analysed subgroup of paediatric outpatient episodes (OR 1.02; 95% CI, 0.80 to 1.28).

Six studies [5, 24, 27–30] included death into their composite outcome, whereof four studies in adult patients [24, 27, 28, 30] found no association between prolonged TTA and the investigated composite outcome (Table 3). In contrast, one paediatric study [5] reports a decreased likelihood of adverse events (AE), including in-hospital mortality, admission to the paediatric intensive care unit and/or receipt of ≥ 40 ml/kg of fluid resuscitation within 24 h of presentation in patients treated within 60 min (5.2% versus 14.2% in patients with TTA 61-120 min; OR, 2.88; 95% CI, 1.70 to 4.89). When analysing TTA as a continuous variable, patients with AE only had a slightly longer median TTA (119 min versus 113 min;).The

Table 1 Characteristics of included studies

Author (year pub) Citation	Design Country	Included patients	Exclusion criteria	FN episodes (patients)	Age (years)	Gender (m:f)	TTA (median)	Antibiotics	Diseases
Adult patients									
Butts al.[24] (2017)	Retrospective, observational USA (E)	≥ 18 years, active diagnosis of a haematologic malignancy or stem cell transplant (allo- or autogeneic), admitted to acute care level floor, with FN	Patients with an admitting diagnosis of FN, patients on treatment with antibiotics at time of FN diagnosis	244 (216)	52.1 years average	141:75	10–1495 min With composite outcome: 120 min Without composite outcome: 102 min	Piperacillin/tazobactam (75.4%) Cefepime (11.9%)	Acute leukaemia: 95 (44.0%) Allogeneic stem cell transplant: 38 (17.6%) Autogenic stem cell transplant: 61 (28.2%) Other tumours: 22 (10.2%)
Daniels et al.[25] (2019)	Retrospective, observational USA (E)	Adult patients with a malignancy and FN, admitted to the hospital.	Patients at low risk by MASCC score, and treated with oral ABs. Patients already on appropriate ABs at time of fever. Patients transferred with diagnosis of FN (TTA unknown). Patients who did not receive ABs within 48 h of fever.	3219 (2603)	57.3 years mean 95% CI, 56.9 to 57.8	1904:1315	0–2 h: 50.6% 2–3 h: 13.5% 3–6 h: 12.6% 6–24 h: 18.8% 24–48 h: 4.4%	Piperacillin/tazobactam, cefepime, meropenem, aztreonam, or aminoglycosides	Solid tumours: 399 (12.4%) Lymphoma: 1654 (51.4%) Leukaemia: 1166 (36.2%)
Johannesmeyer et al.[26] (2019)	Retrospective, observational USA (E)	Patients with age 18–89 years, with FN, admitted as an inpatient or presented from the community setting to an ED or an outpatient clinic. Under active treatment for a malignancy with cytotoxic agents.	Induction therapy for an acute leukaemia, undergoing HSCT, history of chronic immunosuppression including infection with HIV, transfers from outside medical facilities, pregnant, diagnosed with invasive fungal infection.	93 (93)	59 years median IQR 41.7 to 65.3	56:37	3.7 h IQR 2.32 to 6.27	No information available	Solid malignancies: 47 (50.5%) Haematological malignancies: 46 (49.5%)
Ko et al.[27] (2015)	Prospective, observational Korea (E)	Adult cancer patients with chemotherapy induced FN, at ED	Managed at other hospitals for FN then transferred to ED	1001 (863)	54.3 years mean SD ± 13.9	345:656	140 min IQR 110 to 180	Piperacillin/tazobactam (P/T) (76.2%) P/T + levofloxacin (8.1%), P/T + vancomycin (2.4%) Cefazolin/ceftazidime (4.7%)	Solid tumours: 785 (78.4%) Haematological malignancies: 216 (21.6%) Breast cancer: 380 (38%) Lung cancer: 95 (9.5%) Stomach cancer: 77 (7.7%) Lymphoma: 194 (19.4%) Leukaemia: 13 (1.3%)

Table 1 (continued)

