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Guideline for Antibacterial Prophylaxis Administration in Pediatric Cancer and Hematopoietic Stem Cell Transplantation

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Summary: This clinical practice guideline presents recommendations for systemic antibacterial prophylaxis administration in pediatric cancer and hematopoietic stem cell transplantation patients. The recommendations were developed by an international panel based on the results of a systematic review of 114 randomized trials.

ABSTRACT

Introduction: Bacteremia and other invasive bacterial infections are common among children with cancer receiving intensive chemotherapy and in pediatric recipients of hematopoietic stem cell transplantation (HSCT). Systemic antibacterial prophylaxis is one approach that can be used to reduce the risk of these infections. Our purpose was to develop a clinical practice guideline (CPG) for systemic antibacterial prophylaxis administration in pediatric cancer and HSCT patients.

Methods: An international and multi-disciplinary panel was convened with representation from pediatric hematology/oncology and HSCT, pediatric infectious diseases (including antibiotic stewardship), nursing, pharmacy, a patient advocate and a CPG methodologist. The panel used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to generate recommendations based on the results of a systematic review of the literature.

Results: The systematic review identified 114 eligible randomized trials of antibiotic prophylaxis. The panel made a weak recommendation for systemic antibacterial prophylaxis for children receiving intensive chemotherapy for acute myeloid leukemia and relapsed acute lymphoblastic leukemia (ALL). Weak recommendations against the routine use of systemic antibacterial prophylaxis were made for children undergoing induction chemotherapy for ALL, autologous HSCT and allogeneic HSCT. A strong recommendation against its routine use was made for children whose therapy is not expected to result in prolonged severe neutropenia. If used, prophylaxis with levofloxacin was recommended during severe neutropenia.

Conclusions: We present a CPG for systemic antibacterial prophylaxis administration in pediatric cancer and HSCT patients. Future research should evaluate the long-term effectiveness and adverse effects of prophylaxis.

Keywords: practice guideline; bacterial infection; prevention; pediatric, oncology, hematopoietic stem cell transplantation

Introduction

Bacteremia and other invasive bacterial infections are common among children with cancer receiving intensive chemotherapy and pediatric recipients of hematopoietic stem cell transplantation (HSCT).[1-3] Systemic antibacterial prophylaxis is one approach that can be used to reduce the risk of these infections. Decision making regarding routine utilization of antibacterial prophylaxis involves weighing measures of efficacy against potential negative consequences. Measures of efficacy of prophylaxis include reductions in fever, bacteremia, sepsis, infection-related mortality and overall mortality. Potential negative consequences of prophylaxis include *Clostridioides difficile* infection, invasive fungal disease, drug toxicities and antibiotic resistance.[4-6]

While decision making regarding antibacterial prophylaxis will be informed by local bacterial resistance patterns and jurisdictional drug availability, development of a clinical practice guideline (CPG) may promote more standardized practice. A CPG was developed by the American Society of Clinical Oncology and the Infectious Diseases Society of America for patients with cancer but the target audience was restricted to adults.[7] Thus, there is the lack of guidance specifically for pediatric patients.

Our objective was to create a CPG for systemic antibacterial prophylaxis administration in pediatric cancer and HSCT patients.

Methods

General CPG Development Approach: We convened a multi-disciplinary and multi-national CPG panel (details in Appendices 1-3). The CPG was created using standard approaches for the development of evidence-based CPGs[8] with the Appraisal of Guidelines for Research & Evaluation II instrument as a framework[9] (details in Appendix 3).

Panel members developed the key clinical questions (Table 1) and identified and rated the importance of outcomes by consensus. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to determine level of evidence and to formulate recommendations.[10] The level of evidence was rated as high, moderate, low or very low based upon

certainty in treatment effects to the target population. Certainty was influenced by limitations in study design, and consistency, precision and directness of the data. Recommendations were either strong or weak. A strong recommendation was made when the benefits clearly outweighed the risks or vice versa and thus, patients should in general receive (or not receive) the recommended intervention as a matter of policy. Conversely, a weak recommendation was made when the benefits and risks of the intervention were closely matched or uncertain. In this setting, preferences and values should impact on intervention administration. In making recommendations, we considered efficacy, safety, costs and resources.

Searching, Selecting and Describing the Evidence: To create this CPG, we focused on randomized trials because in general, they are at lower risk of bias compared to observational studies.[11] We recently conducted a systematic review of randomized trials of systemic antibacterial prophylaxis and described the efficacy and adverse effects associated with different systemic antibiotics.[12] We included both adult and pediatric trials in data synthesis. For this CPG, we updated the systematic review and separately summarized the pediatric data.

We included outcomes that were considered critical or important to recommendation decision making. Resistance was examined in two ways. First, resistance was examined in studies comparing an antibiotic against no antibiotic controls and was defined as resistance to the intervention antibiotic among bacteremia isolates. These results were synthesized. Second, we also described the results of all studies that systematically compared acquisition or prevalence of resistant colonizing organisms at the end of the treatment period between randomized groups. These results were not synthesized. We used the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[13]

Statistical Analysis:

Data were synthesized using the risk ratio (RR) as the effect measure with its 95% confidence interval (CI). In this meta-analysis, a RR < 1 indicates that the intervention is better than control. Treatment effects were estimated by the Mantel-Haenszel approach and weighted by the inverse variance.

Analysis used a random effects model. For primary comparisons, we only synthesized outcomes when there were at least three studies with available data.

We used subgroup analyses to determine whether pre-specified characteristics explained heterogeneity in the treatment effect. We reported stratum effects and the P value for interaction if at least two studies reported an outcome within each stratum.

