**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. Registration: PROSPERO [CRD42018092948].

*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 ≤60min versus >60min 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 optimize treatment guidelines for FN. Controlling for triage and other biases is necessary to gain further evidence.

**Key words:** 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 0.5x109/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 hour 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 minutes 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 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 organisations have defined TTA <60min 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 & Other Non-Indexed Citations, EMBASE, CINAHL, CDSR, CENTRAL and LILACS were performed on May 9th, 2018. The search was updated on April 5th, 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 was 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 hematopoietic 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 hematopoietic 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 was 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 & Laird estimator using the metafor library [22] within the R programming environment [23]. Statistical heterogeneity was quantified using χ2 tests, the I2 and tau2 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 Figure 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 5,186 and 2,461 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{, 2013 #9808}. 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°C to ≥38.5°C. Eleven studies defined neutropenia as an absolute neutrophil count (ANC) <0.5x109/l, in seven studies patients with an ANC expected to decrease to <0.5x109/l were included. Two studies defined neutropenia as ANC <1.0x109/l. One study[17] also included non-neutropenic patients, but 51% of the included patients had an ANC <0.5x109/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: 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 were 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 ≤30min (3.0%) compared to patients with a TTA 31-60min (18.1%) and TTA was longer (median 1.66h; IQR 5.17) in patients who died, compared to patient who survived (median 0.33h; IQR 1.0) (HR, 1.18; 95% CI, 1.10 to 1.26). Each increase of one hour 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 hours (OR 1.57) and 24 to 48 hours (OR 2.08, mortality 13%) when compared to TTA 0 to 2 hours (mortality 5%). This effect was not seen when TTA was only moderately delayed (2 to 3 hours; OR 0.87), and not statistically significant for the group treated from 6 to 24 hours (OR 1.37).

Three studies reported death in patients with TTA ≤60min versus >60min [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 (I2= 56.1%, tau2 = 1.05, Figure 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 hours of presentation; in patients treated within 60min (5.2% versus 14.2% in patients with TTA 61-120min; 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 (119min versus 113min;).The 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 122min versus 97min 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 <60min versus >60min 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 (I2= 83.5%, tau2 = 0.56, Figure 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 ≤60min (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 >60min and death or ICU admission.

**Primary outcomes: Treatment adequacy**

No study reported relapses of primary infection, persistence of fever for more than five 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 <60min (25% with bacteraemia) and >60min (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 hours; IQR, 4 to 24 hours), 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 <60min (median 1.0 days) and >60min (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 one hour delay resulted in approximately eight hours increase in LOS. Sammut et al. [31] plotted LOS against TTA and showed a positive linear correlation between both variables (R = 0.84, R2 = 0.7). The eighth study [19] found an increased LOS (median 9 days (IQR, 7 to 15)) in patients with TTA ≤60min compared to TTA >60min (median 8 days (IQR, 6 to 12)), but only in 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 (R2 Ward = 0.69, R2ED = 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 <60min (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 ≥90mg/L or ≤8days between end of last chemotherapy together with a platelet count ≤50x109/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 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 versus weekday presentation [5].

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

One study [17] was undertaken in a lower-middle country, 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].

Additional, in the protocol not predefined subgroup analysis of patients with bacteraemia or severe sepsis/septic shock, were found in three studies. One study [27] found no significant relationship between TTA and mortality in both of these subgroup analysis, 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 30min 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 health care 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, are 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 ≤60min. 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 summarising 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 affects 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 centers 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 prioritized 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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**References**

1. Bodey GP, Buckley M, Sathe YS & Freireich EJ (1966) Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med64, 328-340

2. Pizzo PA (1981) Infectious complications in the child with cancer. I. Pathophysiology of the compromised host and the initial evaluation and management of the febrile cancer patient. J Pediatr 98, 341-354

3. McCavit TL & Winick N (2012) Time-to-antibiotic administration as a quality of care measure in children with febrile neutropenia: a survey of pediatric oncology centers. Pediatr Blood Cancer 58, 303-305