Author (year pub) Citation	Design Country	Included patients	Exclusion criteria	FN episodes (patients)	Age (years)	Gender (m:f)	TTA (median)	Antibiotics	Diseases
Lee et al.[28] (2018)	Retrospective, observational Korea (E)	Patients with malignancies, older than 18 years, with FN	No information available	104 (104)	60.8 mean SD ± 13.6	41:63	107 min IQR 83 to 135	Anti-pseudomonal Beta-lactam antibiotics (cefepime and piperacillin tazobactam) used empirically	Solid tumours: 69 (66%) Haematological malignancies: 35 (34%) Breast cancer: 34 (33%) GIT cancer: 14 (13%) Other cancers: 21 (20%) Leukaemia: 11 (11%)
Lynn et al.[29] (2013)	Retrospective, observational Taiwan (E)	> 18 years, with chemotherapy for underlying malignancy within 5 weeks prior to ED visit, neutropenia	Patients who had been treated at other hospitals for FN and subsequently transferred to ED	81 (78)	59.0 years median IQR 47 to 69	38:43	With complications: 122 min Without complications: 97 min	Cefepime 46 (57%) Tazocin 9 (11%) Piperacillin + amikacin 19 (23%) Tazocin + amikacin 1 (1%) Others 6 (7%)	Lung cancer: 19 (23.5%) Breast cancer: 18 (22.2%) Leukaemia/lymphoma: 16 (19.8%) Other cancers: 28 (34.6%)
Perron et al.[30] (2014)	Retrospective, observational Canada (E)	≥ 18 years, diagnosis of malignancy treated by chemotherapy that was causative of or contributive to neutropenia, admitted from ED or ambulatory care facility to oncology ward with FN.	Not the first febrile episode occurring in a patient during study period. No documented malignancy.	105 (105)	60 years median range 18 to 89	43:62	All: 2.5 h range 0.03–50 h High risk: 3 h range 0.22–19 Low risk: 2.5 h range 0.03–50	Broad spectrum penicillin 88 (84%) Prophylactic filgrastim or antibiotics: 50 (47%)	Haematological malignancies: 46 (44%) Leukaemia: 17 (17.6%)
Rosa et al.[18] (2014)	Prospective, observational Brazil (E)	> 18 years, with cancer, admitted to haematology ward with FN, at least 7 days free from signs or symptoms of infection after treatment of another FN episode	Palliative treatment only, indication for outpatient treatment, neutropenia due to a specific aetiology other than adverse reaction to chemotherapy	307 (169)	40.7 years mean SD ± 14.2	159:148	Mortality group: 1.66 h IQR 5.17 Survival group: 0.33 h IQR 1.0	Cefepime, piperacillin/tazobactam, or a carbapenem; vancomycin only in cases with hemodynamic instability, suspected catheter-related infection or skin and soft tissue infection	Haematological malignancies: 242 (78.8%) AML: 149 (48.5%) ALL: 45 (14.6%) CML: 18 (5.8%) Multiple myeloma: 30 (9.7%) Lymphoma: 51 (16.6%) Other solid tumours: 14 (4.5%)
Sammut et al.[31] (2012)	Retrospective, observational UK (E)	Adults, presented and admitted to hospital with FN	Haematological malignancies no chemotherapy within 2 months of presentation, not neutropenic on presentation but developed FN during stay	32 (32)	52 years median range 20 to 70	12:20	Oncology ward 66 min IQR 65 to 112 ED 154 min IQR 116 to 211	Piperacillin/tazobactam and gentamicin, addition of vancomycin if central venous catheter present	Breast cancer: 17 (53%) Lower GIT cancer: 5 (16%) Lung cancer: 3 (9%) Sarcoma cancer: 2 (6%) Testicular cancer: 2 (6%) Upper GIT cancer: 2 (6%) Bladder cancer: 1 (3%)

Table 1 (continued)

Author (year pub) Citation	Design Country	Included patients	Exclusion criteria	FN episodes (patients)	Age (years)	Gender (m:f)	TTA (median)	Antibiotics	Diseases
Paediatric patients									
De la Maza et al.[19] (2015)	Prospective, observational Chile (E)	< 18 years, cancer patients treated with chemotherapy with FN	HSCT	338 (226)	7 years median IQR 3 to 12	115:111	132 min IQR 60 to 246	High risk: anti-pseudomonal (third-generation cephalosporin + aminoglycoside) + therapy for gram-positive cocci Low risk: ceftriaxone	Haematological cancer (leukaemia, lymphoma, and leukaemia relapse): 167 (74%) Solid tumours: 59 (26%)
Fletcher et al.[5] (2013)	Retrospective, observational USA (E)	Patients with new episode of fever, neutropenia and current treatment for cancer at institution	HSCT, initial presentation to other facility, onset FN after initial presentation, severe sepsis on initial presentation (defined as systolic hypotension)	1628 (653)	6.7 years median IQR 3.5 to 11.8	834:794	114 min IQR 71–167 With AE: 119 min IQR 86 to 165 Without AE: 113 min IQR 66 to 168	Monotherapy: third-generation cephalosporin: 26.1% other monotherapy: 6.5% Dual-therapy (anti-PSDMN, AG): 14.4%, triple-therapy (anti-PSDMN, AG, anti-GP) 48.5% Other combination: 4.6%	ALL: 799 (49.1%) AML: 122 (7.5%) Sarcoma: 244 (15.0%) CNS tumour: 181 (11.1%) Non-Hodgkin's lymphoma: 129 (7.9%) Neuroblastoma: 49 (3.0%) Other tumours: 106 (6.5%)
Gavidia et al.[17] (2012)	Prospective, observational El Salvador (E)	< 17 years, with ALL or AML	Initial palliative intent of treatment	379 (251)	5.2 years median IQR 2.8 to 9.2	133:118	Hospital to AB 3.5 h IQR 2.2–5.5 Fever to AB 16.0 h IQR 8.3–26.0 Inpatient: fever to AB 2.0 h IQR 0.8–5.0	No information available	ALL: 215 (85.7%) AML: 36 (14.3%)
Salstrom et al.[20] (2015)	Retrospective, prospective, interventional USA (E)	Paediatric patients, oncologic diagnosis, FN and admitted for further management	No information available	116 (116)	< 2 years: 8 (6.9%) 2–12 years: 67 (57.8%) > 12 years: 41 (35.3%)	52:64	Baseline: 134 min Mean: 164 min SD 118.6 Data-based: 43 min Mean: 45.2 min SD 24.3	No information available	Myeloid leukaemia: 8 (7%) Lymphoma: 3 (3%) Extracranial solid tumour: 27 (23%) Brain tumour: 14 (12%) Other tumours: 2 (2%)