Results

There were 114 publications included in the systematic review; the flow diagram of study identification and selection is described in Appendix 4. Characteristics of included trials are presented in Appendix 5. There were four comparisons amenable to funnel plots (data not shown). Publication bias was only suggested in the comparison of fluoroquinolone vs. no antibiotic for the outcome of overall mortality; Appendix 6 shows the plot and results of the fill and trim approach.

Table 2 shows all evaluated interventions including the three main comparisons against no antibiotic, namely a fluoroquinolone, trimethoprim-sulfamethoxazole and a cephalosporin. Fluoroquinolone prophylaxis significantly reduced bacteremia (RR 0.56, 95% CI 0.41-0.76), fever (RR 0.70, 95% CI 0.57-0.86) and fever and neutropenia (FN, RR 0.88, 95% CI 0.82-0.95). Fluoroquinolone prophylaxis was not significantly associated with more *C. difficile* infection, invasive fungal disease and musculoskeletal toxicities, while it was significantly associated with more fluoroquinolone resistance in bacteremia isolates (RR 3.35, 95% CI 1.12-10.03). Trimethoprim-sulfamethoxazole prophylaxis significantly reduced bacteremia (RR 0.59, 95% CI 0.41-0.85) and infection-related mortality (RR 0.61, 95% CI 0.39-0.94). However, it also increased trimethoprim-sulfamethoxazole resistance in bacteremia isolates (RR 2.91, 95% CI 1.65-5.12). Cephalosporin prophylaxis significantly reduced bacteremia (RR 0.30, 95% CI 0.16-0.58). Table 2 also shows that rifampin and fluoroquinolone co-administration significantly reduced bacteremia compared to fluoroquinolone alone (RR 0.36, 95% CI 0.17-0.77).

Appendix 7 shows stratified analyses for a fluoroquinolone, trimethoprim-sulfamethoxazole and a cephalosporin vs. no antibiotic for the outcomes of bacteremia and infection-related mortality. In general,

evaluated factors did not explain heterogeneity in the prophylaxis effect and differences were not observed based upon treatment (chemotherapy, HSCT or both), participant age or risk of bacteremia in the control group. An exception was a marginally statistically significant interaction (P=0.04) for the comparison of cephalosporin vs. no antibiotic for the outcome of bacteremia when stratified by the risk of bacteremia in the control group.

Table 3 shows the details of the 13 pediatric studies stratified by the comparison group. Only three studies were conducted in the last 15 years; all compared a fluoroquinolone vs. no antibiotic. The largest and most recent study included 624 patients and stratified the analysis by (a) acute myeloid leukemia (AML) and relapsed acute lymphoblastic leukemia (ALL), and (b) myeloablative autologous and allogeneic HSCT.[14] All pediatric studies of trimethoprim-sulfamethoxazole vs. no antibiotic were published in 1987 or earlier.

Appendix 8 summarizes the studies that evaluated resistance in colonizing organisms at the completion of the study period. Among three fluoroquinolone vs. no antibiotic studies, the largest was the pediatric study that compared levofloxacin vs. no antibiotic.[14] This study evaluated development of resistance to levofloxacin, cefepime, imipenem and penicillin among *a priori* defined stool commensals and did not show a difference between randomized groups. The other two studies also showed no difference in resistance to ciprofloxacin[15] or norfloxacin[16] associated with fluoroquinolone administration. In contrast, the two trimethoprim-sulfamethoxazole vs. no antibiotic studies both suggested more resistant colonizing organisms in the intervention group.

Table 1 presents health questions, recommendations, strength of recommendation, level of evidence and remarks. Explanations are outlined below. Table 4 shows identified research gaps.

Recommendation 1: Consider systemic antibacterial prophylaxis administration in children with AML and relapsed ALL receiving intensive chemotherapy expected to result in severe neutropenia (absolute neutrophil count < 500/uL) for at least seven days

Weak recommendation, high quality evidence

Explanation: The panel deliberated the overall analyses, direct pediatric data and resistance information in formulating this recommendation. Direct data for pediatric patients with AML and relapsed ALL were available in the trial that compared levofloxacin vs. no antibiotic where the risk of bacteremia in the control group was 43.4%.[14] Levofloxacin prophylaxis significantly reduced bacteremia in this group (RR 0.50, 95% CI 0.32-0.78). Prophylaxis also significantly reduced *C. difficile* positive tests, and exposure to broad-spectrum antibiotics including aminoglycosides, third and fourth generation cephalosporins and antibiotics used as empiric therapy for FN among all patients (Table 3). The panel agreed that absolute reductions in bacteremia and FN were meaningful. Effects were consistent across analyses and populations, increasing quality of evidence. Further, the panel deliberated the trade-off of greater exposure to prophylactic antibiotics against decreasing exposure to other broad-spectrum antibiotics. These considerations led to a recommendation for systemic antibacterial prophylaxis in this population.

However, the panel had major reservations about making a strong recommendation for systemic antibacterial prophylaxis. First was the clear signal of increased antibiotic resistance in bacteremia isolates associated with prophylaxis (Table 2). The panel was concerned that widespread adoption of prophylaxis could increase resistance to an extent that would preclude utilization of that antibiotic either for prophylaxis or treatment.[17, 18] Second, the panel highlighted that the evidence was obtained from studies in which selected patients (those randomized to the intervention group) were administered prophylaxis over a finite period of the clinical trial. The impacts of a universal prophylaxis strategy over multiple treatment periods at both the patient and institutional level are uncertain.[17] Third, the panel discussed the potential for emergence of cross-resistance beyond the administered prophylactic agent. Understanding local resistance epidemiology is critical to the decision of whether to implement prophylaxis. Finally, the synthesis failed to show that systemic antibiotic prophylaxis reduced overall mortality.

