A survey on hematology-oncology pediatric AIEOP centers: prophylaxis, empirical therapy and nursing prevention procedures of infectious complications

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ABSTRACT

A nationwide questionnaire-based survey was designed to evaluate the management and prophylaxis of febrile neutropenia in pediatric patients admitted to hematology-oncology and hematopoietic stem cell transplant units. Of the 34 participating centers, 40 and 63%, respectively, continue to prescribe antibacterial and antimycotic prophylaxis in low-risk subjects and 78 and 94% in transplant patients. Approximately half of the centers prescribe a combination antibiotic regimen as first-line therapy in low-risk patients and up to 81% in high-risk patients. When initial empirical therapy fails after seven days, 63% of the centers add empirical antimycotic therapy in low- and 81% in high-risk patients. Overall management varies significantly across centers. Preventive nursing procedures are in accordance with international guidelines. This survey is the first to focus on prescribing practices in children with cancer and could help to implement practice guidelines.

Key words: infectious diseases, neutropenia fever, pediatric, empirical therapy, prophylaxis.

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Introduction

Febrile neutropenia (FN) is a relatively frequent event in pediatric patients receiving cancer treatment. It is a potentially life-threatening condition that requires prompt medical intervention. Despite improvements in long-term survival, infection remains a common complication and is the cause of the majority of chemotherapy-associated deaths.[1] Prophylaxis and empirical treatment with antimicrobial agents before microbiological documentation of infection is justified in the pediatric patient with FN. Recent studies have identified factors associated with increased risk of infection and suggested a more appropriate approach to empirical therapy and prophylaxis.[2] No well defined guidelines, such as those long established for adults, have so far been formulated for pediatric patients with FN.

Design and Methods

A standardized questionnaire was sent out to all 49 hematogy-oncology units belonging to the Italian Paediatric Hematology-Oncology Association (AIEOP). The survey was designed to assess the current practice of empirical antimicrobial chemotherapy and chemoprophylaxis for FN. The questionnaire was made up of four parts according to the patient's risk of infection: i) low-risk (LR) patients: less than ten days of expected neutropenia after chemotherapy; ii) high-risk (HR) patients: more than ten days of expected neutropenia; iii) autologous (AUTO) transplantation patients; iv) allogeneic (ALLO) transplantation patients.

Furthermore, another questionnaire was designed to assess the current precautions used by nurses, focusing on hand hygiene procedures, barrier precautions, and safe work and isolation practices for patients on ordinary and isolation wards.

A complete list of the members of participating members of the Infectious Diseases Working Group of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) is reported in the "Appendix".

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The answers were required to represent the local policies; therefore, faithfully reflecting current practice and not personal opinion. The results were analyzed with EpiInfo (Centers for Diseases Control, Atlanta , GA, USA) statistical software.

Results and Discussion

A total of 34 centers (response rate 70%) filled in the survey questionnaire; 58% of the participating units performed allogeneic and autologous bone marrow transplantations. For the prophylaxis, we analyzed antibacterial, antimycotic, antiviral and anti-*Pneumocysis jiroveci* (PCP) treatments. The percentage of centers adopting antibacterial prophylaxis varied across the risk categories: 40% in LR, 63% in HR patients, and 78% in both allogeneic and autologous recipients (Table 1).The most commonly prescribed antibiotic regimen for antibacterial prophylaxis, both in LR and HR groups, was amoxicillin/clavulanate (60 and 75%, respectively) and fluoroquinolones (10 and 20%). In transplanted patients, heterogeneity of treatment was higher, with a more frequent use of fluoroquinolones.

The use of antimycotic prophylaxis varied from 47% in LR to 94% in allogeneic transplant patients, with 81% in HR and 91% in autologous subjects. Fluconazole was the most widely used agent in all risk groups, often substituted with other antifungal agents like itraconazole, liposomal amphotericin and echinocandin in HR patients. Twenty percent of centers employed antiviral prophylaxis for LR patients (16% of centers exclusively in AbHSV+ patients), and 28% for HR (20% exclusively in AbHSV+ patients). Antiviral prophylaxis was used by 62% of the centers (19% in AbHSV+ patients) in autologous transplant patients, and by 95% (6% in AbHSV+ patients) in allogeneic transplant patients. Acyclovir was the drug of choice. *Pneumocystis jiroveci* prophylaxis was administered to all patients undergoing allogeneic and autologous transplants; LR and HR patients received prophylaxis in 85% (10% only in selected patients) and in 91% (3% only in selected patients) of cases, respectively. The most commonly prescribed drug in all groups was trimethoprim sulfamethoxazole (TMP-SMZ), while pentamidine was prescribed less frequently.