AB antibiotics, *AG* aminoglycoside, *ALL* acute lymphatic leukaemia, *AML* acute myelogenous leukaemia, *anti-GP* anti-gram-positive agent, *anti-PSDMN* anti-pseudomonal agent, *CML* chronic myelogenous leukaemia, *CNS* central nervous system, *ED* emergency department, *E* English, *FN* fever and neutropenia, *GIT* gastrointestinal tract, *HIV* human immunodeficiency virus, *HSCT* haematopoietic stem cell transplantation, *pub* published, *SD* standard deviation, *TTA* time to antibiotics

Table 2 Risk of bias assessment with ROBINS-I tool

Author and citation (year pub)	Baseline confounding	Selection of participants	Classification of intervention	Deviation from intended intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Adult patients								
Butts al.[24] (2017)	Serious	Low	Low	NI	NI	Low-moderate	Moderate	Serious
Daniels et al.[25] (2019)	Low-moderate	Low	Low	NI	Low	Low	Low	Low
Johannesmeyer et al.[26] (2019)	Serious	Low	Low	NI	Low	Moderate	Low	Serious
Ko et al.[27] (2015)	Moderate	Low	Moderate	NI	Low	Low	Low	Moderate
Lee et al.[28] (2018)	Moderate	Low	Low	NI	NI	Low	Low	Moderate
Lynn et al.[29] (2013)	Moderate	Moderate	Moderate	NI	Low	Moderate	Low	Moderate
Perron et al.[30] (2014)	Moderate	Low	Low	NI	Low	Low	Moderate	Moderate
Rosa et al.[18] (2014)	Low	Low	Low	NI	Low	Low	Low	Low
Sammut et al.[31] (2012)	Moderate	Low	Low	NI	NI	Moderate	Low	Moderate
Paediatric patients								
De la Maza et al.[19] (2015)	Moderate	Low	Moderate	NI	Moderate	Low	Low	Moderate
Fletcher et al.[5] (2013)	Moderate	Low	Low	NI	Low	Low	Moderate	Moderate
Gavidia et al.[17] (2012)	Moderate	Low	Moderate	NI	Low	Low	Low	Moderate
Salstrom et al.[20] (2015)	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate

NI no information, *pub* published

sixth study [29] found a longer TTA in 25 (31%) adult patients with serious complications. Eleven (44%) of these 25 patients with serious complications died. The difference of median TTA 122 min versus 97 min was significant in Fisher's exact test ($p = 0.014$), but not in multivariable logistic regression analysis (OR 1.008; 95% CI, 0.999 to 1.017; $p = 0.070$).

ICU admission in TTA < 60 min versus > 60 min was reported by the three paediatric studies [5, 19, 20], with a total of 2236 FN episodes and meta-analysis showed no clear association with TTA (OR 1.43; 95% CI, 0.57 to 3.60), with considerable statistical heterogeneity ($I^2 = 83.5\%$, $\tau^2 = 0.56$; Fig. 2b).

ICU admission was collected and included in the analysed composite outcome by four adult studies [24, 27, 28, 30]. These did not find an association between prolonged TTA and the investigated composite outcome.