The panel discussed the possibility of alternative approaches to antibacterial prophylaxis such as

optimizing management of bacteremia/sepsis. However, these approaches were not thought to be mutually exclusive as prevention of bacteremia and improving the management of bacteremia/sepsis are both desirable. It is also worth noting that in recent periods, mortality due to bacteremia in pediatric high-risk populations is very rare and no deaths were reported in the large pediatric levofloxacin prophylaxis trial.[14]

Recommendation 2: We suggest that systemic antibacterial prophylaxis not be used routinely for children receiving induction chemotherapy for newly diagnosed ALL

Weak recommendation, low quality evidence

Explanation: In terms of studies conducted within the last 15 years, only two trials included children undergoing induction therapy for ALL. One study comparing ciprofloxacin vs. placebo was conducted in Thailand;[19] prevalence of bacteremia in the control group was 2%. The second study was conducted in Indonesia and also compared ciprofloxacin vs. placebo.[20] At baseline, 37/110 were undernourished and abandonment during induction occurred in 10/110. The panel believed that neither of these studies were applicable to the setting of induction ALL in high income countries, where the risk of bacteremia associated with contemporary induction ALL regimens is typically greater than 10%.[21-23]

The panel recognized that a recommendation for administration of systemic antibacterial prophylaxis would have a large impact since ALL is the most common pediatric cancer diagnosis. The weak recommendation against routine prophylaxis was based upon the lower risk of bacteremia in the absence of prophylaxis (when compared to children with AML and relapsed ALL),[24] the uncertain benefit in this specific population and the more certain impact on resistance in bacteremia isolates. However, the panel also recognized heterogeneity in the risk of FN and bacteremia based upon treatment protocol and patient-related factors such as Down syndrome. Further data are required to identify sub-groups of pediatric ALL patients who might particularly benefit from prophylaxis and to describe the effectiveness of prophylaxis in these groups. The effectiveness of prophylaxis is even more uncertain

during other phases of intensive ALL treatment outside of induction. Consideration could be given to extending this recommendation to blocks of intensive ALL chemotherapy outside of induction associated with prolonged severe neutropenia.

Recommendation 3: Do not use systemic antibacterial prophylaxis for children whose therapy is not expected to result in severe neutropenia (absolute neutrophil count < 500/uL) for at least seven days
Strong recommendation, moderate quality evidence

Explanation: The relative effect of prophylaxis to reduce bacteremia did not differ based upon control group bacteremia risk (Appendix 7). However, the panel noted that the absolute risk reduction becomes clinically unimportant when the risk of bacteremia decreases sufficiently. Thus, for patients whose therapy is not expected to result in prolonged severe neutropenia, the panel made a strong recommendation against systemic antibacterial prophylaxis because patients would be exposed to adverse effects of prophylaxis without realizing clinically important benefits.

Recommendation 4: We suggest that systemic antibacterial prophylaxis not be used routinely for children undergoing autologous HSCT
Weak recommendation, moderate quality of evidence

Explanation: The rationale for this weak recommendation against routine use of antibacterial prophylaxis is similar to that supporting Recommendations 2 and 3. That is, a smaller clinical benefit in comparison to children with AML and relapsed ALL related to the lower risk of bacteremia in the absence of prophylaxis, and the same anticipated downsides, including impact on resistance. The risk of bacteremia was derived from the recent pediatric trial[14] (Table 3) that showed a control group risk of 11.5% among autologous HSCT recipients compared to 43.4% among the AML and relapsed ALL group. The lack of interaction observed by treatment group (chemotherapy, HSCT or both) (Appendix 7) and the direct

evidence from the recent pediatric trial that included autologous HSCT patients[14] (Table 3) support similar relative effects of prophylaxis on infection outcomes in this population. However, because the baseline risk of bacteremia is lower in HSCT patients compared to AML and relapsed ALL patients, the absolute risk reduction is consequently smaller. The panel concluded that this smaller clinical benefit was outweighed by the impact of prophylaxis on resistance.

There was debate about factors in autologous HSCT patients that could change the balance of risks and benefits. The shorter duration of neutropenia in autologous HSCT with briefer exposure to prophylaxis may diminish impact on resistance. However, use of tandem autologous HSCTs and resultant multiple cycles of prophylaxis could increase impact on resistance. The panel also noted that autologous HSCT is often the final intensive course of treatment and that this sequence could reduce the impact of resistance at the individual level although would not alter impact at the institutional level. While the panel made a weak recommendation against prophylaxis, institutions or providers may opt for prophylaxis if the reduction in bacteremia risk enables transition to outpatient therapy.

Recommendation 5: We suggest that systemic antibacterial prophylaxis not be used routinely for children undergoing allogeneic HSCT

Weak recommendation, moderate quality of evidence

Explanation: The panel acknowledged that the granularity of available data did not allow a different recommendation for allogeneic compared to autologous HSCT recipients. Thus, the evidence base that underlies this recommendation is very similar to that made for autologous HSCT. Further, as these patients are routinely managed in hospital during the high-risk period, there is opportunity for very early empiric antibiotic administration and supportive care to reduce complications of bacteremia and severe sepsis. The panel noted that allogeneic HSCT recipients often have preceding conditions that could be associated with prophylaxis (for example, AML or relapsed ALL), have prolonged neutropenia during the HSCT process, and are at risk for graft-versus-host disease and subsequent intensive immunosuppressive

therapies, which could influence the effectiveness and adverse effects associated with prophylaxis.

