



Discrepancies between national and local guidelines for the management of paediatric oncology patients with fever and neutropenia (FN): A need for alignment?

Benedikt D. Spielberger^a, Markus Hufnagel^a, Katharina Reifenrath^b, Arne Simon^b, Katharina Last^{c,d}, Cihan Papan^{c,d,*}

^a Division of Paediatric Infectious Diseases and Rheumatology, Department of Pediatrics and Adolescent Medicine, University Medical Centre, Medical Faculty, University of Freiburg, Freiburg, Germany

^b Paediatric Oncology and Hematology, Children's Hospital, Saarland University, Homburg, Germany

^c Centre for Infectious Diseases, Institute of Medical Microbiology and Hygiene, Saarland University, Homburg, Germany

^d Institute for Hygiene and Public Health, University Hospital Bonn, Bonn, Germany

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ABSTRACT

Background: We previously demonstrated in a large multicentre point prevalence study (PPS) a marked variability across German and Austrian centres regarding the management of fever and neutropenia (FN) in children, and a high rate of inappropriate treatments compared to recommendations in the German national FN guidelines. **Methods:** We analysed local FN standard operating procedures (SOPs) of participating centres and rated their concordance with the German national FN guidelines. To this end, we defined items derived from the German national FN guidelines that we considered essential for any local FN SOP, and assigned points per items. The items comprised “basic requirements of a SOP”; “risk analysis”; “diagnostic approach”; and “use of antibiotics including dosing recommendations”, including sub-categories.

Results: Of the 30 participating centres' SOPs, 29 were of sufficient granularity for detailed analysis. Only 19/29 (66%) and 20/29 (69%) of the SOPs provided a definition of fever and of neutropenia, respectively. The top scoring sub-categories were “empiric treatment” (mean percentage 69%), “laboratory investigations” (62.4%), and “SOP basics” (59.7%). The worst scoring sub-categories were “definitions” (37.7%), “risk analysis” (32.3%), and “outpatient treatment” (15.7%).

Conclusions: The majority of the local FN SOPs demonstrated a lack of concordance with the German national guidelines on the management of paediatric FN. These discrepancies may explain the high rate of inappropriate antimicrobial treatments in our previous PPS. Our data indicate that local SOPs should be better adapted to national guidelines, and national guidelines should be conceived with the feedback of end-users, thereby anticipating barriers and facilitating acceptance.

1. Background

Fever in neutropenia is a common complication in paediatric cancer patients receiving intensive chemotherapy [1,2]. Due to an increased risk of a complicated clinical course in case of an infection, national and international guidelines advise timely inpatient treatment with intravenous antibiotics and additional supportive care [3–6]. Recently, our group evaluated patterns of antimicrobial use in 30 paediatric oncology and haematology centres in Germany and Austria utilising a point prevalence approach combined with a qualitative external expert panel

assessment [7]. Unexpectedly, this study, which comprised a thoroughly performed multi-step qualitative adjudication process, revealed 33.8% of all therapies being labelled inappropriate based upon institutional standards, with an even higher inappropriate rate (47.9%) when national guidelines were taken into consideration. The most frequent reasons for inappropriate therapy were incorrect dosage (26.2%) and (de-)escalation/spectrum-related errors (20.6%) [8]. The participating centres were asked to provide us with their internal standard operation procedure (SOP) document (or any written standard), which they used for internal guidance.

* Correspondence to: Institute for Hygiene and Public Health, University Hospital Bonn, Venusberg-Campus 1, Building 63, 53127 Bonn, Germany.
E-mail address: cihan.papan@ukbonn.de (C. Papan).

