Clinical practice guidelines for the management of fever and neutropenia in South African children and adolescents with cancer

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Background. Infection poses a serious risk in children and adolescents with cancer, often leading to severe morbidity and occasionally, death. Inconsistent management of fever with neutropenia (FN) may affect clinical outcomes. Despite the frequent occurrence of this complication during cancer treatment, no South African (SA) clinical practice guideline (CPG) has been developed to support clinicians in its management.

Objective. To develop an evidence-based CPG providing recommendations for diagnosis, prognosis and management of children and adolescents with FN undergoing cancer treatment in SA.

Method. We developed an evidence-based CPG for managing this condition, tailored to the unique and diverse healthcare system in which children and adolescents with cancer are treated in SA. We established a working group comprising representatives from the clinical care pathway for SA children and adolescents with cancer. We then employed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to formulate the CPG recommendations.

Conclusion. We present two definitions and 29 recommendations for managing children and adolescents with FN. The CPG development process has yielded recommendations similar to those of other FN CPGs; however, they reflect the unique context of SA, and guide elements such as tuberculosis evaluation, focusing on essential factors including availability, accuracy, affordability and diagnostic capacity. Furthermore, the systematic review conducted as part of the evidence synthesis emphasises the need for high-quality evidence from SA settings.

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Modern cancer therapy has improved the survival rates of children and adolescents with cancer, albeit with a significant risk of infection,[1,2] a leading cause of treatment-related mortality. A lack of evidence-based approaches for managing children and adolescents with cancer who develop fever and neutropenia (FN) impacts overall survival. An evidence-based clinical practice guideline (CPG) may improve outcomes, including survival and resource use, by guiding treatment approaches that minimise morbidity and mortality. We aimed to develop an evidence-based CPG providing recommendations for diagnosis, prognosis and management of children and adolescents with FN undergoing cancer treatment in South Africa (SA). The CPG is intended for use by healthcare providers and policy-makers.

Methods

Representatives from 13 public-sector hospitals in SA formally assessed children's and adolescent cancer services using the St. Jude Paediatric Oncology Facility Integrated Local Evaluation Exercise (ProFILE) tool[3] to prioritise areas for intervention and to enhance cancer care, including the development of a national protocol to address the management of children and adolescents with FN.[4]

CPG panel development

The panel lead invited representatives of the 13 public-sector institutions that provide care to children with cancer in SA to participate in the CPG panel. Additionally, the Childhood Cancer Foundation SA (CHOC), a non-governmental parent organisation, was invited to nominate parent representatives to join. The goal was to assemble a team with expertise in oncology, infectious diseases, microbiology, pharmacy, nursing and patient experience. The CPG development panel compiled a list of 35 initial questions for question prioritisation.

Question prioritisation and prioritisation survey

The initial list of 35 questions was distributed to the members of the South African Association of Paediatric Haematology Oncology (SAAPHO) for online review and voting. The members were asked to review and vote on the importance of each question for inclusion in the CPG for use by clinicians (i.e. target users). Any question with an 80% favourable vote was considered the threshold for inclusion in the CPG for addressal.

Evidence search, selection, data abstraction and synthesis

A systematic search of the PubMed database, updated to the end of April 2023, was conducted for all questions included in the CPG. The search strategy for each question is provided in Appendix 1. Comparative studies or synthesised evidence from comparative studies were eligible for inclusion. For questions where we did not find comparative evidence or synthesised evidence from comparative studies, we included synthesised evidence from single-arm studies. Additionally, a manual review of references from all included studies was performed to identify additional studies of interest. The CPG panel members, excluding the patient representatives, evaluated all studies to determine their eligibility for each question, and extracted study characteristics and outcomes. The risk of bias was assessed using the Cochrane risk-of-bias 2 tool for randomised controlled trials[5] and the Newcastle-Ottawa Scale for observational studies.[6] When appropriate, we pooled data on similar outcomes from similar studies using a random-effects model. We assessed the heterogeneity between studies using the I^2 statistic. Evidence synthesis was performed using the RevMan software package version 5 (The Cochrane Collaboration, Denmark). The certainty of the evidence for each outcome was summarised using the GRADE methodology and presented as a summary of findings (SoF) table.[7]

Training of CPG panel members

All CPG members, including patient representatives, received training in the fundamentals of study design, the interpretation of diagnostic, prognostic and intervention study measures, the assessment of risk of bias and the GRADE methodology, culminating in a final session that simulated the voting process.