Recommendation 6: Levofloxacin is the preferred agent if antibacterial prophylaxis is planned

Strong recommendation, moderate quality evidence

Explanation: If used, prophylaxis should be directed at pathogens that are responsible for severe or difficult-to-treat infections. The strong recommendation to use levofloxacin if antibacterial prophylaxis is planned was based upon recent trials, direct data and the microbiological spectrum of activity. Although fluoroquinolones, trimethoprim-sulfamethoxazole and cephalosporins were all effective at reducing bacteremia, recent trials focused on fluoroquinolones. Trimethoprim-sulfamethoxazole was not recommended because those studies were at higher risk of bias (Appendix 7), potential for increased resistance in colonizing organisms (Appendix 8) and risk for drug-induced myelosuppression[25]. Levofloxacin in particular was preferred related to the recent large pediatric trial showing benefits[14] and broad-spectrum activity against important organisms in pediatric high-risk populations.

The panel noted that levofloxacin or pediatric-friendly levofloxacin dosage forms may not be available in all countries. Availability of oral suspension will impact on feasibility of levofloxacin administration in young children treated as outpatients. If levofloxacin is not able to be used, ciprofloxacin is an alternative although reduced activity relative to levofloxacin against Gram positive bacteria, including viridans group streptococci, may reduce the benefits of prophylaxis. Understanding local resistance epidemiology is critical to the decision of whether to implement fluoroquinolone prophylaxis.

Although the data supported administration of a fluoroquinolone if systematic antibacterial prophylaxis is planned, the panel was concerned about reported adverse effects associated with these agents and levofloxacin in particular.[6, 26] Patients and families should be informed about potential short and long-term fluoroquinolone-related adverse effects prior to administration and this information

may lead to some families choosing against prophylaxis. If fluoroquinolones are not available or cannot be used, providing no systemic antibacterial prophylaxis is an important option to consider.

Recommendation 7: If antibacterial prophylaxis is planned, we suggest that administration be restricted to the expected period of severe neutropenia (absolute neutrophil count < 500/uL)
Weak recommendation, low quality evidence

Explanation: There are no randomized trials to support different approaches to initiation and discontinuation of systemic antibacterial prophylaxis in this patient population. Thus, this is a weak recommendation based on low quality evidence. This recommendation reflects the available evidence and the panel's desire to minimize duration of prophylaxis administration.

Discussion

In this CPG, we present recommendations for the administration of systemic antibacterial prophylaxis in pediatric cancer and HSCT patients. Several issues were repeatedly emphasized during panel discussions. First was the weighing of short-term benefits in reducing bacteremia and FN balanced against the more long-term potential consequences of increasing resistance rates in patients and within institutions. If prophylaxis is implemented, institutions should closely monitor resistance rates over time. Second was the acknowledgement that the trials, while critical to making recommendations, do not reflect consequences of a universal prophylaxis strategy either related to effectiveness or risks of prophylaxis. Third, although the panel recommended, based upon available trials, a fluoroquinolone as the agent for prophylaxis, concern was raised about the adverse effect profile. Patients and families will need to be informed about these risks, and these outcomes require further study in centers where prophylaxis is instituted.

A limitation of the evidence base is that the number of pediatric trials precluded restricting the synthesis to children. In addition, trials were not conducted in the era of increasing use of immunotherapy

and more data in this setting are required. As with all CPGs, establishing implementation processes including local adaptation are important steps. Institutions will also need to decide what threshold of antibacterial resistance would mandate a change in policy regarding systemic antibacterial prophylaxis.

In summary, we present a CPG for systemic antibacterial prophylaxis administration in pediatric cancer and HSCT patients. Future research should evaluate the long-term effectiveness and adverse effects of prophylaxis.

Author contributions:

Study concepts and design: TL, BF, PDR, LS

Data acquisition: GE, PDR

Data analysis: PDR, LS

Data interpretation: All

Drafting the manuscript or revising it critically for important intellectual content: All

Final approval of version to be published: All

Agreement to be accountable for all aspects of the work: All

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Conflicts of Interest Statements

TL has a consultant relationship with Gilead Sciences, Merck/MSD, and Astellas, and received unrestricted research support from Gilead Sciences

BF's research institute receives support for the research he does on behalf of Pfizer and Merck and he serves on a Data Safety and Monitoring Board for Astellas

B. P. reports involvement with the development of a clinical trial to test the benefit of prophylactic fluroquinolones in pediatric acute leukemia.

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EC served as consultant and speakers' bureau for Astellas, Basilea Pharmaceutica, Gilead, Pfizer

AHG has received research support from Gilead, Merck, Sharp & Dohme and Pfizer, is or has been a consultant to Amplyx, Astellas, Basilea, F2G, Gilead, Merck, Sharp & Dohme, and Pfizer, and served at the speaker's bureau of Astellas, Basilea, F2G, Gilead, Merck, Sharp & Dohme and Pfizer

WJS is on the Scientific Advisory Board for Astellas and Merck and reports other financial support (site in clinical trial) from Astellas and Merck

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All other authors declare no conflict of interest

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Table 1: Summary of Recommendations for Systemic Antibacterial Prophylaxis in Children with Cancer and Pediatric Hematopoietic Stem Cell Transplant Recipients