The total number of patients with sepsis was reported by three studies [17, 19, 27]; two of them [17, 19] analysed the association of sepsis and TTA in paediatric patients and both found a shorter TTA in patients with sepsis. The first study [17] reports an OR of 0.79 (95%CI 0.63 to 0.99) for TTA and sepsis in outpatients. The second study [19] found an increased frequency of sepsis in patients with TTA ≤ 60 min (24% versus 14%), significant in univariable, but not in multivariable analysis. This was also the only study that assessed all individual components of safety (death, ICU admission and sepsis), but without including them into a composite outcome. This study found no association between TTA > 60 min and death or ICU admission.

Primary outcomes: treatment adequacy

No study reported relapses of primary infection, persistence of fever for more than 5 days or recurrence of fever without a new infection.

Secondary outcomes: control outcomes

The same heterogeneity in reporting as for the primary outcomes was seen for the secondary outcomes. The studies were searched for analysis of microbiologically defined infection, new infections and modification of antibiotics with TTA. One study [20] found no significant difference between paediatric patients with TTA < 60 min (25% with bacteraemia) and >

Table 3 Outcomes and study conclusions

Author and citation (year pub)	Outcomes reported by the study	Predefined primary outcomes	Predefined secondary outcomes	Comparator	Sensitive analysis	Study results and conclusion	Association of TTA found with:
Adult patients							
Butts al.[24] (2017)	Negative clinical outcome ≥ one of: in-hospital mortality, ICU admission or vasopressor requirement (norepinephrine, vasopressin, epinephrine, or phenylephrine).	Safety: death (overall and in composite outcome) ICU admission (overall and in composite outcome) Treatment adequacy: NIA	Culture proven bacterial infection (overall)	TTA < 60 min vs. ≥ 60 min TTA < 120 min vs. ≥ 120 min TTA as a continuous variable	No association between TTA and negative clinical outcome in patients with culture proven bacterial infection.	Prolonged TTA not associated with negative clinical outcomes (OR, 0.98; 95% CI, 0.441–2.118). TTA in patients with negative outcome: 120 min (median). TTA in patients without negative outcome: 102 min (median).	No association found
Daniels et al.[25] (2019)	30-day mortality, ICU admission, hospital length of stay (LOS).	Safety: death, ICU admission Treatment adequacy: NIA	Blood stream infection (overall) Length of stay	0-2 h 2-3 h 3-6 h 6-24 h 24-48 h Mortality vs. survival	TTA 0-2 h: 5% mortality TTA > 24 h: 13% mortality ($p < 0.01$) Compared to TTA 0-2 h, TTA 2-3 h and 6-24 h was not associated with increased mortality or ICU admission.	Mortality: when compared to TTA 0-2 h, patients with TTA 3-6 h and 24-48 h had an OR of 1.57 ($p = 0.04$) and 2.08 ($p = 0.02$). ICU admission: When compared to TTA 0-2 h, patients with TTA 3-6 h had OR of 1.98 ($p < 0.001$).	Longer TTA with increased 30-day mortality and ICU admission. No association with LOS
Johannesmeyer et al.[26] (2019)	Hospital mortality, need for ICU admission, total hospital length of stay (LOS)	Safety: death, ICU admission Treatment adequacy: NIA	Length of stay	TTA as a continuous variable	No association between TTA and LOS in patients with more severe SAPS II scores.	In patients who survived TTA did not show a significant correlation to LOS ($p = 0.71$). TTA failed to significantly predict mortality or need for ICU admission	No association found
Ko et al.[27] (2015)	Unfavourable outcome defined as: serious medical complications (detailed definition given in paper), including death.	Safety: death, ICU admission (in composite outcome) Sepsis or septic shock (overall) Treatment adequacy: NIA	Source of infection and culture proven bacteraemia (overall) Duration of fever (overall)	TTA: ≤ 1 h vs. > 1 h ≤ 2 h vs. > 2 h ≤ 3 h vs. > 3 h ≤ 4 h vs. > 4 h	No impact of TTA on the mortality rate in patients with bacteraemia or severe sepsis or septic shock.	After adjusting for potential confounders no statistically significant relationship between TTA and the outcomes of FN was found (for all time cutoffs).	No association found

Table 3 (continued)