Development of recommendations

The voting on recommendations took place during an in-person meeting in Johannesburg, SA, on 31 May and 1 June 2023. This meeting was moderated by a methodology team that did not participate in the voting process. The evidence-to-decision framework began with the presentation of questions, followed by a summary of the systematic review, along with associated forest plots, SoF tables, references to eligible studies (Appendix 2) and panel deliberations. We did not conduct a formal cost analysis or assess the values of target users. Voting was anonymous: panellists first voted for or against a recommendation, then indicated the strength of the recommendation (strong or conditional). The voting results were not disclosed to avoid influencing voting on subsequent questions. A simple majority (>50%) was required to approve the recommendation.

External review

The manuscript, after review by all authors, underwent review by external members at the respective institutions of all authors.

CPG updates

We plan to update the CPG every 5 years.

Results

CPG question prioritisation

A total of 52 participants from seven provinces participated in the prioritisation survey (Table 1). The majority of participants were paediatric oncologists/haematologists (54%), followed by paediatricians (23%) and paediatric infectious disease specialists (13%). Of the 35 questions compiled, 29, together with two definitions, met the threshold of being rated as either important or very important for inclusion in the CPG by 80% of respondents.

Characteristics of CPG panel members

The CPG development panel consisted of 14 representatives: 12 from 10 public-sector institutions and two patient representatives (Table 2). Of these, 71% were female, 50% were paediatric oncologists/haematologists, 21% were paediatric infectious disease specialists, 14% were patient representatives and 7% each were microbiologists and pharmacists.

Definitions

Fever

The panel defined fever as an axillary temperature of 38°C, measured once, or 37.5°C, measured twice, at time points ≥1 hour apart.

Panel deliberations

The panel recognised that there was no consensus in the field or evidence regarding the specific temperature for defining fever. Rectal temperatures should not be taken in patients with FN.

Neutropenia

The panel defined neutropenia as an absolute neutrophil count (ANC) of 500 cells/mm^3, or an ANC anticipated to drop <500 cells/mm^3 within 48 hours.

Panel deliberations

The panellists unanimously favoured a neutrophil threshold of <500 cells/mm^3, based on the definition of 'severe neutropenia' proposed by Dale *et al.*[8] in the early 2000s.

Recommendations

The evidence summaries for all recommendations are summarised in Appendix 3, and the references for these summaries are provided at the end of this document. Table 3 summarises the recommendations.

Table 1. Characteristics of the question prioritisation panel members

Characteristic	*n* (%)
Professional background	
Paediatric oncologist/haematologist	28 (54)
Paediatrician	12 (23)
Paediatric infectious disease specialist	7 (13)
Nurse	2 (4)
Other	2 (4)
General practitioner	1 (2)
Experience with treating FN, years	
<5	17 (33)
5 - 10	9 (17)
>10 - 15	15 (29)
> 15 - 20	6 (11)
>20	5 (10)
Province	
Gauteng	19 (37)
KwaZulu-Natal	11 (21)
Western Cape	12 (23)
Eastern Cape	7 (13)
Free State	1 (2)
Limpopo	1 (2)
Northern Cape	1 (2)
Level of care	
Secondary level facility	4 (8)
Tertiary or quaternary academic centre	48 (92)

FN = fever with neutropenia.

Table 2. Characteristics of the clinical practice guideline panel members

Characteristic	*n* (%)
Sex	
Female	11 (79)
Male	3 (21)
Professional background	
Infectious disease	3 (21)
Paediatric oncologist	7 (50)
Microbiologist	1 (7)
Patient representative	2 (14)
Pharmacist	1 (7)
Practice setting	
Private sector	1 (7)
Public sector	10 (71)
Both private and public sector	3 (22)
Level of care	
Tertiary or quaternary academic centre	12 (86)
Other	2 (14)

Recommendation 1

The panel **recommends** obtaining peripheral blood cultures and blood cultures from central lines at the time of the episode of FN (certainty of evidence: moderate).