Health Questions and Recommendations	Strength of Recommendation and Level of Evidence
Which pediatric patients with cancer and HSCT recipients (if any) should routinely receive systemic antibacterial prophylaxis?	
1. Consider systemic antibacterial prophylaxis administration in children with AML and relapsed ALL receiving intensive chemotherapy expected to result in severe neutropenia (absolute neutrophil count < 500/uL) for at least seven days ***Remarks***: This is a weak recommendation because the benefits of prophylaxis were closely balanced against its known and potential impacts on resistance. The panel valued what is known about efficacy and resistance outcomes of prophylaxis administered within the finite time frame of a clinical trial among enrolled participants, but also considered the less certain impacts of a universal prophylaxis strategy at both the patient and institutional level. Limiting prophylaxis to patient populations at highest risk of fever and neutropenia, bacteremia and infection-related mortality could limit antibiotic utilization to those most likely to benefit from prophylaxis. Careful discussion with patients and families about the potential risks and benefits of prophylaxis is important. Understanding local resistance epidemiology is critical to the decision of whether to implement prophylaxis.	Weak recommendation High quality evidence
2. We suggest that systemic antibacterial prophylaxis not be used routinely for children receiving induction chemotherapy for newly diagnosed ALL ***Remarks****:* The panel acknowledged the paucity of direct contemporary randomized data applicable to children living in high income countries. A recommendation to provide universal systemic prophylaxis to this group could have a substantial impact on institutions given that ALL is the most common cancer diagnosis in children. There is great variability in duration of neutropenia and risk of bacteremia based upon treatment protocol and patient-level characteristics. Further data are required to identify sub-groups of pediatric ALL patients who might particularly benefit from prophylaxis.	Weak recommendation Low quality evidence
3. Do not use systemic antibacterial prophylaxis for children whose therapy is not expected to result in severe neutropenia (absolute neutrophil count < 500/uL) for at least seven days ***Remarks***: This strong recommendation was based upon reduced chance of benefit combined with continued risk of harm associated with systemic antibacterial prophylaxis.	Strong recommendation Moderate quality evidence
4. We suggest that systemic antibacterial prophylaxis not be used routinely for children undergoing autologous HSCT ***Remarks***: This weak recommendation against routine use of antibacterial prophylaxis in autologous HSCT recipients acknowledged the risk reduction of bacteremia among this cohort. However, the panel believed that the lower baseline risk of bacteremia resulted in the impact on resistance (known and potential) outweighing the benefits. The moderate quality of evidence reflected the lack of granular data specifically in autologous HSCT recipients rather than HSCT patients as a group.	Weak recommendation Moderate quality evidence

5. We suggest that systemic antibacterial prophylaxis not be used routinely for children undergoing allogeneic HSCT ***Remarks***: The panel acknowledged that the granularity of available data did not allow a different recommendation for allogeneic compared to autologous HSCT recipients. However, the panel noted that allogeneic HSCT recipients often have preceding conditions that could be associated with prophylaxis (for example, AML or relapsed ALL) and have prolonged neutropenia during the HSCT process, which could influence the effectiveness and adverse effects associated with prophylaxis.	Weak recommendation Moderate quality evidence
Which agents should be used for systemic antibacterial prophylaxis in children with cancer and HSCT recipients?	
6. Levofloxacin is the preferred agent if systemic antibacterial prophylaxis is planned *Remarks:* The strong recommendation to use levofloxacin is related to direct contemporary data in children and its microbiological spectrum of activity. If levofloxacin is not available or not able to be used, ciprofloxacin is an alternative although lack of activity against Gram positive bacteria including viridans group streptococci may reduce the benefits of prophylaxis. Patients and families should be informed about potential short and long-term fluoroquinolone-related adverse effects. Understanding local resistance epidemiology is critical to the decision of whether to implement fluoroquinolone prophylaxis. If fluoroquinolones are not available or cannot be used, providing no systemic antibacterial prophylaxis is an important option to consider.	Strong recommendation Moderate quality evidence
When should systemic antibacterial prophylaxis be started and stopped?	
7. If systemic antibacterial prophylaxis is planned, we suggest that administration be restricted to the expected period of severe neutropenia (absolute neutrophil count < 500/uL) Remarks: This is a weak recommendation based on low quality evidence because there are no trials that compared different start and stop criteria. In general, trials administered prophylaxis during severe neutropenia and thus, this recommendation reflects the available evidence and the panel's desire to minimize duration of prophylaxis administration.	Weak recommendation Low quality evidence

Abbreviations: AML – acute myeloid leukemia; ALL – acute lymphoblastic leukemia; HSCT – hematopoietic stem cell transplantation

Table 2: Synthesized Outcomes of All Systemic Antibacterial Prophylaxis Comparisons (Includes Pediatric and Adult Trials)

