

Review

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Review

Bacterial Detection in Paediatric Cancer Patients with Febrile Neutropenia, From Conventional Microbiological Testing to Advanced Molecular Techniques: A Scoping Review Protocol

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Abstract

Objective: The objective of this scoping review is to understand the extent and type of evidence in relation to bacterial diagnostic approaches in paediatric cancer patients with febrile neutropenia (FN), with the goals of highlighting the best practice approach to conventional microbiological testing used in current clinical practice and explore the role of emerging technologies as potential diagnostic tools. **Introduction:** FN is a common complication for children undergoing chemotherapy for cancer, with bacterial bloodstream infection responsible for the majority of serious adverse events. Current diagnostic approaches have limited sensitivity and long turnaround times. Improved diagnostics are required to strengthen clinical decision rules and support the safer use of reduced-intensity management pathways. **Eligibility Criteria:** Children up to their 18th birthday with a diagnosis of cancer will be included, looking at bacterial diagnostic methods used in the evaluation of FN. Studies conducted across all healthcare settings will be considered. Studies focusing exclusively on viral or fungal diagnostics will be excluded, as will those not involving human participants. **Methods:** The review will be conducted in accordance with Joanna Briggs Institute and PRISMA-Scoping Review methodology. A comprehensive search of MEDLINE, Embase, Web of Science Core Collection and grey literature will be conducted to identify published and unpublished studies from 2011 onwards, with no language restrictions. Primary research studies of any design will be included, however case reports with fewer than 10 participants will be excluded. Two independent reviewers will screen studies and extract data. Any discrepancies will be resolved by consensus, involving a third reviewer if necessary. Findings will be synthesised and presented using tables and figures, accompanied by a narrative synthesis to address the research question.

Keywords: bacterial diagnostics; cancer; febrile neutropenia; paediatric

Introduction

Febrile neutropenia (FN) is a common complication of chemotherapy, with approximately 40% of neutropenic episodes in paediatric oncology patients complicated by fever. [1] FN can be described as an absolute neutrophil count of less than $1.0 \times 10^9/L$ in the presence of a temperature greater than $37.5^\circ C$, acknowledging variation exists in the literature due to the absence of international consensus. [2,3] In children undergoing treatment for cancer, FN can have serious consequences; including sepsis, intensive care admission and death. [4] A microbiologically defined infection – where a microorganism is identified on laboratory testing – is typically identified in around a quarter of FN episodes. [5] Bacteraemia, defined as the isolation of a recognised pathogen from one or more blood cultures, is most commonly responsible for the serious adverse events described. [3,4]

International guidelines recommend that blood cultures should be obtained from each lumen of a central venous access device at the onset of FN. [6] In current clinical practice, bacterial detection relies primarily on conventional microbiological culture. This is a time-consuming process, demanding at least 48 hours for an initial result, with a limited diagnostic yield of around 12%. [7] There is additional controversy surrounding the need for paired peripheral cultures in the paediatric population. A systematic review performed as part of the 2017 guideline update for the Management of Fever and Neutropenia in Children with Cancer and Hematopoietic Stem-Cell Transplantation Recipients found that 12% of bacteraemia episodes were solely identified through positive peripheral cultures. [8] In clinical practice, peripheral cultures are often not performed in the paediatric population due to concerns of causing unnecessary pain, the risk of phlebitis, and the increased possibility of isolating skin contaminants which can have subsequent impacts on antimicrobial treatment. [9] Consequently, paired peripheral cultures remain a conditional recommendation in the 2023 guideline update, as the clinical impact of increased bacteraemia detection has not been defined. [6]

Suspected FN is a medical emergency, requiring prompt administration of empirical intravenous antibiotics within 60 minutes from the onset of symptoms, or arrival to hospital. [10,11] Historically, intravenous antimicrobial therapy would have continued in the inpatient setting until the cessation of fever and evidence of bone marrow recovery, guided by microbiology results. A mean length of stay of 8 days illustrates the substantial burden FN places on patients, families and oncology services. [12]

In recent years FN management has evolved, with international guidelines promoting a risk-stratified approach, supporting the use of reduced-intensity regimens for patients believed to be at lower risk from infection. [8,13] Numerous clinical decision rules (CDRs) have been developed by researchers to support clinician decision making in determining infection risk. [5,14,15]