Author and citation (year pub)	Outcomes reported by the study	Predefined primary outcomes	Predefined secondary outcomes	Comparator	Sensitive analysis	Study results and conclusion	Association of TTA found with:
Lee et al.[28] (2018)	Cases: death or ICU admission. Controls: admitted at general ward and discharged.	Safety: death and ICU admission Treatment adequacy: NIA	NIA	TTA as a continuous variable Cases versus controls	TTA cases: 101 min (median) IQR 85 to 119 TTA controls: 110.5 min (median) IQR 83 to 139	No difference was observed between the groups in terms of TTA.	No association found
Lynn et al.[29] (2013)	Serious complications: hypotension (systolic blood pressure < 90 mmHg) requiring IV fluid challenge or inotropic agents, respiratory distress requiring high flow oxygen supplement (oxygen mask) or endotracheal tube intubation, altered level of consciousness (GCS < 14), new onset arrhythmia requiring intervention, and death during hospitalization.	Safety: death (overall and in composite outcome) Treatment adequacy: NIA	Length of stay (overall)	Serious complication vs. no serious complications TTA as continuous variable	TTA, pneumonia and platelet counts $\leq 50{,}000/mm^3$ were identified as independent factors associated with serious complications of FN.	TTA longer in episodes with serious complications. Median 122 min versus 97 min, $p = 0.0014$ Risk of serious complications increased by every minute increase in TTA, OR = 1.008; 95% CI 0.999–1.017 TTA in minutes was most important variable to predict serious complications. Cutoff 104 min.	Longer TTA in episodes with serious complications. Statistically significant difference in Fisher's test, but not in uni- and multivariable logistic regression
Perron et al.[30] (2014)	Serious adverse events: ICU admission and mortality. Length of stay (LOS)	Safety: death, ICU admission (both overall and in composite outcome) Treatment adequacy: NIA	Length of stay	High risk vs. low risk group. TTA as a continuous variable	No differences between the two MASCC risk groups with respect to TTA High risk: 3 h, range 0.22 to 19 Low risk: 2.5 h, range 0.03 to 50	TTA did not correlate with serious adverse events (no data shown). Delay in antibiotics administration associated with a longer hospital stay, (regression coefficient 0.31 days; 95% CI, 0.13–0.48).	Longer TTA with longer LOS No association with serious adverse events
Rosa et al.[18] (2014)	All-cause mortality 28 days after the onset of FN.	Safety: death Treatment adequacy: NIA	Bacteraemia (overall)	Mortality vs. Survival TTA ≤ 30 min vs. 31–60 min TTA as continuous variable	TTA mortality group: 1.66 h (median) IQR 5.17 TTA survival group: 0.33 (median) IQR 1.0 (HR, 1.18; 95% CI, 1.10 to 1.26)	TTA independently associated with mortality within 28 days, each increase of 1 h in TTA raised the risk of mortality within 28 days by 18%. Patients with TTA of ≤ 30 min had lower 28-day mortality rate than those with TTA 31–60 min (3.0% vs. 18.1%; log-rank $p = 0.0002$)	Longer TTA with increased mortality within 28 days
Sammut et al.[31] (2012)	Length of stay	Safety: death (overall) Treatment adequacy: NIA	Length of stay	TTA as a continuous variable	Patients received first dose of antibiotics faster when presented to oncology ward rather than ED.	Plotting length of stay against TTA showed a linear positive correlation between both variables ($R = 0.84$; $R^2 = 0.7$)	Longer TTA with longer LOS

Table 3 (continued)