The survey also assessed the use of combination therapy *versus* monotherapy as empirical antibiotic treatment (Table 2). Combination therapy was most frequently employed in all patients; a high frequency of combination therapy was observed in the treatment of HR patients (81 *vs*. 19% of monotherapy) as compared with LR patients (57 *vs*. 43%, respectively), where combination and single agent therapies were almost equally employed. In auto-transplant patients, combined therapy and monotherapy were chosen in similar proportions (55 *vs*. 45%, respectively). Allogeneic transplant patients received combination therapy two times more frequently than monotherapy (67 *vs.* 33%, respectively). Piperacillin/tazobactam, 3rd (ceftazidime and ceftriaxone) and 4th generation (cefepime) cephalosporins were the most frequently used molecules in monotherapy. The preferred combination regimen consisted of amikacine plus piperacillin/tazobactam or a 3rd generation cephalosporin. The most common approach was to add a glycopeptide (immediately at onset or within 48 h) to the ongoing regimen (ranging from 64% of units on LR patients to 76% in the allogeneic transplants) (Table 2), with teicoplanin chosen approximately three-fold as often as vancomycin.

Empirical antifungal therapy was administered by 81% of centers in HR and by 78% in HSCT subjects, while in LR patients it was given less frequently but still at a high rate (approximately 63%). The choice of antifungal agent for empirical treatment varied according to the risk of infection; however, liposomal amphotericin was the molecule of choice in most cases.

Regarding the nursing prevention strategies, specific protocols were applied in 80% of centers, both on ordinary and on isolation wards (Table 3). Hand washing was reported either before or after patient contact in nearly 90% of centers, with no difference observed among the two types of wards as far as the use of antiseptic soaps (80%) and common detergents was concerned. The use of caps, disposable overalls and masks differed among the two wards, reaching almost 90% on the isolation wards as compared to 50% on the ordinary wards. Overshoes were mainly employed on isolation wards (60%). There was no substantial difference in the use of gloves between the two types of ward. On the isolation wards, nurses took exclusive care of patient hygiene in 40% of cases; sterile water was used in 20%, and antiseptic soap and sterile sheets in 50% of cases. When transfer of patients was required, masks were used in 80% of cases, independently of ward type and FFP2/FFP3 type were employed in 30% of patients on isolation wards only. Disposable material and chlorine-containing agents were used for cleaning the ward in more than half of the centers, independently of the ward type. The preparation of chemotherapeutical agents and parenteral nutrition bags was centralized in 50 and 80% of centers, respectively. In 80% of centers, food was prepared as pre-packed individual meals and was distributed employing standard precautions (wearing a cap, mask and washing hands) in the same percentage, while gloves were used in less than half of the centers.

Patients suffering from neutropenia may undergo severe infections and the risk increases according to the duration and degree of the neutropenia. Surveys on the management of FN have been carried out only in adult populations,[3-5] and no surveys in the pediatric hematology-oncology popula-

Table 1. Prophylaxis (antibacterial, antimycotic, antiviral, anti-PCP).

	Antibacterial (%)	Antimycotic (%)	Antiviral (%)	Anti-PCP (%)
LR (neutrophil count < 10 days)	40	47	20	85
HR (neutrophil count > 10 days)	63	81	28	91
autologous transplant	78	91	62	100
allogeneic transplant	78	94	95	100

Table 2. Empirical antimicrobial therapy.

	Combination therapy (%)	Monotherapy (%)	Empirical glycopeptides[1] (%)	Empirical antimycotic[2] (%)
LR (neutrophil count < 10 days)	57	43	64	63
HR (neutrophil count > 10 days)	81	19	71	81
autologous transplant	55	45	71	73
allogenic transplant	67	33	76	78

[1]at start of treatment or after 48 h; [2]after 5-7 days of antibiotic treatment.

Table 3. Nursing prevention/precautionary rules.

	% Centers
Use of protocols	80
Hand washing before/after contact with the patient	90
Use of antiseptic soap	80
Use of cap, disposable overall, mask	
Isolation ward	90
Ordinary hospitalization	50
Use of overshoes on isolation ward	60
Patient's hygiene procedures on isolation ward	
Nurse care	40
Sterile water	20
Antiseptic soap and sterile sheets	50
Use of mask during patient transport	80
Room cleaned with disposable material and chlorine by-products	> 50
Pharmacy-centralized preparation	
Chemotherapy	50
Parenteral nutrition	80
Pre-packed individual meal	80

tion have been published. Furthermore, little data have been reported and there are no guidelines on antimicrobial prophylaxis outlined for this patient group. Also, empirical therapies have only been assessed in a few pediatric trials, and not all molecules have been approved for pediatric use.