Panel deliberations

Panellists emphasised the importance of obtaining a blood culture at the onset of an FN episode. In resource-limited settings, patients may not have a central venous line; however, if one is available, its use for blood collection may minimise discomfort. Nonetheless, the likelihood of a positive result increases when samples are taken from both peripheral and central lines. Therefore, blood cultures from both peripheral and central lines may be indicated to enhance diagnostic accuracy in patients with persistent fever or clinical instability. A positive central line blood culture may necessitate consideration for line removal.

Recommendation 2

The panel **suggests** performing urinalysis and urine culture in children and adolescents with FN if obtaining a specimen is non-invasive and does not delay therapy (certainty of evidence: very low).

Panel deliberations

Parent advocates raised concerns regarding the utility, invasiveness and psychological effects of urine testing. Urine dipstick analysis may be unreliable in neutropenic patients, and interpreting culture results can be challenging, particularly because collecting a clean midstream urine specimen from children is often difficult. Furthermore, suprapubic aspiration might be contraindicated in patients with thrombocytopenia.

Recommendation 3

The panel **suggests** testing for stool pathogens using culture and *Clostridioides difficile* assays in children and adolescents with FN and diarrhoea (certainty of evidence: very low).

Panel deliberations

Considering the cost and availability of diagnostic tests in resource-limited settings is crucial; decisions regarding testing should be based on the test's impact on patient management. Patients undergoing cancer treatment may experience diarrhoea due to both infectious and non-infectious causes, and appropriate testing can guide management. Multiple hospital admissions or antibiotic exposure increase the risk of *C. difficile* infection. Moreover, outbreaks of *C. difficile* in healthcare settings may necessitate an increased use of stool diagnostic studies.

Recommendation 4

The panel **suggests against** routinely testing for respiratory viruses in children and adolescents with FN and respiratory symptoms (certainty of evidence: very low).

Panel deliberations

Tests for respiratory viruses can be costly and limited in availability. A positive result for a respiratory virus may affect the duration and management of antibiotic treatment, particularly in clinically stable patients with negative blood cultures. For influenza A, it is recommended to add oseltamivir within 48 hours of symptom onset. Parent representatives noted that a nasal swab is less invasive than chest radiography.

Recommendation 5

The panel is **uncertain about recommending** a risk-stratification strategy for managing FN in children and adolescents (certainty of evidence: very low).

Panel deliberations

Panellists emphasised the need to develop a precise, reproducible risk-stratification tool to delineate the risk of adverse outcomes in