The Australia-UK-Swiss (AUS) rule was adopted by a number of UK centres during the COVID-19 pandemic following circulation of a collaborative protocol. [11] The AUS rule constitutes 3 equally weighted variables – intensity of chemotherapy, total white cell count and platelet count – to predict the risk of bacterial infection. Scores range from 0 to 3, corresponding to very low, low, intermediate and high risk, respectively. A minimum period of inpatient clinical observation is recommended on the basis of the risk category. If the responsible clinician is satisfied that the patient has remained well following the period of observation, and they meet a predetermined set of homecare eligibility criteria, the child is considered appropriate to transition to care in the community with oral antibiotics.

The AUS rule has undergone evaluation across multiple settings. External validation was performed in the derivation study demonstrating reproducibility on an independent dataset. [15] Following implementation in UK clinical practice, a prospective service evaluation was conducted. [16] No child eligible for homecare was admitted to intensive care or died, demonstrating safety and supporting the use of reduced-intensity regimens in low-risk patients. However, significant variation was observed, with the percentage of homecare eligible patients ranging from 0 to 42% between sites. Furthermore, under half of patients identified as suitable for homecare were subsequently discharged by 24 hours. The heterogeneity of the cohorts needs to be evaluated; with review of local variations in application of the discharge criteria and assessment of barriers to discharge. In 2025, a study looking at the performance of the AUS rule specifically in sarcoma patients, concluded that it performs inadequately in this group, with numerous missed cases of likely bacterial infection. [17] This raises the concern of how the AUS rule performs in other rarer tumour types; assuming they are also underrepresented in the datasets used in initial risk prediction models.

While meaningful progress has been made in the management of FN, further improvement is required to safely expand the use of reduced-intensity treatment strategies. Current CDRs, including the AUS rule, rely on surrogate markers of immunosuppression to estimate infection risk. There is a clear need to explore the role of biomarkers and bacterial diagnostics, both to optimise the management of infection and to enhance the predictive accuracy of risk stratification tools.

The objective of this review is to assess the extent of the literature relating to bacterial diagnostic approaches in paediatric cancer patients with FN. The review will systematically map the available evidence, clarify key concepts and identify gaps in the research. This scoping review will be conducted in accordance with the Joanna Briggs Institute (JBI) and PRISMA-Scoping Review methodology. [18,19]

A preliminary search of MEDLINE was conducted to identify any existing reviews on the topic. No systematic or scoping reviews addressing the research question were identified. A systematic review published in 2022, evaluated the most recent evidence, at the time, regarding the approach and therapeutic strategies utilised in the management of paediatric FN. [20] Although this discusses the microbiological profile of causative pathogens in paediatric FN, and acknowledges the prevalence of bacterial bloodstream infections, it does not address methods of bacterial detection. Novel diagnostic tests, such as metagenomic next-generation sequencing (mNGS), are being evaluated in the context of pathogen detection in immunocompromised individuals. In September 2025, a systematic review and meta-analysis was registered on PROSPERO looking at the diagnostic utility of mNGS in febrile neutropenia. [21] This review is currently ongoing, and although may prove to be a valuable contribution, is not specific to the paediatric cancer population, investigating FN in patients with haematological malignancies in all age groups. As the extent of the paediatric literature on bacterial diagnostics in FN is unknown, a scoping review is appropriate in the first instance.

Review Question

This review will examine the diagnostic tests for bacteraemia in febrile neutropenia, in children undergoing chemotherapy for cancer. The primary objectives are to highlight the best practice approach to conventional microbiological testing used in current clinical practice and explore the role of emerging technologies as potential diagnostic tools.

Methods

The proposed scoping review will be conducted in keeping with JBI methodology. [18] The Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist (see Appendix I) will additionally be referenced to strengthen methodology. [19] The checklist will be reported in full in the final review.

Eligibility Criteria

The eligibility criteria are defined using the Population – Concept – Context (PCC) framework as recommended by JBI, and are as follows:

Population

The review will include studies involving paediatric patients, up to their 18th birthday, who are experiencing febrile neutropenia in the context of a cancer diagnosis, inclusive of both solid tumours & haematological malignancies. Due to lack of consensus, FN will be defined as per the selected study. The parameters will be noted to allow for description of the variation in definition across all studies included in the review. Only human clinical studies will be included.