Author and citation (year pub)	Outcomes reported by the study	Predefined primary outcomes	Predefined secondary outcomes	Comparator	Sensitive analysis	Study results and conclusion	Association of TTA found with:
Paediatric patients							
De la Maza et al.[19] (2015)	Death, ICU admission, sepsis hypotension, days of fever, days of hospitalization	Safety: death, ICU admission, sepsis Treatment adequacy: NIA	Days of fever Length of stay	> 60 min vs. ≤ 60 min	ED vs. outpatient clinic vs. oncology service: significant difference in TTA with longest at ED. Admission time: no difference. Different hospitals: significant difference in TTA.	TTA > 60 min not related to increased days of fever, frequency of hypotension, transfers to ICU or mortality. In univariate analysis, patients with TTA ≤ 60 min had increased LOS ((median (IQR)) 9 days (7–15) vs. 8 days (6–12); $p = 0.012$)) and increased frequency of sepsis (24% vs. 14%; $p = 0.022$)	In univariate analysis shorter TTA associated with increased LOS and frequency of sepsis
Fletcher et al.[5] (2013)	Adverse event (AE): in-hospital mortality and/or: admission to the paediatric intensive care unit and/or receipt of ≥ 40 ml/kg of fluid resuscitation within 24 h of presentation. ICU admission, length of stay	Safety: death (in composite outcome and overall), ICU admission Treatment adequacy: NIA	Length of stay Bacteraemia: (overall)	≤ 60 min vs. 61–120 min 60 min intervals of TTA TTA as a continuous variable	Presentation to the ED increases the risk for AE. In univariate analysis patients presenting at the weekend had more AEs (14.3%) than patients with weekday presentation (9.5%) ($p = 0.004$). Weekend presentation was not included into multivariate analysis.	Univariate analyses: admissions with composite AE outcome had higher median TTA (119 min vs. 113 min; OR 1.29; 95% CI, 1.02–1.64) Multivariate analysis: no association of TTA with AE outcome (as a continuous variable, OR 0.89; 95% CI, 0.65–1.24). 60-min TTA intervals were independently associated with increasing likelihood of AE (OR 1.81; 95% CI, 1.01–3.26) TTA and TTA 60-min intervals were not associated with PICU admission and LOS.	Longer TTA in patients with AEs (in univariate but not in multivariate analysis) No association with ICU admission and LOS
Gavidia et al.[17] (2012)	Infection death, Sepsis, overall number of ICU admissions. Invasive infection	Safety: death, sepsis, ICU admission (overall) Treatment adequacy: NIA	Invasive infection (overall)	TTA as continuous variable	Time to reach hospital was not predictive of sepsis or infectious death.	TTA not predictive for death, OR 1.02 (95% CI, 0.80 to 1.28; $p = 0.889$). Patients with sepsis had shorter TTA (OR 0.79 (95% CI, 0.63 to 0.99; $p = 0.041$). Hours from fever to IV antibiotics not associated with sepsis, OR 0.98 (95% CI 0.88–1.08; $p = 0.51$)	Shorter TTA in patients with sepsis No association with death
Salstrom et al.[20] (2015)	Death, ICU consultation or admission, length of hospitalization, duration of fever, need for imaging workup to search for occult infection, bacteraemia	Safety: death, ICU admission Treatment adequacy: NIA	Duration of fever Length of stay Bacteraemia	> 60 min vs. < 60 min	Death, LOS, duration of fever, need for imaging workup and bacteraemia did show a significant change after the intervention.	TTA < 60 min associated with decreased mortality (2.1% vs. 4.4%). This did not reach significance by Fisher's exact test but represents an absolute risk reduction of 3.2%, a relative risk reduction of 82.1%, and number needed to treat of 31. When maintenance phase was included into calculations, a statistically significant decreased need for ICU level care was shown for TTA < 60 min (12.6%) vs. > 60 min (29.9%).	Longer TTA with more ICU admission after inclusion of the maintenance phase. No association with death, LOS, duration of fever and bacteraemia

AE adverse event, *CI* confidence interval, *DIC* disseminated intravascular coagulation, *FN* fever and neutropenia, *ICU* intensive care unit, *LOS* length of hospital stay, *IV* intravenous, *MASC* Multinational Association for Supportive Care in Cancer risk index score, *NIA* no information available, *OR* odds ratio, *pub* published, *SIRS* systemic inflammatory response syndrome, *TTA* time to antibiotics

