Office of Evidence Based Practice (EBP) – Critically Appraised Topic: Acetaminophen for Oncology and Bone Marrow Transplant Patients

Specific Care Question In childhood cancer patients and bone marrow transplant (BMT) patients, does the use of acetaminophen versus opioid medications lead to delayed recognition of fever and a subsequent increase in poor outcomes due to infection?

Recommendations Based on Current Literature (Best Evidence) Only

No recommendation can be made for or against the use of acetaminophen versus opioids medications. When there is a lack of scientific evidence, standard work should be developed, implemented, and monitored.

Literature Summary

Background. Febrile neutropenia can occur in oncology and BMT patients and without prompt antibiotic treatment can lead to increased mortality rates (Portenoy, Ahmed, & Keilson, 2019). Before discharge at Children's Mercy (CM), all patients (BMT and oncology) are prescribed opioids for pain as CM clinicians believe acetaminophen will mask a fever in this population.

Opioid therapy is the first-line drug for moderate or severe chronic pain in populations with cancer (Portenoy et al., 2019). The World Health Organization (WHO) recommends a stepwise approach to management of cancer pain that includes both opioid and nonopioid drugs with the use of acetaminophen for mild to moderate cancer-related pain (WHO, 2019). A Cochrane Review (Wiffen et al., 2017) on the use of oral acetaminophen for cancer pain, reported there is no high-quality evidence to support or refute the use of acetaminophen alone or in combination with opioids for cancer pain. Measures of harm (serious adverse events, other adverse events, and withdrawal due to lack of efficacy) were inconsistently reported and provided no clear evidence of difference (Wiffen et al., 2017).

Study characteristics. The search for suitable studies was completed on August 20, 2019. J. Thompson, MD reviewed 15 titles and/or abstracts found in the search and identified four single studies believed to answer the question. After an in-depth review of the remaining articles, none of the studies answered the question (see Figure 1). While no studies were found that answered the question directly, two studies were identified that might provide an understanding of attitudes and problems that need to be considered for future research.

In a survey (Weinkove, Clay, & Wood, 2013) of doctors and nurses (N = 88) from New Zealand, 68% of doctors indicated that they would allow a neutropenic patients to take acetaminophen as needed for pain, and a further 15% would allow a neutropenic outpatient to take regular acetaminophen. Nurses were more likely than doctors to advise a neutropenic patient to avoid acetaminophen, $p < 0.05$.

In a cohort study from India (Oberoi, Trehan, Marwaha, & Bansal, 2013) febrile neutropenic children (N = 320) with acute lymphoblastic leukemia (ALL) were evaluated for delayed presentation to the hospital. The most common reason for delay was false reassurance secondary to defervescence resulting from intake of acetaminophen (30%). Intake occurred despite counseling sessions, where patients were advised to avoid intake of acetaminophen at the onset of fever.

Identification of Studies

Search Strategy and Results (see Figure 1)

("Antipyretics"[MeSH Terms]) AND ("Neutropenia"[MeSH Terms] OR "febrile neutropenia" OR "neutropenic fever")
(symptom to door) AND ((cancer AND (fever OR "Neutropenia"[Mesh])) OR "Febrile Neutropenia"[Mesh] OR "Chemotherapy-Induced Febrile Neutropenia"[Mesh]) ("Cancer Pain"[Mesh]) AND (fever OR "Neutropenia"[Mesh] OR "Febrile Neutropenia"[Mesh] OR "Chemotherapy-Induced Febrile Neutropenia"[Mesh]) ("Cancer Pain"[Mesh]) AND (infection) ("Cancer Pain"[Mesh]) AND ("Neutropenia"[Mesh] OR "Febrile Neutropenia"[Mesh] OR "Chemotherapy-Induced Febrile Neutropenia"[Mesh]) ((((("Induction Chemotherapy"[Mesh]) OR "Neutropenia"[Mesh]) OR "Immunosuppression"[Mesh]) OR ("Antineoplastic Combined Chemotherapy Protocols"[Mesh] OR "Antineoplastic Agents"[Mesh])) AND "Acetaminophen"[Mesh]
"Acetaminophen"[Mesh] AND ("Chemotherapy-Induced Febrile Neutropenia"[Mesh] OR "Febrile Neutropenia"[Mesh] OR cancer[tiab] OR oncology[tiab] OR neoplasms[Mesh] OR "bone marrow transplant") "Acetaminophen"[Mesh] AND ("Chemotherapy-Induced Febrile Neutropenia"[Mesh] OR "Febrile Neutropenia"[Mesh] OR cancer OR oncology OR neoplasms OR bone marrow transplant) "Acetaminophen"[Mesh] AND ("Chemotherapy-Induced Febrile Neutropenia"[Mesh] OR "Febrile Neutropenia"[Mesh] OR "neutropenia"[Mesh] OR cancer OR oncology OR neoplasms OR bone marrow transplant)