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A previous survey from our group had depicted a remarkable variability in local practice concerning the management of fever and neutropenia in GPOH¹ centres [9]. The German national guideline [5] differs from the most often cited international guideline [3,10] in few aspects [11]. It has been developed in 2016 by an interdisciplinary expert panel as S2k (consensus) guideline following the regulatory framework of the association of the scientific medical societies in Germany (AWMF). It includes the treatment of patients with septic shock or sepsis with multiple organ dysfunction and patients after allogeneic stem cell transplantation. According to the German national guideline, blood culture sampling should be performed from the central venous access (Hickman/Broviac/Port) only and not (additionally) from a peripheral vein. The German guideline states how much blood should be drawn for blood cultures depending on the patient's bodyweight. In addition, ceftazidime is not recommended as monotherapy for patients with severe mucositis (e.g., after induction treatment for acute myeloblastic leukaemia), and carbapenems are not recommended for clinically stable patients with FN without any history of colonisation with Gram-negative multidrug-resistant organisms (MDRO). The German guideline provides the local physicians with precise dosing recommendations for the most important antibiotics and antifungals. It does not refer to any definition of a "low-risk group" since none of the corresponding predictive models has been validated in GPOH paediatric cancer centres until 2016 [12].

The aim of this article was to describe the local guidance documents from our previous study [8] using a framework of core questions derived from the German national guidelines for Diagnostics and Treatment in Paediatric Cancer Patients with Fever and Neutropenia.

2. Methods

A group of experts (MH, CP and AS) defined a core set of items derived from the German national guideline that should be represented in the local standard operating procedures (SOP). A translated version of the most important items of the German national guideline can be found in the [Appendix](#).

The core set of items consisted of four sections: (1) basic requirements of a SOP; (2) risk analysis; (3) diagnostic approach; and (4) use of antibiotics including dosing recommendation. For the ease of comparison, items within the sections were grouped into sub-categories ("SOP basics", "definitions"; "physical examination", "laboratory investigations", "blood culture", "additional microbiological tests"; "Empiric treatment", "combination treatment and therapeutic drug monitoring (TDM)", "treatment escalation", "antifungal treatment", "cessation of treatment", and "outpatient treatment") (Table 1).

The SOPs were then analysed by another author (BS) including field notes from the expert panel process [7] and compared with the German national guideline for the treatment of paediatric FN. For each item, either 1 or 2 points were assigned. The maximum total score equalled 109 points. Data analysis and visualisation were done in R (Version 4.2.2).

3. Results

3.1. General results

Out of the 30 centres from Germany and Austria participating in the previous point prevalence study [8], 29 SOPs were granular enough for detailed evaluation. The complexity and the scope of the SOPs was highly variable, resulting in page length of one to 16 pages, with an average length of three pages. Of all 29 SOPs, 27 (93.1%) were declared as mandatory for clinical routine management in patients with FN.

Table 1

Items used to assess concordance of local standards (SOPs) with the German national guideline on febrile neutropenia in children, per section/subcategory. Max. points indicates the maximum number of points assigned per item.

Section/Subcategory	Item	Max. points	
"Basic requirements of a SOP" / "SOP basics"	Is the standard formally recognisable as a mandatory SOP?	2	
	Does the standard define patients to whom it should apply?	2	
	Is there a version date?	2	
	Is the version date from less than 2 years ago?	2	
"Basic requirements of a SOP" / "Definitions"	Can the following definitions be found in the standard?		
	o Fever	1	
	o Granulocytopenia	1	
	o Prolonged granulocytopenia > 10 days	1	
	o Time-to-antibiotics	1	
	Is documentation of time-to-antibiotics required?	2	
	Does the standard identify FN as an emergency?	2	
	Does the standard differentiate between fever without focus and sepsis (sepsis is a separate SOP if applicable)?	2	
	"Risk Analysis"	Are there any references in the standard to the following items of an individual risk analysis?	
		o Oncological initial disease vs. recurrence	1
o Vascular catheters and other invasive devices		1	
o Pre-existing organ dysfunction		1	
o Special concomitant medications (possibility of interactions)		1	
o Colonisation or infection with MDRO		1	
o Prior treatment with antimicrobial drugs		1	
o History of infections		1	
o Allergy to first-line antibiotics		1	
o Concurrent illness of close contacts		1	
o Department-specific pathogen and resistance statistics		1	
"Diagnostic approach" / "physical examination"		Is there evidence in the standard of the following items of a prompt thorough physical examination?	
	o Documentation of initial vital signs	2	
	o Are there any special clues to the physical examination? (e.g., mucous membranes, perianal lesions, catheter entry site)	2	
	o Does the standard indicate clinical warning signs of (incipient) sepsis? (e.g., general condition, consciousness, respiration, cutaneous circulation, urine output)	2	
"Diagnostic approach" / "Laboratory investigations"	Does the standard describe the routine laboratory work-up required?		
	o Blood count with differentiation	1	
	o Inflammatory markers (e.g., CRP, PCT, IL-6, IL-8)	1	
	o Organ function markers (e.g., electrolytes, blood gases, lactate, liver enzymes)	1	
"Diagnostic approach" / "Blood cultures"	Does the standard describe blood culture diagnostics according to the following criteria?		
	o Collection before the start of antibiotic therapy	1	