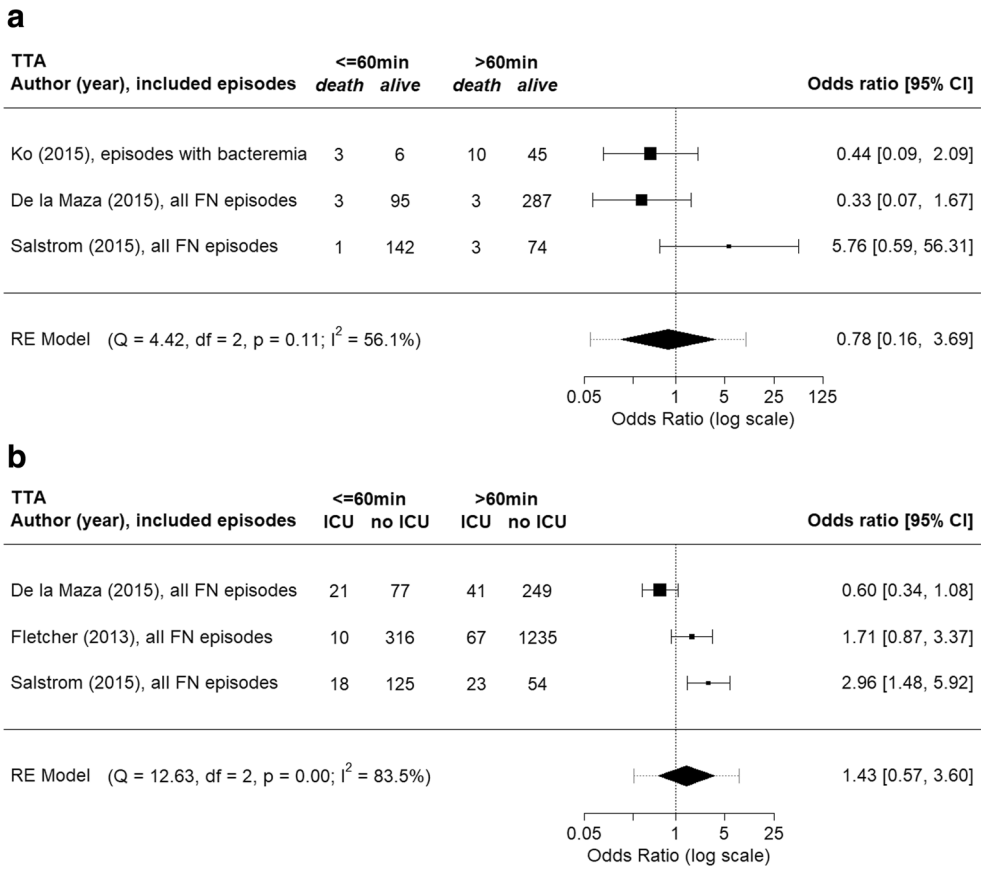

Fig. 2 **a** Meta-analysis on the association of TTA with death, paediatric and adult studies. **b** Meta-analysis on the association of TTA with ICU admission, all paediatric studies

60 min (11.8% with bacteraemia). No other study reported on association of these outcomes with TTA.

Secondary outcomes: duration of illness

Finally, the studies were screened for two additional outcomes: duration of fever and length of hospital stay (LOS). Average duration of fever for all included episodes (12 h; IQR, 4 to 24 h) was reported by one study [27]. The study reporting bacteraemia [20] also reported days of fever and likewise found no difference in days of fever in paediatric patients with TTA < 60 min (median 1.0 days) and > 60 min (median 2.0 days). Eight studies had data about length of hospital stay (LOS) [5, 19, 20, 25, 26, 29–31]. One study reported median LOS of all included patients; the seven other studies looked for an association between TTA and LOS. The two studies in paediatric patients [5, 20] found no association between LOS and TTA, as did the two of the adult studies [25, 26]. In contrast, Perron et al. [30] found a statistically significant Pearson correlation of 0.26 between TTA and LOS and 1 h delay resulted in approximately 8 h increase in LOS. Sammut et al. [31] plotted LOS against TTA and showed a positive linear correlation between both variables ($R = 0.84$, $R^2 = 0.7$). The eighth study [19] found an increased LOS (median 9 days (IQR, 7 to 15)) in patients with TTA ≤ 60 min compared to TTA > 60 min (median 8 days (IQR, 6 to 12)), but only in univariable, but not in multivariable analysis. Due to the clinical and statistical heterogeneity, meta-analysis was not considered appropriate for the secondary outcomes.

Subgroup analysis

For predefined subgroup analyses, the following results were available:

Paediatric and adult studies did show the same heterogeneity within the different outcomes as did the combined analysis. No further splitting was undertaken due to the small number of studies. The same confounders were identified for paediatric and adult patients.

To distinguish high risk versus low risk patients, one study [31] calculated an early warning score (EWS) for each adult patient and found a correlation between TTA and EWS (R^2 Ward = 0.69, R^2 ED = 0.57); the sicker the patient appeared, the more promptly antibiotics were delivered. Likewise, a second study [19] found that children with high-risk FN were more likely to receive the first dose of antibiotics in < 60 min (85% versus 74%). High-risk FN was defined as FN episode with one of the following factors at admission: relapse of leukaemia as cancer type, hypotension or CRP ≥ 90 mg/l or ≤ 8 days between end of last chemotherapy together with a platelet count ≤ 50×10^9/l. Five adult studies reported the risk status of

patients with the Multinational Association for Supportive Care in Cancer (MASCC) risk index score [18, 25–27, 30] and one with the quick sepsis-related organ failure assessment (qSOFA) score [28], but none analysed TTA according to the risk status. In one of them [30], higher risk status was correlated with longer LOS but not with death and ICU admission. In the other five [18, 25–28], higher risk status was associated with impaired safety, whereof one [26] additionally found a correlation with longer LOS.

The localisation of presentation was evaluated in three studies [5, 19, 31], and all three showed that TTA was longer in patients presenting at the ED compared to oncology ward or outpatient clinic. Additionally, in one of those studies [31], ED patients tended to have longer LOS, than those admitted directly to the ward, and in one study [5], significantly more adverse events occurred in patients presenting at the ED.

Admission time did not influence TTA in two studies; there was no difference in TTA between working and nonworking hours [19] and between weekend and weekday presentations [5].

No study gave enough data to distinguish between patients with severe versus non-severe neutropenia, with versus without comorbidities and with versus without antibiotic prophylaxis or inpatient versus outpatient FN.

One study [17] was undertaken in a lower-middle country and one study [18] in an upper-middle income country, both in Latin America. One of them had shown an association of longer TTA with increased mortality, the other did not and both of these studies had a shorter TTA in patients with sepsis. All other studies were undertaken in high-income countries [32].