Concept

The review will examine the evidence relating to bacterial diagnostic methods used in the evaluation of FN. This will include, although is not limited to, microbiological tests, such as blood cultures currently used in clinical practice, molecular diagnostics and biomarker assays. Studies without a bacterial diagnostic component, focusing exclusively on viral or fungal testing, will be excluded.

Context

All healthcare settings will be considered, including inpatient and outpatient oncology care facilities, and emergency departments. No geographic limitations will be applied.

Types of Sources

This scoping review will consider primary research studies of any study design. Grey literature will also be included. Case reports of fewer than 10 cases will be excluded.

Search Strategy

The search strategy will aim to locate both published and unpublished studies, utilising a three-step search strategy. An initial limited search of MEDLINE (Ovid) was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy (see Appendix II).

The search strategy, including all identified keywords and index terms, will be adapted for each included database. The databases to be searched comprise MEDLINE, Embase and Web of Science Core Collection. Sources of unpublished studies and grey literature will be searched for using Google Scholar; to identify any preprints or obscure articles not indexed in the databases.

A date limit will be applied, restricting to sources published between 1st January 2011 and 1st January 2026. This is to ensure that data contributing to the latest international guidelines is captured, whilst ensuring evidence is recent and relevant to current clinical practice. [6] No language restrictions will be applied. Artificial intelligence will be used to translate articles that are not published in the English language.

Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded into Covidence and duplicates removed. Following a pilot test, titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant sources will be retrieved in full. The full text of selected citations will be then assessed in detail against the inclusion criteria, again, by two independent reviewers. Reasons for exclusion of sources of evidence at full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion, or with an additional reviewer. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA flow diagram. [19]

Data Extraction

Data will be extracted from papers included in the scoping review by two independent reviewers using a data extraction tool (see draft, Appendix III). The data extracted will include specific details about the participants, concept, context, study methods and key findings relevant to the review question. The draft data extraction tool may be modified and revised as necessary during the process of extracting data from each included evidence source. Modifications will be detailed in the scoping review. Any disagreements that arise between the reviewers will be resolved through discussion, or with an additional reviewer. If appropriate, authors of papers will be contacted to request missing or additional data, where required.

Data Analysis and Presentation

Extracted data will be collated, summarised and presented to map the nature and extent of the available evidence on the bacterial diagnostic approaches for the evaluation of FN in paediatric cancer patients. Key characteristics of included studies will be presented in tabular form; highlighting important source details, how the evidence relates to the PCC defined in the research question, and specifically identifying the diagnostic approach investigated.

Individual studies will not undergo formal critical appraisal, since a scoping review is providing an overview of the research rather than an assessment of quality, however, to conceptualise where the field is at, the evidence relating to different diagnostic approaches will be graded using a traffic light system. A red grade will be awarded if the evidence base is limited and consists of predominantly low-quality evidence such as case series, highlighting a need for primary research. An amber grade will reflect an emerging field, with increasing empirical studies; although anticipated to have inconsistent methodologies there will be a need for standardisation. Only if there are multiple high-quality studies with consistent methods, will a green grade be awarded.

The volume and spread of evidence will be presented in the form of figures to visually depict the distribution of evidence across diagnostic modalities. The numerical analysis will be accompanied by a narrative synthesis, to describe how different bacterial diagnostic tests are used, and report on any relevant outcomes. Evidence will be categorised by type of diagnostic test, to delineate patterns or similarities, and subsequently highlight knowledge gaps. This will help to inform future research.