"Acetaminophen"[Mesh] AND ("Chemotherapy-Induced Febrile Neutropenia"[Mesh] OR "Febrile Neutropenia"[Mesh] OR ("neutropenia"[Mesh] AND (cancer OR oncology))) (cancer[tiab] OR oncology[tiab] OR "Neoplasms"[Mesh] OR "Cancer Pain"[Mesh] OR "Bone Marrow Transplantation"[Mesh]) AND "Acetaminophen"[Mesh] AND ("Chemotherapy-Induced Febrile Neutropenia"[Mesh] OR "Febrile Neutropenia"[Mesh] OR "Fever"[Mesh] OR "Infection"[Mesh]) AND (child OR children OR pediatr* OR paediatr*) "Acetaminophen"[Mesh] AND ("Chemotherapy-Induced Febrile Neutropenia"[Mesh] OR "Febrile Neutropenia"[Mesh] OR ("neutropenia"[Mesh] AND (cancer OR oncology))) AND (child OR children OR pediatr* OR paediatr*) ("Cancer Pain"[Mesh]) AND "Acetaminophen"[Mesh] (cancer[tiab] OR oncology[tiab] OR "Neoplasms"[Mesh] OR "Cancer Pain"[Mesh] OR "Bone Marrow Transplantation"[Mesh]) AND "Acetaminophen"[Mesh] AND ("Fever"[Mesh] OR "Infection"[Mesh]) AND (child OR children OR pediatr* OR paediatr*)

Records identified through database searching *n* = 15
Additional records identified through other sources *n* = 0

Studies Included in this Review

Citation	Study Type
No studies identified	

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Dokko (2015)	Review article
Oberoi et al. (2013)	Did not compare to opioid
Reymond et al. (1997)	Inpatient setting looking at IV acetaminophen
Weinkove et al. (2013)	Survey

Methods Used for Appraisal and Synthesis

[a]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

bThe Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

[a]Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews, 5*(1), 210. doi:10.1186/s13643-016-0384-4

[b]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 **For more information, visit www.prisma-statement.org.**

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Acronyms Used in this Document

Acronym	Explanation
ALL	Acute lymphoblastic leukemia

BMT	Bone marrow transplant
CM	Children's Mercy
EBP	Evidence Based Practice
WHO	World Health Organization