4. Kapil P, MacMillan M, Carvalho M, Lymburner P, Fung R, Almeida B et al (2016) Assessment of Fever Advisory Cards (FACs) as an Initiative to Improve Febrile Neutropenia Management in a Regional Cancer Center Emergency Department. J Oncol Pract 12, e858-863

5. Fletcher M, Hodgkiss H, Zhang S, Browning R, Hadden C, Hoffmann T et al (2013) Prompt administration of antibiotics is associated with improved outcomes in febrile neutropenia in children with cancer. Pediatr Blood Cancer 60, 1299-1306

6. Koenig C, Morgan J, Ammann RA, Sung L & Phillips B (2019) Protocol for a systematic review of time to antibiotics (TTA) in patients with fever and neutropenia during chemotherapy for cancer (FN) and interventions aiming to reduce TTA. Syst Rev 8, 82

7. Klastersky J, de Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M et al (2016) Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. Ann Oncol 27, v111-v8

8. Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK et al (2018) Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol 36, 1443-1453

9. Lehrnbecher T, Robinson P, Fisher B, Alexander S, Ammann RA, Beauchemin M et al (2017) Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2017 Update. J Clin Oncol 35, 2082-2094

10. Deutsche Gesellschaft für Pädiatrische Infektologie (DGPI) und Gesellschaft Pädiatrische Onkologie und Hämatologie (GPOH) (2016) AWMF S2K Leitlinie: Diagnostik und Therapie bei Kindern mit onkologischer Grunderkrankung, Fieber und Granulozytopenie (mit febriler Neutropenie) außerhalb der allogenen Stammzelltransplantation. AWMF-Registernummer 048/14, finale Version 23.01.2016. https://www.awmf.org/uploads/tx\_szleitlinien/048‑014l\_S2k\_onkologische\_Grunderkrankung\_Fieber\_Granulozytopenie\_2016‑04‑verlaengert.pdf. Accessed 18.04.2018

11. Sterling SA, Miller WR, Pryor J, Puskarich MA 6 Jones AE (2015) The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis. Crit Care Med 43, 1907-1915

12. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S et al (2006) Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 34, 1589-1596

13. Proulx N, Frechette D, Toye B, Chan J & Kravcik S (2005) Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. QJM 98, 291-298

14. Bodilsen J, Dalager-Pedersen M, Schønheyder HC & Nielsen H (2016) Time to antibiotic therapy and outcome in bacterial meningitis: a Danish population-based cohort study. BMC Infect Dis 16, 392

15. Keng MK, Thallner EA, Elson P, Ajon C, Sekeres J, Wenzell CM et al (2015) Reducing time to antibiotic administration for febrile neutropenia in the emergency department. J Oncol Pract 11, 450-455

16. Van Vliet M, Potting CM, Sturm PD, Donnelly JP & Blijlevens NM (2011) How prompt is prompt in daily practice? Earlier initiation of empirical antibacterial therapy for the febrile neutropenic patient. Eur J Cancer Care 20, 679-285

17. Gavidia R, Fuentes SL, Vasquez R, Bonilla M, Ethier MC, Diorio C et al (2012) Low socioeconomic status is associated with prolonged times to assessment and treatment, sepsis and infectious death in pediatric fever in El Salvador. PLoS One 7, e43639

18. Rosa RG & Goldani LZ (2014) Cohort study of the impact of time to antibiotic administration on mortality in patients with febrile neutropenia. Antimicrob Agents Chemother 58, 3799-3803

19. De la Maza V, Simian D, Castro M, Torres JP, Lucero Y, Sepúlveda F et al (2015) Administration time for the first dose of antimicrobials in episodes of fever and neutropenia in children with cancer. Pediatr infect Dis J 34, 1069-1073

20. Salstrom JL, Coughlin RL, Pool K, Bojan M, Mediavilla C, Schwent W et al (2015) Pediatric patients who receive antibiotics for fever and neutropenia in less than 60 min have decreased intensive care needs. Pediatr Blood Cancer 62, 807-815

21. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M et al (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, i4919

22. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010, 36, 1-48.