Additionally, in the protocol, no predefined subgroup analysis of patients with bacteraemia or severe sepsis/septic shock was found in three studies. One study [27] found no significant relationship between TTA and mortality in both of these subgroup analyses, accordingly to their overall results. Likewise, another study [24] confirmed their overall results of no clear association between TTA and negative clinical outcome in a subgroup with proven bacteraemia. Contradicting this, Rosa et al. [18] found a lower mortality rate in patients treated within 30 min in subgroup analysis of patients with bacteraemia.

Discussion

When controlling for triage bias was undertaken, studies showed an association between safety and TTA [5, 18, 25], but there is still no clear data on a ‘safe’ TTA or an unequivocal direct association between TTA and death, admission to ICU or severe sepsis/septic shock. No data is available for the association of TTA and treatment adequacy. The results for the association of TTA and LOS were inconsistent, and due to lack of reporting, we cannot draw a conclusion for other secondary outcomes either. The assessment of outcomes and TTA is difficult due to various confounding factors, bias and inconsistent reporting among the published articles. Triage bias was identified to have a particularly strong influence.

Fletcher et al. [5] suggests that there are three patient populations with FN: (1) those who present with severe sepsis and are very likely to have poor outcomes in spite of short TTA, (2) those who present with mild FN in whom TTA will not influence the likelihood of poor outcome and (3) those who present with FN and other risk factors for poor outcome in whom TTA may meaningfully contribute to outcome. While these populations are theoretically distinct, they may overlap clinically.

If this theoretical model is true, the results of studies which investigate TTA by analysing the whole FN population do not show an association of longer TTA and safety outcomes. Inclusion of the first population creates triage bias, because healthcare professionals may be aware of patients at higher risk for poor outcome or complications. This influences the speed of assessment and may shorten TTA. Accordingly, patients from the second population may receive treatment later but still show a good outcome. The signal from the third population, where modification of TTA may lead to modified outcomes, is swamped by the other patients.

The authors of three studies at moderate risk for bias [17, 19, 30] stated in their articles that patients with high-risk FN received the first dose of antibiotics sooner than those with lower risk, creating exactly these biases. This may explain the result of one of those studies [19] in which sepsis was more common in patients with TTA ≤ 60 min. Three studies tried to control for triage bias by excluding sepsis patients [5] or excluding patients with reason for outpatient treatment [18] and with low risk score [25]. Those were the studies who found an association between impaired safety and longer TTA. Two studies judged at moderate risk for bias [20, 29] report an association between safety and TTA but had methodological weaknesses. The result of a longer TTA in patients with serious medical complications, in the study of Lynn et al. [29], was reported as statistically significant by the Fisher’s exact test, and the other study [20] describes extending the study period when the results were not significant, without describing the number of nature of the interim analyses.

The key strength of this manuscript lies in its thorough application of systematic review methodology. It thus provides the first in-depth assessment of the evidence base surrounding TTA and clinical outcomes in FN, across both adult and paediatric populations.

There were several challenges to summarizing the primary data sources. Analysis of treatment adequacy was planned to see whether a shorter TTA stops dissemination and protraction of an infection and therefore produces better treatment efficiency. The lack of data on treatment adequacy means we cannot judge if the potential benefits of investing in shortening TTA may improve overall outcomes compared with time-consuming further diagnostic tests that could reveal that some

patients do not need treatment at all. Although some studies tried to control for confounders by identification of risk status [19, 27, 30] or exclusion of specific patients [5, 18], we were unable to investigate most of the expected confounders. Subgroup analysis would be essential for further knowledge but were rarely possible. The different definitions of TTA and FN affect the comparability of the included studies, as do the differences within included patients. The studies were undertaken in different countries, and their results must be interpreted in the context of different healthcare provisions.

Our review emphasises the heterogeneity of studies examining TTA. Further research should include the suggested core set of minimal collected and reported outcomes [33] when investigating TTA to ensure consistency and comparability between studies in FN. Presentation at ED was identified as reason of longer TTA [19, 31] and even more frequent adverse events [5]. High workload due to high patient volumes or lack of training in care for oncology patients may explain this. This finding suggests oncology centres improve management of FN patients by making an effort to reduce TTA in patients presenting to the ED or providing direct-to-oncology access pathways. It has been shown that TTA can be effectively reduced by very different interventions, such as nurse-led administration of first-dose of antibiotics [34] or the implementation of guidelines [35].

Conclusion

There is a strong influence of triage bias and confounding factors, when investigating TTA. Controlling for these is possible and necessary to gain further evidence. Despite inconsistent evidence and acknowledged difficulty in achieving prompt TTA, experts and guidelines insist that timely and appropriate antibiotic administration is essential for adequate patient care [7–9] and we equally recommend to continue an administration of antibiotics as soon as possible in patients with FN during chemotherapy for cancer, as the question how antibiotics should be prioritised remains unanswered.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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