Comparison and Outcomes	Number Studies	RR***	95% CI	I^2 (%)	P
Fluoroquinolone vs. No Antibiotic**					
Bacteremia	14	0.56	0.41 to 0.76	58	0.0002
Fever	9	0.70	0.57 to 0.86	71	0.0008
Neutropenic fever	8	0.88	0.82 to 0.95	0	0.0008
Infection-related mortality	16*	0.72	0.45 to 1.16	0	0.17
Overall mortality	15*	0.86	0.62 to 1.17	24	0.34
C. difficile infection	3	0.62	0.31 to 1.24	0	0.17
Invasive fungal disease	6	1.25	0.75 to 2.08	0	0.39
Musculoskeletal adverse effects	3	0.66	0.39 to 1.13	0	0.13
Antibiotic resistance#	4	3.35	1.12 to 10.03	64	0.03
Fluoroquinolone vs. Non-absorbable Antibiotic					
Fever	3	0.98	0.91 to 1.05	0	0.50
Infection-related mortality	3	0.43	0.18 to 1.05	0	0.06
Trimethoprim-sulfamethoxazole vs. No Antibiotic**					
Bacteremia	7	0.59	0.41 to 0.85	0	0.005
Fever	5	0.77	0.56 to 1.07	91	0.11
Infection-related mortality	13	0.61	0.39 to 0.94	0	0.03
Overall mortality	5	0.61	0.28 to 1.33	32	0.21
Invasive fungal disease	7	1.19	0.43 to 3.27	27	0.74
Antibiotic resistance#	5	2.91	1.65 to 5.12	0	0.0002
Cephalosporin vs. No Antibiotic**					
Bacteremia	4	0.30	0.16 to 0.58	42	0.0004
Fever	4	0.83	0.71 to 0.98	65	0.03
Infection-related mortality	4*	1.03	0.27 to 3.95	0	0.96
Overall mortality	3*	NSP			
Antibiotic resistance#	3*	NSP			
Parenteral Glycopeptide vs. No Antibiotic**					
Bacteremia	3	0.45	0.08 to 2.66	84	0.38
Infection-related mortality	3	1.13	0.30 to 4.23	10	0.85
Fluoroquinolone vs. Trimethoprim-sulfamethoxazole					
Bacteremia	7	0.86	0.48 to 1.54	66	0.60
Fever	3	0.65	0.31 to 1.37	89	0.26
Infection-related mortality	6	1.10	0.50 to 2.39	0	0.82
Invasive fungal disease	6	0.78	0.35 to 1.75	0	0.55
Rifampin and Fluoroquinolone vs. Fluoroquinolone					
Bacteremia	3	0.36	0.17 to 0.77	0	0.008
Infection-related mortality	3*	NSP			
Overall mortality	3*	NSP			

Abbreviations: RR- risk ratio; CI – confidence interval; NSP – no synthesis possible
* One or more studies had zero events in both arms
** No antibiotic includes no antibiotic prophylaxis and placebo control groups
*** RR < 1 favors intervention
# Resistance was examined in studies comparing an antibiotic against no antibiotic controls and was defined as resistance to the intervention antibiotic among bacteremia isolates

Table 3: Details of Exclusively Pediatric Studies (N=13)

Author	Year Pub	Study Characteristics	Findings
Fluoroquinolone vs. No Antibiotic			
Alexander[14]	2018	**Comparison:** Levofloxacin vs. no antibiotic **Population:** AML, relapsed ALL and HSCT **Number of patients:** 624 **Age range:** 3-16 **Country:** US and Canada **Duration of antibiotic prophylaxis**: (1) Patients with acute leukemia: Two consecutive cycles of chemotherapy starting Day 1 or 3; (2) HSCT recipients: One transplant procedure starting day -2 from stem cell infusion. Prophylaxis continued until: ANC >200/uL after nadir, day 60 or initiation of next chemotherapy cycle **Bacteremia frequency in control:** **AML:** 25/63 (40%) **Relapsed ALL:** 18/36 (50%) **Autologous HSCT:** 9/78 (12%) **Allogeneic HSCT:** 27/130 (21%) **Systematic surveillance of colonizing organisms tested for resistance:** Yes **Other:** Primary analysis stratified by acute leukemia vs. HSCT	**Bacteremia:** Prophylaxis reduced bacteremia among 195 leukemia patients (RD 21.6%, 95% CI 8.8% to 34.4%) but not among 418 HSCT recipients (RD 6.3%, 95% CI 0.3% to 13.0%). **FN:** In both groups combined, prophylaxis reduced FN (RD 10.8%, 95% CI 4.2% to 17.5%). **Mortality:** No deaths were attributed to bacterial infection. **CDI and IFD:** Prophylaxis did not increase *Clostridium difficile* associated diarrhea (RD 2.9%, 95% CI -0.1% to 5.9%) or IFD (RD -1.0%, 95% CI -3.4% to 1.5%). **Resistance:** Qualitatively, higher rate of resistance in bacteremia isolates in prophylaxis compared to control group. Significantly less exposure to aminoglycosides, third or fourth generation cephalosporin and antibiotics commonly used to treat FN in prophylaxis group.
Laoprasopwattana[19]	2013	**Comparison:** Ciprofloxacin vs. placebo **Population:** Lymphoma and ALL undergoing induction or consolidation **Number of patients:** 95 **Age range:** 0.25-18 **Country:** Thailand **Duration of antibiotic prophylaxis**: Beginning within 5 days after starting chemotherapy and was discontinued when ANC of 1,000/uL after 2 weeks of chemotherapy. Median duration of prophylaxis was 18 days in ciprofloxacin group and 10 days in placebo group **Bacteremia frequency in control:** 1/50 (2%) **Systematic surveillance of colonizing organisms tested for resistance:** Patient level data not reported	**Bacteremia:** In the prophylaxis group, 2/45 developed bacteremia vs. 1/50 receiving placebo. **FN and Fever:** In those who developed neutropenia, prophylaxis reduced the occurrence of fever (RD -23.0%, 95% CI -45.0% to -9.0%). In patients with ALL, prophylaxis reduced the occurrence of fever in those undergoing induction (RD -23.7 95% CI -45.6 to -1.8), but not in consolidation (RD 9.8, 95% CI -17.8 to 37.5). **CDI and IFD:** Not reported. **Mortality:** Not reported. **Resistance:** In all 3 cases of bacteremia, the causative organism was susceptible to ciprofloxacin.
Widjjanto[20]	2013	**Comparison:** Ciprofloxacin vs. placebo **Population:** Induction ALL **Number of patients:** 110 **Age range:** 1-14 **Country:** Indonesia **Duration of antibiotic prophylaxis**: From start of chemotherapy until completion of induction treatment **Bacteremia frequency in control:** Not reported **Systematic surveillance of colonizing organisms tested for resistance:** No **Other:** At baseline, 37/110 were under-nourished. Abandonment as a reason for induction failure: 10/110	**Bacteremia:** Not reported. **Fever:** In the prophylaxis group, 29/58 had at least one fever compared to 17/52 in the placebo group (P=0.07). **Mortality:** In the prophylaxis group, 11/58 died compared to 3/52 in the placebo group (P=0.05). **CDI and IFD:** Not reported. **Resistance:** Not reported. **Other:** Clinical sepsis occurred in 29/58 patients receiving prophylaxis and in 20/52 patients receiving placebo (P=0.22).
Trimethoprim-sulfamethoxazole vs. No Antibiotic			
Van Eys[27]	1987	**Comparison:** TMP-SMX vs. no antibiotic **Population:** Newly diagnosed ALL **Number of patients:** 126 **Age range:** Not reported **Country:** US **Duration of antibiotic prophylaxis**: Starting week 5 of therapy and continuing for 3 years or until relapse **Bacteremia frequency in control:** Not reported **Systematic surveillance of colonizing organisms tested for resistance:** No	**Bacteremia:** Not reported. **FN and Fever:** Not reported. **Mortality:** One infectious death occurred in each group. **CDI and IFD:** Not reported. **Resistance:** Not reported. **Other:** No effect of prophylaxis on disease-free survival at 3 years.