(continued on next page)

¹ German Society for Paediatric Oncology and Haematology. Centres from Austria and Switzerland often follow the GPOH treatment protocols.

Table 1 (continued)

Section/Subcategory	Item	Max. points
	o Collection of an aerobic/ anaerobic blood culture set	1
	o Collection from all lumens of a central catheter	1
	o Indications for a hygienically correct collection technique	1
	o Sufficient volume depending on body weight	2
“Diagnostic approach” / “Additional microbiological tests”	Are additional microbiological tests described in the standard?	1
	o Bacteriological specimens in case of additional symptoms	1
	o Virological diagnostics in case of additional symptoms or positive history	1
	o Screening for colonisation with multidrug resistant organisms (MDRO)	1
“Use of antibiotics including dosing recommendation” / “Empiric treatment”	Are recommendations made for initial empiric antibiotic therapy?	2
	Empirical antibiotic therapy with a broad spectrum of activity as monotherapy with piperacillin-tazobactam or ceftazidime or cefepime	2
	Recommendation against carbapenems as empirical first-line therapy without additional risk factors (e.g., MDRO colonisation)	2
	Are antibiotic dosages understandable and clearly indicated? (e.g.,	2
	o piperacillin-tazobactam 300 mg/kg/day referring to the piperacillin portion in 3 single doses over 1 h each or	
	o piperacillin-tazobactam single dose 100 mg/kg related to the piperacillin portion 3 times a day over 1 h	
	Are dose indications for antibiotics consistent with those in the German national guideline?	2
	Is there a reference to the rational use of carbapenems? (e.g., in case of known colonisation with MDRO)	2
“Use of antibiotics including dosing recommendation” / “Combination treatment and TDM”	Does the standard define criteria for initial combination therapy with aminoglycosides?	2
	Does the standard provide guidance on TDM with aminoglycosides?	2
	Are the TDM indications correct / consistent?	1
	Is there a "stopping rule" for aminoglycosides (e.g., usually after 72 h)?	2
	Does the standard define criteria for initial combination therapy with a glycopeptide? (e.g., vancomycin, teicoplanin, or linezolid)	2
	Does the standard provide guidance on TDM with vancomycin?	2
	Are these TDM references correct / consistent?	1
	Is a target for vancomycin trough level defined?	1
	Is there a "stopping rule" for the glycopeptides? (e.g., usually after 72 h)	2
“Use of antibiotics including dosing recommendation” / “Treatment escalation”	Are recommendations made for escalation therapy?	2
	Is there an indication of when to escalate AB if the patient is stable	2

Table 1 (continued)