Table 3. Summary of recommendations

Recommendation	Certainty of evidence	Strength and direction of the recommendation
1. The panel recommends obtaining peripheral blood cultures and blood cultures from central lines at the time of the episode of FN.	Moderate	Strong for
2. The panel suggests performing urinalysis and urine culture in children and adolescents with FN if getting a specimen is non-invasive and does not delay therapy.	Very low	Conditional for
3. The panel suggests testing for stool pathogens using culture and *Clostridioides difficile* assays in in children and adolescents with FN and diarrhoea.	Very low	Conditional for
4. The panel suggests against routinely testing for respiratory viruses in children and adolescents with FN and respiratory symptoms.	Very low	Conditional against
5. The panel is uncertain about recommending a risk-stratification strategy for managing FN in children and adolescents.	Very low	Uncertain
6. The panel is uncertain about recommending monotherapy with an antipseudomonal beta lactam, a fourth-generation cephalosporin, or a antipseudomonal carbapenem in children and adolescents with high-risk FN.	Moderate to very low	Uncertain
7. The panel recommends adding a second Gram-negative agent for clinically unstable children and adolescents with FN when a resistant infection is suspected, or at centres with high rates of resistant pathogens.	Moderate to very low	Strong for
8. The panel recommends adding a glycopeptide only for children and adolescents with FN when a Gram-positive infection is suspected at centres with high rates of resistant pathogens.	Moderate to low	Strong for
9. The panel suggests using monotherapy with an antipseudomonal beta-lactam, a fourth-generation cephalosporin, or an antipseudomonal carbapenem in children and adolescents with low-risk FN.	Low to very low	Conditional for
10. The panel recommends initial therapy with either oral or intravenous antibiotics as the route of administration in children and adolescents with low-risk FN.	Low	Strong for
11. The panel suggests against routine use of corticosteroids in children and adolescents with FN who have previously had high-dose steroid exposure and are now clinically unstable.	No comparative studies identified	Conditional against
12. The panel suggests de-escalation to monotherapy after 48 - 72 hours in stable children and adolescents who are neutropenic but have no further fevers and are responding to initial antibiotic therapy in the absence of a clinical or microbiological indication to continue a second agent.	Moderate to very low	Conditional for
13. The panel suggests no change in the initial empirical antibacterial regimen in children and adolescents with FN who are clinically stable but have persistent fever.	Moderate to very low	Conditional for
14. The panel suggests escalating the initial empirical antibacterial regimen in persistently febrile patients to include coverage for resistant Gram-negative, Gram-positive and anaerobic bacteria in clinically unstable children and adolescents with FN.	Moderate to very low	Conditional for
15. The panel does not recommend using G-CSF as a secondary therapy in children and adolescents with FN.	Low to very low	Strong against
16. The panel suggests against using bacterial biomarkers (CRP, PCT, IL-6, and/or IL-8) to guide decisions around therapy modifications for managing children and adolescents with FN.	Very low	Conditional against
17. The panel suggests against routinely performing imaging of the lungs of children and adolescents with prolonged FN without localising signs or symptoms who are at high risk for invasive fungal infection.	Very low	Conditional against
18. The panel suggests against routinely performing imaging of the abdomens of children and adolescents with prolonged FN without localising signs or symptoms who are at high risk for invasive fungal infection.	Very low	Conditional against
19. The panel recommends against routine imaging of the sinuses of children and adolescents with prolonged FN without localising signs or symptoms who are at high risk for invasive fungal infection.	Very low	Strong against
20. The panel recommends against routine imaging of the lungs, abdomens, and/or sinuses in children and adolescents with FN and persistent fever without localising signs or symptoms.	Very low	Strong against
21. The panel recommends testing for active TB in children and adolescents with prolonged FN who have recent TB exposure.	Very low	Strong for
22. The panel suggests against testing for *Pneumocystis jirovecii* in children and adolescents with FN and hypoxaemic pneumonia.	Very low	Conditional against
23. The panel suggests against using galactomannan or β-D-glucan for the diagnosis of invasive fungal disease in children and adolescents with FN who are at high risk for invasive fungal disease.	Very low	Conditional against

(continued)

Table 3. (continued) Summary of recommendations

Recommendation	Certainty of evidence	Strength and direction of the recommendation
24. The panel suggests administering empirical antifungal therapy in children and adolescents with FN and prolonged fever who are at high risk for fungal disease.	Moderate to low	Conditional for
25. The panel suggests against routinely removing indwelling lines in children and adolescents with FN with a current positive blood culture.	Very low	Conditional against
26. The panel suggests stopping empirical antibiotics in children and adolescents with high-risk FN who have negative blood cultures at 48 hours and are afebrile for at least 24 hours.	Moderate to very low	Conditional for
27. The panel recommends stopping empirical antibiotics in children and adolescents with low-risk FN who have had negative blood cultures for 48 hours and have been afebrile for at least 24 hours.	Moderate to low	Strong for
28. The panel suggests early discharge within 72 hours for children and adolescents with high-risk FN who have reliable follow-up, negative blood cultures at 48 hours, have been afebrile for at least 24 hours, and have evidence of marrow recovery.	Moderate to low	Conditional for
28. The panel suggests early discharge within 24 - 36 hours for children and adolescents with low-risk FN with reliable follow-up who have negative blood cultures at 24 - 36 hours and are afebrile for at least 24 hours, regardless of marrow recovery status.	Moderate	Conditional for