Author	Year Pub	Study Characteristics	Findings
Goorin[28]	1985	**Comparison:** TMP-SMX vs. placebo **Population:** Newly diagnosed ALL (induction, consolidation, early maintenance) **Number of patients:** 61 **Age range:** 1-16 **Country:** US **Duration of antibiotic prophylaxis**: Immediately after diagnosis and continued daily during induction, intensification and early maintenance phases for ~40 weeks **Bacteremia frequency in control:** Not reported **Systematic surveillance of colonizing organisms tested for resistance:** Only for patients in the first year of the study due to difficulties collecting routine stool samples	**Bacteremia:** In the prophylaxis group there were fewer episodes of bacteremia compared to placebo (0 vs. 5). **FN and Fever:** Not reported. **Mortality:** One death occurred in the study and it was due to an infection in the placebo group. **CDI and IFD:** Not reported. **Resistance:** In the prophylaxis group, 5/19 patients' stool surveillance cultures developed Gram-negative bacilli resistant to TMP-SMX compared to 0/18 in the placebo group (P=0.05).
Kovatch[29]	1985	**Comparison:** TMP-SMX vs. placebo **Population:** Induction ALL and AML; relapsed ALL and solid tumors **Number of patients:** 91 **Age range:** 0.25 -17 **Country:** US **Duration of antibiotic prophylaxis**: Started day 2 or 3 of induction chemotherapy. Continued in the leukemia group until remission and in the solid tumor group until 60 days following chemotherapy initiation **Bacteremia frequency in control:** Overall not reported. In the sub-group that developed neutropenia: Induction leukemia: 6/26 (23%) Reinduction leukemia: 0/2 (0%) Solid tumors: 1/7 (14%) **Systematic surveillance of colonizing organisms tested for resistance:** No	**Bacteremia:** Bacteremia reported for the sub-group of patients that developed neutropenia. In this sub-group, 1/39 receiving prophylaxis vs. 7/35 in the placebo group developed bacteremia. **Fever:** In the prophylaxis group 14/43 had a febrile episode compared to 25/48 in the placebo group (P=0.10). **Mortality:** Two infection-related deaths occurred, both in the placebo group. **CDI and IFD:** No IFD occurred in either group. CDI not reported. **Resistance:** In the neutropenic sub-group developing bacteremia, the 1 bacteremia in the prophylaxis group and 1/7 in the placebo group were resistant to TMP-SMX.
Lange[30]	1984	**Comparison:** TMP-SMX and nystatin vs. no antibiotic **Population:** Newly diagnosed ALL (induction) **Number of patients:** 67 **Age range:** 0.5-16 **Country:** US **Duration of antibiotic prophylaxis**: Not clear **Bacteremia frequency in control:** 5/25 (20%) **Systematic surveillance of colonizing organisms tested for resistance:** No	**Bacteremia:** In the prophylaxis group 2/25 developed bacteremia vs. 5/35 in the no antibiotic group. **Fever:** Not reported. **Mortality:** There was one infection-related death in each group. **CDI and IFD:** One IFD occurred, in the control group. CDI not reported. **Resistance:** Both cases of bacteremia in the prophylaxis group were resistant to TMP-SMX. No information on the control group.
Inoue[31]	1982	**Comparison:** TMP-SMX vs. placebo **Population:** Induction, maintenance and relapsed ALL and AML **Number of patients:** 102 **Age range:** Not reported **Country:** Japan **Duration of antibiotic prophylaxis**: Not clear **Systematic surveillance of colonizing organisms tested for resistance:** Yes **Bacteremia frequency in control:** Not reported	**Bacteremia:** Narratively reported bacterial sepsis occurred less frequently in the group receiving prophylaxis. **Fever:** Not reported. **Mortality:** Not reported. **CDI and IFD:** Not reported. **Resistance:** Not reported.
Fluoroquinolone vs. Trimethoprim-sulfamethoxazole			
Cruciani[32]	1989	**Comparison:** Norfloxacin vs. TMP-SMX **Population** ALL, AML, lymphoma, neuroblastoma **Number of patients:** 44 **Age range:** Not reported **Country:** Italy **Duration of antibiotic prophylaxis**: Children receiving induction remission chemotherapy. Discontinued when neutrophil count exceeded 1000/uL **Bacteremia frequency in control:** Not applicable, as prophylaxis control group **Systematic surveillance of colonizing organisms tested for resistance:** Yes	**Bacteremia:** In the norfloxacin group, 4/21 developed bacteremia vs. 4/23 in the TMP-SMX group. **Fever:** In norfloxacin group, 9/21 had at least one fever vs. 20/23 in the TMP-SMX group. **Mortality:** There was one infection-related death in each group. **CDI and IFD:** Not reported. **Resistance:** Did not report number of patients with newly developed resistance.
Others			
Castagnola[33]	2003	**Comparison:** Amoxicillin/clavulanate vs. placebo **Population**: Leukemia, lymphoma or solid tumor **Number of patients:** 167 **Age range:** 0-18	**Bacteremia:** In the prophylaxis group, 3/84 developed bacteremia vs. 5/83 in the placebo group. **Fever:** **Mortality:** One death occurred in the study and it was due