Section/Subcategory	Item	Max. points
	and cultures are negative (e.g., 72 h)?	
	Is the option to waive escalation in certain situations listed?	2
	Is re-collection of blood cultures required prior to escalation of antimicrobial therapy?	2
	Is a combination of initial monotherapy with aminoglycosides or fosfomycin recommended for escalation?	2
	Is a combination of initial monotherapy with glycopeptides recommended for escalation?	2
	Is therapy with carbapenems recommended for escalation?	2
“Use of antibiotics including dosing recommendation” / “Antifungal treatment”	Are recommendations made for antifungal therapy?	2
	Are specific diagnostics for invasive fungal infections (IFI) required prior to use of antifungal therapy? (e.g., galactomannan serology, CT thorax).	2
	Is a high-risk group defined in which empiric administration of an antifungal agent is recommended after 96 h of fever? (e.g., AML, leukaemia relapse, St. p. allogeneic HSCT, prolonged granulocytopenia, systemic steroid therapy)	2
	Are these HR criteria (for an IFI) in line with the German national guideline?	2
	Is the time course correct (without reasonable evidence of IFI only after 96 h)?	2
	Are liposomal amphotericin B or caspofungin recommended for empiric therapy?	2
	Are the dosages of antifungal agents in accordance with the German national guideline?	2
“Use of antibiotics including dosing recommendation” / “Cessation of treatment”	Is the minimum treatment duration (i.v.) defined?	2
	Is there an option to stop i.v. therapy after 72 h in stable patients with granulocytopenia < 10 days and without mucositis?	2
	Is this option available even if patients are still granulocytopenic?	2
“Use of antibiotics including dosing recommendation” / “Outpatient treatment”	Are recommendations made for outpatient oral antibiotic treatment?	2
	Continuation of antibiotic therapy after inpatient discharge is generally not required	2
	Under certain conditions, oral antibiotic therapy performed on an outpatient basis is recommended (e.g., with amoxicillin + BLI or ciprofloxacin or levofloxacin).	2
	Are the dosages of oral antibiotics consistent with the German national guideline?	2
	If fluoroquinolones are used, does the standard mention the risk of adverse effects? (e.g., hepatotoxicity or neurotoxicity or <i>Clostridioides difficile</i> infection or selection for MRSA/MDRO).	2

Inclusion and exclusion criteria concerning the appropriate allocation of patients to this SOP were clearly defined in 19/29 (66%). A date of the last revision was given for 18/29 (62%), but only 6/29 (21%) were updated and/or revised within the previous 2 years.

3.2. Definitions

Comparing the definitions of the German national guideline with the definitions of the local SOPs showed that only 19/29 (66%) provided a definition of fever and 20/29 (69%) a definition of neutropenia (Table 2). Fever in a paediatric cancer patient with neutropenia was defined as a clinical emergency in only 9/29 (31%). Time to onset of antibiotic therapy was correctly indicated in only 5/29; the targeted time to antibiotics according to the German national guideline from 2016 is less than 60 min after the patient has arrived at the hospital or emergency department.

Table 2

Definitions, risk analysis, and diagnostic approaches in the analysed SOPs and the respective agreement with the German national guideline; ANC: absolute neutrophil count; ID: infectious diseases; MDRO: multidrug resistant organism; WBC: white blood count; CRP: C-reactive protein; IL6: interleukin 6; PCT: procalcitonin; IL8: interleukin 8.