FN = fever with neutropenia; G-CSF = granulocyte colony-stimulating factor; CRP = C-reactive protein; PCT = procalcitonin; IL = interleukin; TB = tuberculosis.

patients with FN. Criteria need to be validated locally to incorporate disease- and episode-specific factors, as well as laboratory and clinical data. Panellists specifically highlighted the need to consider malnutrition, HIV infection, and tuberculosis, cancer type and stage, treatment intensity and the clinical severity of FN episodes. Scoring systems should maximise sensitivity in identifying at-risk patients, accompanied by recommendations for referral to higher levels of care.

Recommendation 6

The panel is **uncertain about recommending** monotherapy with an anti-pseudomonal beta-lactam, a fourth-generation cephalosporin, or an anti-pseudomonal carbapenem in children and adolescents with high-risk FN (certainty of evidence: moderate to very low).

Panel deliberations

Despite multiple efforts, there is no consensus in the field on how to risk-stratify children and adolescents with FN. Practically, clinicians stratify patients based on clinical evaluations and individual assessments. Local antibiograms are crucial for guiding antibiotic selection. The panellists discussed the appropriateness of using carbapenems as empirical therapy in settings with limited access to newer antibiotics. Some units with high rates of extended-spectrum beta-lactamase (ESBL)-producing pathogens, for which carbapenems are the preferred antimicrobial agents, report an increase in carbapenem-resistant Enterobacterales. However, pathogens expressing ESBL often remain susceptible to aminoglycoside antibiotics. The panellists considered the advantages of monotherapy with a carbapenem and dual therapy with a beta-lactamase inhibitor and an aminoglycoside. Some units may experience more FN infections linked to *Klebsiella pneumoniae* and *Escherichia coli* than *Pseudomonas* spp.

Recommendation 7

The panel **recommends** adding a second Gram-negative agent for clinically unstable children and adolescents with FN when a resistant infection is suspected or at centres with high rates of resistant pathogens (certainty of evidence: moderate to very low).

Panel deliberations

The decision to use a second antibiotic targeting Gram-negative bacteria should be made at the treating physician's discretion and guided by local antibiograms, given the lack of clear evidence of benefit. The associated toxicities of treatment may be significant for patients receiving nephrotoxic antimicrobials, particularly aminoglycosides and chemotherapy. Parents emphasised that patients should not be overtreated; clinicians should consider the rational use, toxicity and long-term effects of antimicrobials.

Recommendation 8

The panel **recommends** adding a glycopeptide only for children and adolescents with FN when a Gram-positive infection is suspected at centres with high rates of resistant pathogens (certainty of evidence: moderate to low).

Panel deliberations

The choice of the initial Gram-positive antibiotic and any subsequent modifications should be guided by clinical judgement and the unit's antibiogram. A central line does not necessitate additional Gram-positive coverage; treatment should depend on the patient's clinical presentation, which may include thrombophlebitis, wound sepsis, or infection at the central line or indwelling catheter site. Empiric cloxacillin may be appropriate for the management of wound and soft-tissue infections. Glycopeptides may be warranted in patients with chemotherapy-associated mucosal damage.

Recommendation 9

The panel **suggests** using monotherapy with an antipseudomonal beta-lactam, a fourth-generation cephalosporin, or an antipseudomonal carbapenem in children and adolescents with low-risk FN (certainty of evidence: low to very low).

Panel deliberations

Individual units determine the risk stratification, as no universally accepted tool exists for assessing risk in children and adolescents with FN. Uncertainties surrounding risk stratification could affect decisions regarding the use of monotherapy.

Recommendation 10
The panel **recommends** initial therapy with either oral or intravenous antibiotics as the route of administration in children and adolescents with low-risk FN (certainty of evidence: low).

Panel deliberations
Based on the patient's distance from the treatment facility, the ease of transport to the hospital and family understanding of the risks associated with FN, patients may not qualify for outpatient care. Managing inpatients with oral antibiotics can alleviate staff shortages, reduce costs and lower the risk of line sepsis. The choice of oral antibiotics depends on the availability and accessibility of paediatric formulations.