Author	Year Pub	Study Characteristics	Findings
		Country: Italy **Duration of antibiotic prophylaxis**: Started when neutropenia developed during chemotherapy. Continued until bone marrow recovery (generally 500-1000/uL) **Bacteremia frequency in control:** Not applicable, as prophylaxis control group **Bacteremia frequency in control:** 5/83 (6%) **Systematic surveillance of colonizing organisms tested for resistance:** No	to an infection in the prophylaxis group. **CDI and IFD:** Not reported. **Resistance:** Not reported.
Avril[34]	1994	**Comparison:** Ceftazidime and teicoplanin vs. no antibiotic **Population**: Autologous HSCT **Number of patients:** 60 **Age range:** 2-16 **Country:** France **Duration of antibiotic prophylaxis**: Started 3-4 days before the onset of aplasia and continued until aplasia resolved. **Bacteremia frequency in control:** 7/29 (24%) **Systematic surveillance of colonizing organisms tested for resistance:** No	**Bacteremia:** In the prophylaxis group, 2/30 developed bacteremia vs. 7/29 in the group receiving no prophylaxis. **Fever:** In the prophylaxis group, 28/30 had fever vs. 29/29 in the group receiving no prophylaxis. **Mortality:** Not reported. **CDI and IFD:** Not reported. **Resistance:** Not reported.
Arico[35]	1992	**Comparison:** TMP-SMX daily vs. TMP-SMX three days a week **Population**: Maintenance ALL **Number of patients:** 77 **Age range:** Not reported **Country:** Italy **Duration of antibiotic prophylaxis**: Not clear **Bacteremia frequency in control:** Not applicable, as prophylaxis control group **Systematic surveillance of colonizing organisms tested for resistance:** No	**Bacteremia:** Not reported. **Fever:** Not reported. **Mortality:** Not reported. **CDI and IFD:** Not reported. **Resistance:** Not reported.
Rossi[36]	1987	**Comparison:** TMP-SMX daily vs. TMP-SMX three days a week **Population**: Newly diagnosed and relapsed ALL or AML **Number of patients:** 97 **Age range:** 0.9-15 **Country:** Italy **Duration of antibiotic prophylaxis**: For the duration of antineoplastic treatment starting from the first day of induction. Median duration of prophylaxis was 144 days in the daily group and 110 days in the control group **Bacteremia frequency in control:** Not applicable, as prophylaxis control group. **Systematic surveillance of colonizing organisms tested for resistance:** No	**Bacteremia:** Two episodes of bacteremia in each group. **Fever:** Not reported. **Mortality:** Not reported. **CDI and IFD:** Not reported. **Resistance:** Not reported. **Other:** The number of severe infections and side effects were similar between the groups.

Abbreviations: Pub – published; AML – acute myeloid leukemia; ALL – acute lymphoblastic leukemia; US – United States; NR – not reported; TMP-SMX – trimethoprim-sulfamethoxazole; HSCT – hematopoietic stem cell transplantation; RD – risk difference; CI – confidence interval; FN – fever and neutropenia; CDI – *Clostridium difficile* infection; IFD – invasive fungal disease; ANC – absolute neutrophil count

Table 4: Key Knowledge Gaps Related to Systemic Antibacterial Prophylaxis among Children with Cancer and Pediatric Hematopoietic Stem Cell Transplantation Recipients

To determine whether the effectiveness of systemic antibacterial prophylaxis changes when administered over a prolonged period of time within individuals and within institutions
To determine the consequences of a universal systemic antibacterial prophylaxis strategy within individuals (both those receiving and not receiving prophylaxis) and within institutions
To describe sub-groups of patients undergoing induction chemotherapy for acute lymphoblastic leukemia at higher risk of bacteremia and infection-related mortality
To determine the risks and benefits of systemic antibacterial prophylaxis in children undergoing induction chemotherapy for acute lymphoblastic leukemia
To determine the risks and benefits of systemic antibacterial prophylaxis for children with acute lymphoblastic leukemia receiving intensive chemotherapy phases other than induction such as delayed intensification
To identify sub-groups of patients at higher risk of bacteremia and infection-related mortality (other than those identified in this clinical practice guideline such as child with solid tumor receiving intensive chemotherapy) such that the risks and benefits of systemic antibacterial prophylaxis can be considered
To determine the cost-effectiveness of antibacterial prophylaxis in different patient populations
To compare the risks and benefits of levofloxacin and ciprofloxacin prophylaxis
To identify facilitators of guideline-concordant care