	SOP agreement		
	fully	partly	cumulative
(1) Definitions			
Fever (once >38.5 °C or 1 h > 38.0 °C)	19/29 (66)	0/29 (0)	19/29 (66)
Neutropenia (ANC < 500/μl)	20/29 (69)	0/29 (0)	20/29 (69)
FN = ID emergency	9/29 (31)	1/29 (3)	10/29 (34)
Time-to-antibiotics	5/29 (17)	1/29 (3)	6/29 (20)
(2) Risk analysis			
Recurrence of underlying malignant disease	18/29 (62)	0/29 (0)	18/29 (62)
Catheters or other invasive devices	16/29 (55)	1/29 (3)	17/29 (58)
Organ dysfunction (other than immune)	11/29 (38)	2/29 (7)	13/29 (45)
Possible interaction with medication	10/29 (34)	0/29 (0)	10/29 (34)
Colonisation with any MDRO	16/29 (55)	1/29 (3)	17/29 (58)
Ongoing treatment with antimicrobials	2/29 (7)	1/29 (3)	3/29 (10)
History of infections (self)	6/29 (21)	1/29 (3)	7/29 (24)
Allergy to first-line antibiotics	9/29 (31)	0/29 (0)	9/29 (31)
History of infections in close contacts	2/29 (7)	0/29 (0)	2/29 (7)
Local pathogen and resistance patterns	0/29 (0)	0/29 (0)	0/29 (0)
(3) Diagnostic approach			
Vital signs	16/29 (55)	0/29 (0)	16/29 (55)
Specific physical examination	14/29 (48)	4/29 (14)	18/29 (62)
Investigation for signs of sepsis	9/29 (31)	6/29 (21)	15/29 (52)
WBC + differential	16/29 (55)	9/29 (31)	25/29 (86)
Inflammatory markers (CRP, IL6, PCT, IL8)	23/29 (79)	2/29 (7)	25/29 (86)
Organ function tests (liver, kidney)	16/29 (55)	4/29 (14)	20/29 (69)
(4) Blood culture (BC) diagnostics			
BC before antibiotic treatment	12/29 (41)	2/29 (7)	14/29 (48)
Aerobe and anaerobe blood culture	14/29 (48)	3/29 (10)	17/29 (58)
BC sets from all hubs of the central venous catheter	25/29 (86)	0/29 (0)	25/29 (86)
Aseptic technique	2/29 (7)	0/29 (0)	2/29 (7)
Correct volume for age/weight	9/29 (31)	2/29 (7)	11/29 (38)

3.3. Diagnostic approach

The German national guideline requires the documentation of initial vital signs, lists specific features to be examined during the physical examination, highlights signs of sepsis/SIRS and requires a blood sample with determination of a full blood count with differential blood count, as well as markers of inflammation and of organ dysfunction. A summary comparing the concordance between the local standards with the German national guideline is given in Table 2. Only 16/29 (55%) required the documentation of the initial vital signs as mandatory. Specific features for the physical examination were described in detail in 14 SOPs (48%) and partially in four SOPs (14%). A specific triage examination for signs of sepsis/SIRS was only described by nine (31%) SOPs in full detail and only partly by six (21%) SOPs.

A full blood count with differential blood count was required by 16 (55%) of the SOPs and one without differential by nine (31%). The determination of one or more inflammatory markers (e.g., CRP, IL6, PCT, IL8) was required by 23 (79%) and another two (7%) SOPs used suggestive words (e.g., “inflammation marker”). Laboratory values for organ functions (liver function, kidney function) were required in full by 16 (55%) and incompletely by four (14%) SOPs.

3.4. Blood culture diagnostics

Based on national guidelines, blood culture (BC) diagnostics for FN must be carried out before the start of antibiotic therapy and consists of an aerobic and an anaerobic culture (a “set”) from all access points of the CVAD (e.g., two sets in case of a double lumen Broviac catheter). Aseptic precautions (including local antisepsis of the CVAD hub) to avoid any contamination of the BC sample are important. The appropriate BC volume depends on the weight of the patient [13].

In 48% of the SOPs (14/29), a complete or partial collection of blood cultures before the start of antibiotic therapy was recommended. A total of 58% (17/29) SOPs required aerobic and anaerobic culture collection, while 25 of 29 standards (86%) required collection from any lumen of the CVAD. Only two (7%) SOPs described the aseptic precautions to avoid contamination in detail. The correct filling volume for the respective weight group was described in nine (31%) of the SOPs. In contrast to the national guideline, 5/29 (17%) demanded the additional sampling of a peripheral venous blood culture set.

3.5. Use and dosing recommendations for antibiotics

While antibiotic regimens are variable in different clinics, the German national guideline [5] is very clear regarding dosing recommendations for the most important antibiotics in paediatric cancer patients with FN.