Recommendation 11
The panel **suggests against** routine use of corticosteroids in children and adolescents with FN who have previously had high-dose steroid exposure and are now clinically unstable (certainty of evidence: no comparative studies were identified).

Panel deliberations
Parent representatives emphasised the adverse effects of corticosteroid treatment on the behaviour and mental health of patients undergoing cancer therapy. Given limited data on benefits, routine corticosteroid administration should be reserved for patients receiving continuous corticosteroid therapy or high-dose corticosteroid pulses who present with septic shock or hypoadrenalism.

Recommendation 12
The panel **suggests** de-escalation to monotherapy after 48 - 72 hours in stable children and adolescents who are neutropenic but have no further fevers, and are responding to initial antibiotic therapy without a clinical or microbiological indication to continue a second agent (certainty of evidence: moderate to very low).

Panel deliberations
Antibiotics with the highest toxicity profiles should be discontinued first. Cessation, rather than changing antibiotics, should be considered. Parent representatives emphasised the positive psychological impact of stopping antibiotics on the patient and family.

Recommendation 13
The panel **suggests** no change in the initial empirical antibacterial regimen in children and adolescents with FN who are clinically stable but have persistent fever (certainty of evidence: moderate to very low).

Panel deliberations
The panel found no justification for altering the initial antibiotic treatment in stable febrile patients. Panellists recommended repeating the blood culture and closely monitoring vital signs.

Recommendation 14
The panel **suggests** escalating the initial empirical antibacterial regimen in persistently febrile patients to include coverage for resistant Gram-negative, Gram-positive and anaerobic bacteria in clinically unstable children and adolescents with FN (certainty of evidence: moderate to very low).

Panel deliberations
In facilities with high rates of resistant bacteria, it is recommended to initiate antibiotics that are effective against resistant and anaerobic bacteria, guided by unit-specific antibiograms. Hospital-associated infections must be considered, and blood cultures should be repeated before adding a new antibiotic. Antifungal therapy should be commenced early for patients already receiving antibiotics, to treat multidrug-resistant bacteria.

Recommendation 15
The panel **recommends against** using granulocyte colony-stimulating factor (G-CSF) as a secondary therapy in children and adolescents with FN (certainty of evidence: low to very low).

Panel deliberations
Reducing the duration of neutropenia facilitates adherence to chemotherapy protocols, thereby minimising protocol deviations and the risk of resistance or disease relapse. However, the high cost of G-CSF restricts its routine application in many resource-limited settings.

Recommendation 16
The panel **suggests against** using bacterial biomarkers (C-reactive protein, procalcitonin, interleukin-6 and/or interleukin-8) to guide decisions around therapy modifications for managing children and adolescents with FN (certainty of evidence: very low).

Panel deliberations
The prohibitively high cost and limited accessibility of biomarker tests impede the widespread adoption of bacterial biomarkers in SA. More consistent evidence of sensitivity and specificity is needed before advocating for the routine use of biomarkers.

Recommendation 17
The panel **suggests against** routinely performing imaging of the lungs of children and adolescents with prolonged FN without localising signs or symptoms who are at high risk for invasive fungal infection (certainty of evidence: very low).

Panel deliberations
The panellists endorsed the need to minimise radiation in patients with cancer. Clinicians should avoid indiscriminate reliance on diagnostic imaging.

Recommendation 18
The panel **suggests** against routinely performing imaging of the abdomens of children and adolescents with prolonged FN without localising signs or symptoms who are at high risk for invasive fungal infection (certainty of evidence: very low).

Panel deliberations
The infrequent occurrence of intra-abdominal lesions in children and adolescents with FN, alongside the risks of radiation exposure, were addressed. It was also considered that computed tomography (CT) imaging has limited availability in resource-limited settings. Ultrasound abdominal imaging is more readily accessible.