23. R Core Team (2018) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org

24. Butts AR, Bachmeier CC, Dressler EV, Liu M, Cowden A, Talbert J et al (2017) Association of time to antibiotics and clinical outcomes in adult hematologic malignancy patients with febrile neutropenia. J Oncol Pharm Pract 23, 278-283

25. Daniels LM, Durani U, Barreto JN, O’Horo JC, Siddiqui MA, Park JG et al (2019) Impact of time to antibiotic on hospital stay, intensive care unit admission, and mortality in febrile neutropenia. Support Care Cancer. doi: 10.1007/s00520-019-04701­-8

26. Johannesmeyer HJ & Seifert CF (2019) A retrospective analysis of clinical acuity markers on hospital length of stay in patients with febrile neutropenia. J Oncol Pharm Pract 25, 535-543

27. Ko BS, Ahn S, Lee YS, Kim WY, Lim KS & Lee JL (2015) Impact of time to antibiotics on outcomes of chemotherapy-induced febrile neutropenia. Support Care Cancer 23, 2799-2804

28. Lee SJ, Kim JH, Han SB, Paik JH & Durey A (2018) Prognostic Factors Predicting Poor Outcome in Cancer Patients with Febrile Neutropenia in the Emergency Department: Usefulness of qSOFA. J Oncol 2183179

29. Lynn JJ, Chen KF, Weng YM & Chiu TF (2013) Risk factors associated with complications in patients with chemotherapy-induced febrile neutropenia in emergency department. Hematol Oncol 31, 189-196

30. Perron T, Emara M & Ahmed S (2014) Time to antibiotics and outcomes in cancer patients with febrile neutropenia. BMC Health Serv Res 14, 162

31. Sammut SJ and Mazhar D (2012) Management of febrile neutropenia in an acute oncology service. QJM 105, 327-236

32. World Bank Country and Lending Groups (2018) Word Bank list of economies (June 2018). <http://databank.worldbank.org/data/download/site-content/CLASS.xls>. Accessed 18 April 2019

33. Haeusler GM, Phillips RS, Lehrnbecher T, Thursky KA, Sung L & Ammann RA (2015) Core outcomes and definitions for pediatric fever and neutropenia research: a consensus statement from an international panel. Pediatr Blood Cancer 62, 483-489

34. Mattison G, Bilney M, Haji-Michael P, Cooksley T (2016) A nurse-led protocol improves the time to first dose intravenous antibiotics in septic patients post chemotherapy. Support Care Cancer 24:5001-5005

35. Lim C, Bawden J, Wing A, Villa-Roel C, Meurer DP, Bullard MJ, Rowe BH (2012) Febrile neutropenia in EDs: The role of an electronic clinical practice guideline. Am J Emerg Med 30 (1):5-11.e15

**Table and Figure captions**

**Tables**

**Table 1**: Characteristics of included studies. Key: *AB* antibiotics, *ALL* acute lymphatic leukaemia, *AML* acute myelogenous leukaemia, *CML* chronic myelogenous leukaemia, *CNS* central nervous system, *ED* Emergency department, *E* English, *GIT* gastrointestinal tract, *HIV* Human Immunodeficiency Virus, *HSCT* hematopoietic stem cell transplantation, *anti-PSDMN* anti-pseudomonal agent, *AG* aminoglycoside, *anti-GP* anti-gram-positive agent, *SD* standard deviation.

**Table 2:** Risk of bias assessment with ROBINS-I tool. Key: *NI* No information.

**Table 3:** Outcomes and study conclusions. Key: *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, *SIRS* systemic inflammatory response syndrome, *TTA* Time to antibiotics.

**Figure Captions**

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

**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