Among the beta-lactam antibiotics, piperacillin/tazobactam had dosing recommendations in all SOPs, followed by meropenem (90%; 26/29), ceftazidime (31%; 9/29), cefepime and ceftriaxone (each 14%; 4/29). Among the glycopeptide antibiotics, vancomycin was the most widely used antibiotic with a dosing recommendation included in 62% (18/29) of the SOPs, followed by teicoplanin at 55% (16/29). In the group of aminoglycoside antibiotics, tobramycin was used in 62% (18/29) of SOPs, followed by amikacin and gentamicin at 28% (8/29) each.

3.6. Beta-lactam antibiotics

Using the recommendations of the national guideline as reference, the recommended dosing schedule in the local SOPs for piperacillin/tazobactam was correct in 86% (25/29; no dosing recommendation was given at one centre). For ceftazidime, only 67% (6/9) of the available dosing recommendations were correct, while the remaining 33% (3/9) recommended 100 instead of 150 mg/kg/d. Cefepime was used in four centres and all (100%, 4/4) dosing recommendations were too low (100 instead of 150 mg/kg/d). Ceftriaxone dosing was correct in 75% (3/4)

and too low in 25% (1/4) centres. The correct meropenem dosing regimen was described in 88% (23/29) SOPs, while two (8%) centres had too low dosing recommendations and information was missing in one (4%).

3.7. Glycopeptides

The correct dose for vancomycin was given by five (28%) of the 18 SOPs. The dosage used was too low in 12 (67%) centres (40 mg/kg/d) and too high in one SOP (6%). The maximum daily dose of 2 g/day² was stated correctly in eight (44%) SOPs, too low in two (11%) and too high in four (22%). An additional four SOPs (22%) did not specify a maximum daily dose. Teicoplanin was used in 16 centres, of which 15 (94%) SOPs referred to the correct dosing and one (6%) dose was too low. The maximum daily dose of 400 mg (during maintenance dosing once daily)³ was reported correctly in 13 (81%) SOPs, an elevated daily dose was reported in one SOP (6%) and no maximum dose was reported in two SOPs (13%).

3.8. Aminoglycosides

Tobramycin was used by 18 centres, of these nine (50%) used the correct dosage (7–10 mg/kg/day), another eight (44%) used a lower dose, in the remaining one SOP (6%) no tobramycin dosage was provided. The maximum recommended daily dose (MDD) was 400 mg and was reported correctly in nine (50%) SOPs, two (11%) SOPs described an insufficiently low MDDs and seven (39%) did not comment on this issue.

Amikacin was used by eight centres, and all eight SOPs indicated the correct dosage. The MDD was correctly reported by six (75%), and too low in two (25%) of the SOPs. Gentamicin was also used by eight centres. Only two (25%) of the centres used the correct gentamicin dosage. In five (63%) SOPs, the dosage was too low and in one (13%) SOP it was too high. The correct MDD was described in three (38%) of the SOPs, one SOP (13%) used a lower MDD, and four (50%) SOPs did not specify any MDD of gentamicin.

3.9. Therapeutic drug monitoring

An overview of the corresponding results is given in Table 3. Following the national guideline, a therapeutic drug monitoring (TDM) is mandatory for vancomycin and aminoglycosides. A TDM was requested in 72% (13/18) of the SOPs for vancomycin, in 72% (13/18) for tobramycin, in 88% (7/8) for gentamicin and in 63% (5/8) for amikacin. Timing for TDM was most frequently correct with 77% (10/13) for tobramycin, followed by 60% (3/5) for amikacin, 43% (3/7) for gentamicin and only 31% (4/13) for vancomycin. Often the TDM occurred too late, for example in 69% with vancomycin (9/13). The SOPs contained information on the correct trough levels for vancomycin in 6/13 (46%). Concerning the trough levels of the aminoglycosides (< 2 mg/L for gentamicin and tobramycin, < 5 mg/L for amikacin), SOPs were informative in 46% (6/13) for tobramycin and in 43% (3/7) for gentamicin. Projected amikacin trough levels were either to high [60% (3/5)] or not described in the SOP [40% (2/5)].