Date Developed / Updated

October 2019

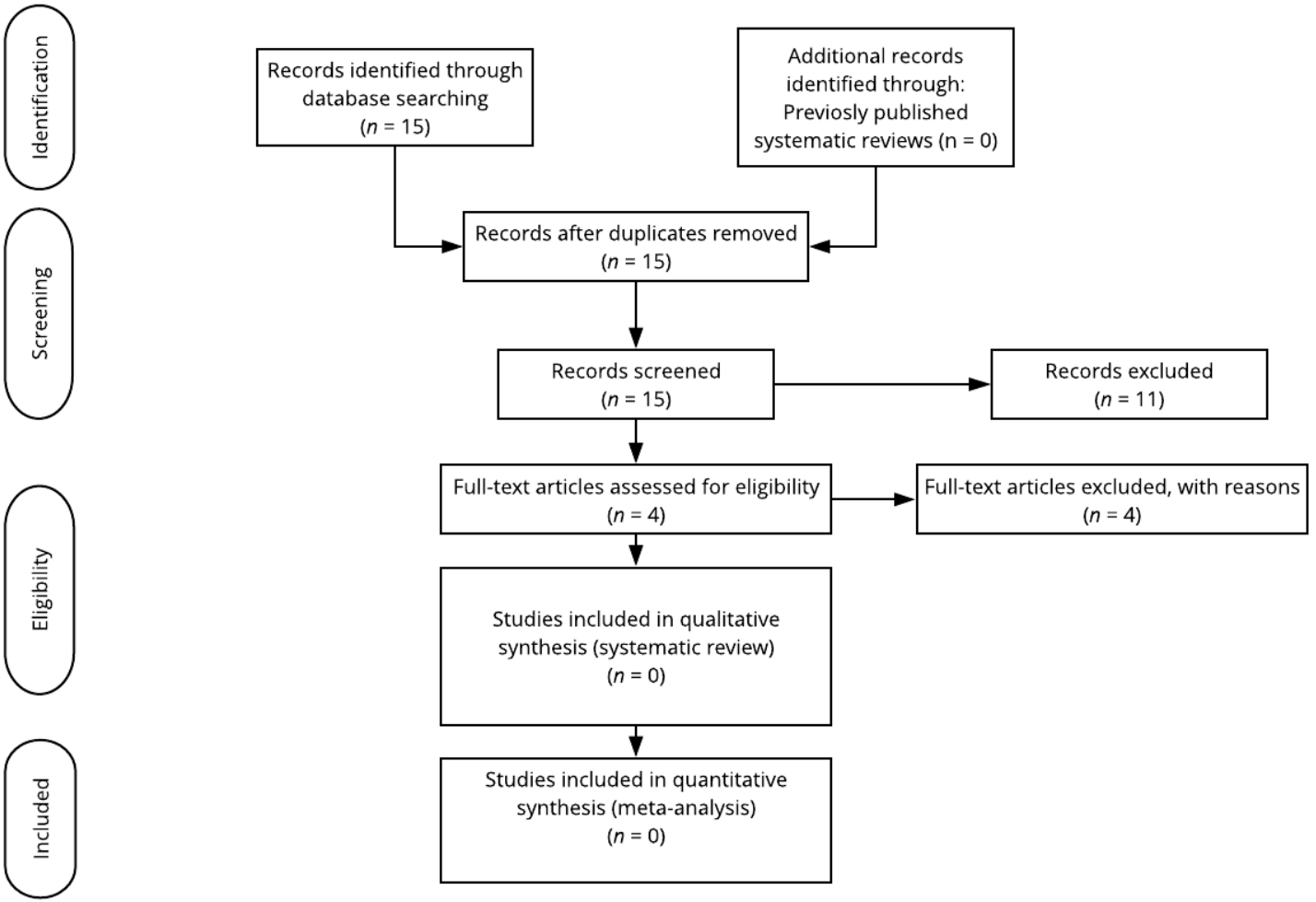

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[e]

References

Dokko, D. (2015). Best practice for fever management with intravenous acetaminophen in pediatric oncology. *J Pediatr Oncol Nurs, 32*(2), 120-125. doi:10.1177/1043454214543018

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Portenoy, R.J., Ahmed, E., Keilson, Y.Y., (2019). Cancer pain management: Use of acetaminophen and nonsteroidal anti-inflammatory drugs. *UptoDate.* Available from https://www.uptodate.com/contents/cancer-pain-management-use-of-acetaminophen-and-nonsteroidal-antiinflammatory-drugs?search=paracetamol%20cancer%20pain&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

Reymond, D., Birrer, P., Luthy, A. R., Rimensberger, P. C., & Beck, M. N. (1997). Antipyretic effect of parenteral paracetamol (propacetamol) in pediatric oncologic patients: a randomized trial. *Pediatr Hematol Oncol, 14*(1), 51-57.

Weinkove, R., Clay, J., & Wood, C. (2013). Temperature management in haematology patients with febrile neutropenia: a practice survey. *N Z Med J, 126*(1373), 62-73.

Wiffen, P. J., Derry, S., Moore, R. A., McNicol, E. D., Bell, R. F., Carr, D. B., . . . Wee, B. (2017). Oral paracetamol (acetaminophen) for cancer pain. *Cochrane Database Syst Rev, 7*, Cd012637. doi:10.1002/14651858.CD012637.pub2

World Health Organization. (2019, January). WHO Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. https://www.who.int/ncds/management/palliative-care/cancer-pain-guidelines/en/