Discussion

FN remains a major cause of morbidity and mortality among children undergoing treatment for cancer. Balancing the risk of bacterial infection with the use of reduced intensity regimens recommended in clinical practice guidelines, poses significant clinical challenges. To enhance the predictive accuracy of risk stratification tools currently in use, we need to incorporate biomarkers of bacterial infection or improve bacterial diagnostic techniques. In recent years advanced molecular techniques have emerged as promising tools capable of enhanced pathogen detection whilst reducing diagnostic delays. However, the extent, characteristics and clinical applicability of these techniques for use in the evaluation of paediatric FN remain unclear. This scoping review intends to systematically map the existing evidence on bacterial diagnostic approaches in this population, addressing the variation in approach to conventional microbiological testing and exploring advanced molecular techniques. It is expected that the main limitations will include the heterogeneity of included studies, variability in diagnostic platforms and outcomes, and possibly the availability of paediatric-specific evidence. By synthesising the available evidence, the review will identify gaps related to diagnostic performance, feasibility and potential for integration into clinical practice. It will inform future research priorities to support the development of more effective strategies for managing FN in the paediatric cancer cohort.

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Author Contributions: EC conceptualised and designed the study, wrote and revised the protocol, and collaborated with a specialist subject librarian on the search strategies. HD, HG and TW critically revised the protocol.

Conflicts of Interest: There are no conflicts of interest in this project.

Appendix I. PRISMA-ScR Checklist [19]

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods,	1

		results, and conclusions that relate to the review questions and objectives.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	2-4
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	5,6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	NA - protocol
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5,6
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	6
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Appendix II
Selection of sources of evidencet	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	6,7
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	7

Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Appendix III
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	7
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	7,8
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	NA – protocol
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	NA – protocol
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA – protocol
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	NA – protocol
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	NA – protocol
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	NA - protocol
Limitations	20	Discuss the limitations of the scoping review process.	8
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	8
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding	NA

		for the scoping review. Describe the role of the funders of the scoping review.	
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JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews. * Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites. † A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote). ‡ The frameworks by Arksey and O’Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting. § The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of “risk of bias” (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

Appendix II: Search Strategy

Ovid MEDLINE ALL

1 exp Child/ 2308037
 2 exp Infant/ 1331053
 3 exp Adolescent/ 2378748
 4 Pediatrics/ 60822
 5 (pediatric* or paediatric*).mp. 616909
 6 exp Neoplasms/ 4198763
 7 (cancer* or neoplasm* or malignan* or tumor* or tumour* or leukemia* or leukaemia* or lymphoma* or oncolog*).mp. 5674700
 8 exp Febrile Neutropenia/ 1807
 9 exp Neutropenia/ 21378
 10 neutropeni*.mp. 56068
 11 exp Fever/ 49420
 12 exp Bacterial Infections/ 1014766
 13 exp Bacteremia/ 35383
 14 exp Sepsis/ 154471
 15 (bacteremia or bacteraemia or bloodstream infection*).mp. 63610
 16 exp Diagnosis/ 9996156
 17 exp Diagnostic Tests, Routine/ 15999
 18 exp Molecular Diagnostic Techniques/ 23252
 19 exp Microbiological Techniques/ 391908
 20 exp Blood Culture/ 2285
 21 exp Biomarkers/ 979105
 22 (diagnos* or detect* or test* or assay*).mp. 13328925
 23 1 or 2 or 3 or 4 or 5 4416728
 24 6 or 75934812
 25 8 or 9 or 10 or 11 102479
 26 12 or 13 or 14 or 15 1131829
 27 16 or 17 or 18 or 19 or 20 or 21 or 22 17711619
 28 23 and 24 and 25 and 26 and 27 1326
 29 limit 28 to yr="2011 -Current" 575

Appendix III. Data Extraction Plan

Adapted from JBI methodology guidance for scoping reviews. [18]

Category:	Data to be extracted:
Source information	Title Author(s) Year of publication Publication source Publication type (e.g., journal) Study origin (location source conducted/ published)
(P) Population characteristics	Age range Cancer type(s) Chemotherapy/ treatment status Definition of FN used Sample size
(C) Clinical setting	Healthcare setting Timeframe of data collection
(C) Diagnostic test(s)	Test name Test category (e.g., microbiological, molecular, biomarker) Specimen type Timing of specimen Test platform/ method (assay type) Test thresholds Turnaround time
Outcomes reported	Reference standard used Presence of bacteraemia Measures of diagnostic accuracy Clinical outcomes Impact on management
Key findings and author conclusions	Summary of key results Author conclusions Study limitations

	Knowledge gaps
Relevance to review objectives	

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