Recommendation 19
The panel **recommends against** routinely performing imaging of the sinuses of children and adolescents with prolonged FN without localising signs or symptoms who are at high risk for invasive fungal infection (certainty of evidence: very low).

Panel deliberations
More robust evidence is needed on benefits before recommending routine sinus imaging.

Recommendation 20
The panel **recommends against** routine imaging of the lungs, abdomen and/or sinuses in children and adolescents with FN and persistent fever without localising signs or symptoms (certainty of evidence: very low).

Panel deliberations
The panellists highlighted the need for close attention to clinical signs and symptoms, suggesting that chest imaging may be necessary for suspected lower respiratory tract infections, abdominal imaging for neutropenic enterocolitis, and sinus imaging for suspected sinusitis. Meanwhile, parent representatives argued against routine imaging and advocated for a tailored approach.

Recommendation 21
The panel **recommends** testing for active tuberculosis (TB) in children and adolescents with prolonged FN who have recent TB exposure (certainty of evidence: very low).

Panel deliberations
Given the high prevalence of TB in SA, it is advisable to test patients with prolonged fever and recent exposure to the disease for TB. Young children and those living with HIV are at an increased risk of developing TB. Clinicians should remain vigilant and maintain a low threshold for TB testing.

Recommendation 22
The panel **suggests against** testing for *Pneumocystis jirovecii* in children and adolescents with FN and hypoxaemic pneumonia (certainty of evidence: very low).

Panel deliberations
Testing for *P. jirovecii* pneumonia (PCP) in resource-limited settings may be constrained by the availability and cost of resources. Furthermore, likely owing to routine prophylaxis, PCP is uncommon in patients with cancer. In specific units, empirical treatment for PCP might be started before investigations are completed owing to delays in obtaining radiology results and suboptimal test quality, with therapy discontinued as needed.

Recommendation 23
The panel **suggests against** using galactomannan or β-D-glucan for the diagnosis of invasive fungal disease in children and adolescents with FN who are at high risk for invasive fungal disease (certainty of evidence: very low).

Panel deliberations
Existing research focuses on galactomannan, with no studies identified on β-D-glucan in the paediatric population. Galactomannan testing identifies *Aspergillus* spp. infections, but may not detect *Candida* spp. infections. Studies evaluating the utility of galactomannan did not include test outcomes from the era of antifungal prophylaxis. Furthermore, β-D-glucan tests currently cannot influence the decision to initiate antifungal therapy, owing to prolonged turnaround times.

Recommendation 24
The panel **suggests** administering empirical antifungal therapy in children and adolescents with FN and prolonged fever who are at high risk for fungal disease (certainty of evidence: moderate to low).

Panel deliberations
Definitions of prolonged fever vary from 96 to 120 hours. Amphotericin B is the primary treatment for invasive fungal disease, whereas micafungin is employed more selectively. Because of its widespread use in fungal prophylaxis, fluconazole is unsuitable for empirical therapy. It is important to initiate antifungal treatment for patients at high risk of fungal infection who continue to have a fever after 96 hours of broad-spectrum antibacterial therapy.

Recommendation 25
The panel **suggests against** routinely removing indwelling lines in children and adolescents with FN with a current positive blood culture (certainty of evidence: very low).

Panel deliberations
Cost considerations for indwelling catheters, along with surgical and anaesthetic risks in patients, pose challenges for administering antimicrobials and chemotherapy to children and adolescents with limited venous access. These factors greatly influence the timing of line removal. Additionally, the source of blood cultures, the identified organism, culture positivity rates, the patient's clinical condition and line colonisation may also affect the decision to remove indwelling catheters.

Recommendation 26
The panel **suggests** stopping empirical antibiotics in children and adolescents with high-risk FN who have negative blood cultures at 48 hours and are afebrile for at least 24 hours (certainty of evidence: moderate to very low).

Panel deliberations
Panellists emphasised the challenges in implementing this recommendation, arising from ineffective laboratory systems that hinder the timely assessment of blood culture samples, the low rate of positive blood cultures in this group, and the unclear implications of a negative blood culture result. Furthermore, antibiotics may be continued when an infection site, such as pneumonia, is suspected, even if a blood culture is negative.