3.10. Score performance

The mean score across all 29 SOPs that were analysed was 48.7/109 (45%), with the lowest and highest scores of nine (8%) and 76 (70%), respectively. Overall, only 11/29 SOPs reached a score of 50% or above.

The top scoring three categories were “empiric treatment” (mean score 5.5/8, mean percentage 69%), “laboratory investigations” (1.9/3,

Table 3

Accordance of analysed SOPs with German national guideline with regard to recommended therapeutic drug monitoring (TDM); MRSA: methicillin-resistant *Staphylococcus aureus*; h: hours.

	Vancomycin	Amikacin	Gentamicin	Tobramycin
Recommendation	immediately	trough	trough	trough 8–10
trough	before 3rd	8–10 h	8–10 h after	h after 3rd
measurement	dose	after 3rd	3rd dose	dose
Drug used (%)	18 (62)	8 (28)	8 (28)	18 (62)
TDM requested (%)	13 (72)	5 (63)	7 (88)	13 (72)
Correct timing (%)	4 (31)	3 (60)	3 (43)	10 (77)
Timing too late (%)	9 (69)	2 (40)	3 (43)	3 (23)
Timing too early (%)	0 (0)	0 (0)	1 (14)	0 (0)
Recommended trough level	5–10 mg/L, MRSA: 15–20 mg/L	< 5 mg/L	< 2 mg/L	< 2 mg/L
Correct level (%)	6 (46)	0 (0)	3 (43)	6 (46)
Level too low (%)	0 (0)	0 (0)	2 (29)	0 (0)
Level too high (%)	4 (31)	3 (60)	1 (14)	0 (0)

62.4%), and “SOP basics” (4.7/8, 59.7%). On the other extreme, the worst scoring categories were “definitions” (3.8/10, 37.7%), “risk analysis” (3.2/10, 32.3%), and “outpatient treatment” (1.3/8, 15.7%). A heatmap of the concordance of each category with the national guideline is shown in Fig. 1.

4. Discussion

Our recent point prevalence study with qualitative external expert panel assessment revealed a high rate of inappropriate therapies (47.9% [68/142]) when national guidelines were taken into consideration [8]. A second look at the local SOPs provided by the participating paediatric cancer centres partly explains these findings. Many details of the local SOPs examined in our current study are not in accordance with the national guideline [5]. Diagnostics and treatment in paediatric cancer patients with FN is a complex clinical task and needs unambiguous easy to follow decision algorithms to foster a high-quality, evidence-based and good clinical practice treatment approach. All these aspects are necessary to guarantee patients’ safety.

If one refers to a list of important items comprising a complete clinical pathway for FN management, our detailed analysis revealed that many local SOPs show an unexpectedly high proportion of missing or even incorrect information. Clinical practice, which ignores local SOPs, gives rise to the question “Why don’t physicians follow clinical practice guidelines?”, extensively discussed by Cabana et al. more than 20 years ago [14].

Our current study asks for explanation to the question “Why is the framework of the national guideline not translated sufficiently into local SOPs?” How do we succeed in making the scientific progress concerning the rational use of antibiotics and antifungals in paediatric cancer patients [4,6,15,16] available in clinical practice (for the benefit of our patients)?

One reason for the differential levels of concordance with the national guideline that we observed among the core set of items may be the fact that some aspects are weighed more (or less) by local teams. We tried to account for these anticipated differences in perceived importance by providing a high-granularity scoring system. For instance, overall concordance for the subsection “empiric treatment” was high, as this is understandably the single most important detail of a local SOP that gives advice on how to manage paediatric FN. By contrast, concordance for the subsection “definitions” was poor, which may relate to the fact that writers of local SOPs may want to keep their internal guidance documents as succinct as possible and omit certain definitions of, e.g., fever, that may appear trivial. It is noteworthy, however, that

² Not referring to patients with meningitis.

³ In case of a life-threatening infection max. 800 mg/day.