The data collected in our survey add an interesting contribution to the field. The use of antibacterial prophylaxis, despite the absence of recognized guidelines, is frequently employed, even in LR patients. The use of antibacterial prophylaxis in HR subjects is now widely accepted in adult populations, and this is reflected in our pediatric survey. In pediatric transplant patients, an *ad hoc* prophylaxis is almost always used, according to adult guidelines.[6-7] The lack of proper recommendations could explain the very heterogeneous use of antimicrobials in the transplant setting, whereas in LR and HR patients data show a prevalent use of amoxicillin/clavulanate, and a relevant use of fluoroquinolones, consistent with relevant pediatric studies.[8-9] Furthermore, we observed that 80% of HR patients and 47% of LR patients receive antifungal prophylaxis. In contrast to adult patients,[10-11] no well designed clinical trials evaluating antimycotic prophylaxis in children have been performed, and the few prospective and retrospective studies have provided only limited evidence of benefit.

The Second European Conference on Infections in Leukemia guidelines underline that antiviral prophylaxis is indicated in HSV-seropositive patients undergoing ALLO-SCT (AI) and in HSV-seropositive patients treated with chemotherapy for acute leukemia (BIII).[12] In spite of this, our data show that, in addition to HSV-positive patients, also the majority of HSV-negative subjects received antiviral prophylaxis. Anti-PCP prophylaxis was widely used in all patient categories.

This survey has shown that the most commonly used antibiotic for first-line empirical treatment in pediatric neutropenic patients is represented by 3rd generation cephalosporins or by piperacillin-tazobactam in combination with an aminoglycoside, thus showing that combination therapy is widely employed in all patient groups, even in LR subjects (approximately one half of the patients).

The rationale for the use of combination therapy is the rapid bactericidal action of amikacine, its synergy with β-lactams, and a less common onset of resistance.

Antibiotic monotherapy is still less frequently used, despite the positive results of meta-analyses on the empirical treatment of febrile neutropenia in adults.[13-14] These studies suggest that monotherapy is preferable, and treatment with a single drug belonging to the beta-lactam class is associated with better outcome and survival, while side-effects are more frequent with combination therapy (particularly as far as nephrotoxicity is concerned), as confirmed by recent publications.[15-16]

In the HSCT patient group (both autologous and allogeneic), combination therapy is less frequently used (55% for autologus and 67% for allogeneic tranplants), as compared to LR and HR groups (57% in LR and 81% in HR), probably due to a better management of HSCT patients on the basis of more recent evidence. The addition of a glycopeptide, such as teicoplanin or vancomycin, to the empirical therapy has generated a heated debate on the risk of the development of resistance, especially concerning enterococci. Our survey showed that 64-76% of our different patient categories receive a glycopeptide at the beginning of the empirical therapy or within 48 h; however, this practice is not supported by the indications reported in the current literature. Present evidence shows that the addition of anti-Gram-positive treatment with glycopeptides, in the absence of proven Gram-positive infection, does not improve outcome, and is associated with increase of adverse events.[17] Their empirical use is currently recommended only when there is clinical suspicion of a catheter-related infection, skin and soft tissue infections, bone and joint infection, and severe mucositis.[18-19]

The empirical antifungal therapy is adopted in 63% of centers for LR patients and in more than 70% for patients belonging to other categories. Only two randomized studies have been carried out in pediatric patients, but none of them adopted a *nil placebo* control.[20-21] A recent Italian randomized study indicated empirical antifungal therapy was clearly not necessary in LR patients (D Caselli, submitted paper, 2011). These results confirm the need for a different approach, made possible by recent improvements in diagnosis, with the use of pre-emptive antifungal therapy when there is a suggestion of fungal disease.[22] Many drugs have been tested for these indications, and this heterogeneity was reflected in our survey; only a recent pediatric study has been published on liposomal Amphotericin B *versus* Caspofungin.[20]

The nursing survey confirmed that Standard Precautions are applied in the majority of centers (protocols are used in 80%) where they represent a mainstay for preventing infection transmission during routine patient care.

In conclusion, our survey was focused only on antimicrobial agents and nursing prevention procedures, but at the same time contributes an original snapshot of the actual prescribing practices in children with cancer. A high number of AIEOP units are still using combination therapy in the empirical treatment of FN, despite indications available in literature. Antifungal prophylaxis was also widely used in all categories, which is not in line with reports so far. As far as empirical antifungal therapy is concerned, it is still widely used in LR patients despite the fact that adult guidelines and pediatric studies do not recommend its use in this setting. This survey confirms the absolute need for accurate guidelines and/or recommendations for the treatment of

neutropenia in children affected by cancer. To this end, well designed clinical trials are mandatory.

Appendix

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