Recommendation 27
The panel **recommends** stopping empirical antibiotics in children and adolescents with low-risk FN who have had negative blood cultures for 48 hours and have been afebrile for at least 24 hours (certainty of evidence: moderate to low).

Panel deliberations
The panel's deliberations mirrored those of recommendation 26. Following up on blood culture results after hospital discharge is essential to ensure that they remain negative throughout the entire incubation period. Effective communication between the laboratory, clinicians and caregivers is crucial for initiating a callback if the culture test is positive after discharge.

Recommendation 28
The panel **suggests** early discharge within 72 hours for children and adolescents with high-risk FN who have reliable follow-up, negative blood cultures at 48 hours, have been afebrile for at least 24 hours and have evidence of marrow recovery (certainty of evidence: moderate to low).

Panel deliberation

The recovery of bone marrow, the clinical status of patients, the frequency of antibiotic administration, the distance from the hospital to the patient's residence and the availability of transport to the hospital influence the decision to either continue antibiotic treatment in the inpatient setting, or transition to outpatient care with periodic hospital visits for antibiotic administration. If possible, parents prefer to discharge the patient to home care.

Recommendation 29

The panel **suggests** early discharge within 24 - 36 hours for children and adolescents with low-risk FN with reliable follow-up who have negative blood cultures at 24 - 36 hours and are afebrile for at least 24 hours, regardless of marrow recovery status (certainty of evidence: moderate).

Panel deliberation

Considerations for the low-risk population are the same as those for the high-risk population, except that bone marrow recovery is not a concern for the low-risk population. Clinicians must ensure that families have reliable transport to return to the hospital.

Conclusion

The CPG development process has several notable conclusions. Most recommendations align with international FN CPGs, but several reflect the unique context of SA, which should enhance their applicability. Responding to panel priorities, this CPG includes recommendations for assessing suspected TB and *P. jirovecii*. During deliberations, when the panel failed to recommend risk stratification, despite acknowledging this common clinical practice, they highlighted not only the poor performance of existing tools but also the need to include context-specific factors in a SA tool. The frequency of conditional recommendations likely reflects awareness of variable availability, accuracy and affordability of diagnostic tests and therapeutic approaches, as well as patient preferences. These results highlight the importance of following a methodological approach to generate recommendations, as other factors, in addition to evidence, likely influenced panellists' votes.

Our comprehensive search of available evidence has revealed the need for more robust data from local settings. This highlights the importance of generating and regularly updating the evidence base to ensure that it accurately reflects context-specific medical knowledge that may vary across regions and populations. Across SA centres, there is wide variation in access to timely laboratory investigations, imaging and rapid diagnostic tools, as well as in the availability of antibiotics, blood products and isolation facilities. Human-resource constraints are also pronounced, with a limited number of trained paediatric oncologists, infectious disease specialists, pharmacists, microbiologists and oncology nurses concentrated in tertiary centres. These disparities lead to inconsistencies in the recognition and management of FN. Implementing the recommendations in the CPG will significantly enhance informed decision-making and, in turn, improve patient outcomes by ensuring that interventions are relevant and effective.

A crucial outcome of the guideline development process was the systematic identification and highlighting of key research priorities to address existing gaps in the current knowledge base, particularly those related to regional contextual needs. Furthermore, guideline updates should systematically leverage data from methodologically rigorous research, including monitoring adherence to guideline-recommended practices, to thoroughly evaluate guideline implementation and assess their impact on patient outcomes across diverse settings, thereby refining understanding and optimising care in this critical field of healthcare.

The panel, comprising representatives from various regions of SA, including both urban and rural areas, adopted a comprehensive, evidence-based approach applicable to the country's diverse management contexts. These carefully crafted recommendations aim to promote a patient-centred approach to care, emphasising the significance of collaboration among healthcare providers, patients and their families. By fostering a compassionate and inclusive framework for treatment, the panel sought to enhance the overall quality of healthcare delivery across SA, ensuring that all individuals receive the support and attention they deserve throughout their treatment journey.

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