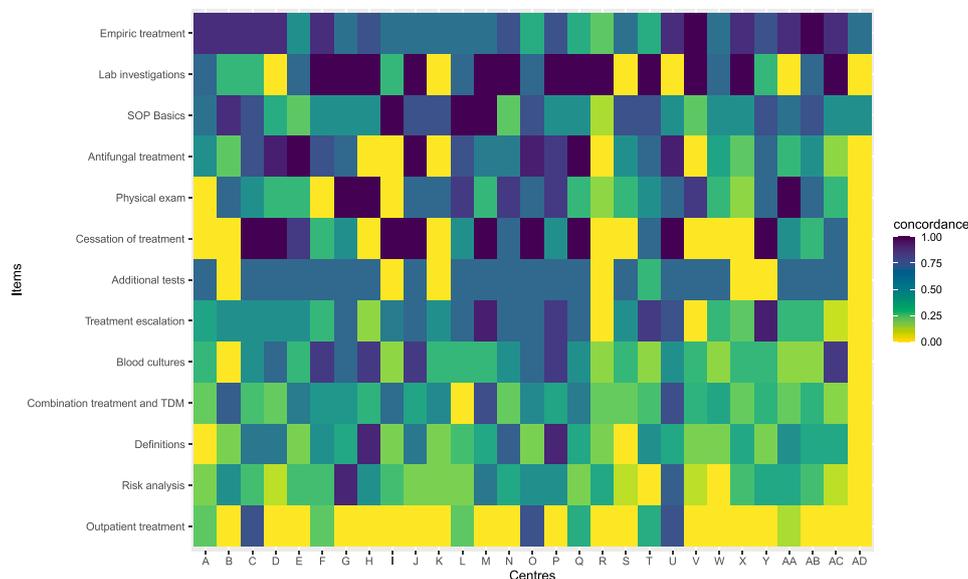


Fig. 1. Heatmap of the concordance between each centre's SOP and the German national guideline, per sub-category. SOP: standard operating procedure; TDM: therapeutic drug monitoring.

certain definitions and classifications, such as the fact that FN should be regarded as an emergency, may have immediate effects on the level of care provided and patient-relevant outcomes, and therefore should not readily be discarded.

Another example is the subsection “outpatient treatment”. Here, we observed the lowest overall concordance. It should be acknowledged that some centres may have additional, alternative SOPs, other than those pertaining to FN, that we did not systematically obtain but in which at least parts of the core items may have been addressed.

Interdisciplinary consented SOPs detailing the clinical management in common treatment situations are very important to provide the attending physicians (and other healthcare workers) with reliable knowledge and skills concerning the expected practice [17,18]. The local standard must not be defined by a prescribing etiquette (“Which senior consultant is actually on charge?”) [19] but by an evidence-based treatment strategy. SOPs (local guidelines) are important complementary measures of antibiotic stewardship [20] and support the education and training of new members of the treatment team [21]. They assist in making health care processes reliable and verifiable (e.g., by internal audits) [22,23].

Our results underline that it is necessary to continue to shed light into the “black box” of inappropriate antibiotic use in paediatric oncology [24]. This should be done with maximum involvement of those who work relentless hours at the bedside of the patients. Their feedback and buy-in is urgently needed for the successful implementation of any SOP [25,26]. At the same time, writing a guideline should entail an implementation approach and try to account for local specifics and reasons that may act as barriers or facilitators. Tomlinson et al. recently described the complex and time-consuming process of creating and adapting an infection management pathway in paediatric oncology [23]. Their aim was to increase the consistency of their current approach, to improve patients' outcomes by integrating evidence informed strategies and to reduce the burden of clinical decision making. It may be necessary to discuss all these issues in more detail with the potential users of our national paediatric FN guideline, which is currently re-evaluated and revised by an interdisciplinary expert group. Our data will potentially be helpful not only for the final draft but also throughout the dissemination of the updated national paediatric FN guideline in 2024, e.g., by offering centre-specific workshops and courses, and by providing checklists that can be used by authors of local SOPs.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejcped.2023.100030](https://doi.org/10.1016/j.ejcped.2023.100030)

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