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

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Running title: Infections in pediatric hematology-oncology units

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Key words: infectious diseases, neutropenia fever, paediatric, empiric therapy, prophylaxis.
ABSTRACT

A nationwide questionnaire-based survey was designed to evaluate the management and prophylaxis of febrile neutropenia in paediatric patients admitted to Hematology-Oncology and Hematopoietic Stem Cell Transplant Units. Of the 34 participating centres, 40 and 63% respectively, continue to prescribe antibacterial and antimicotic prophylaxis in Low Risk subjects and 78 and 94% in transplant patients. Approximately half of the centers prescribes 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 7 days, 63% of the centres add empirical antimicotic 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 focused on prescribing practices in children with cancer and could facilitate implementing practice guidelines.

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 causes the majority of chemotherapy-associated deaths. 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 empiric therapy and prophylaxis. No well defined guidelines, such as those long established for adults, have been devised so far 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 comprises four parts according to the patient’s risk of infection:

1. Low Risk (LR) patients: less than 10 days of expected neutropenia after chemotherapy;
2. High Risk (HR) patients: more than 10 days of expected neutropenia, and
3. Autologous (AUTO) transplantation patients; 4. Allogeneic (ALLO) transplantation patients.

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

The answers were required to represent the local policies, therefore faithfully reflecting current practice and not personal opinion. The results were entered and analyzed with ÉpiInfo (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 *Pneumocystis 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 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.

Furthermore, the survey 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, third (ceftazidime and ceftriaxone) and fourth generation (cefepime) cephalosporins were the most frequently used molecules in monotherapy. The preferred combination regimen consisted of amikacin plus piperacillin/tazobactam or a third generation cephalosporin. The most common approach was to add a glycopeptide (immediately at onset or within 48 hrs) to the ongoing regimen (ranging from 64% of units on LR patients to 76% in the allogeneic transplant ones) (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 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 in ordinary and 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.
Donning of caps, disposable overalls and masks differed among the two wards, reaching almost 90% in the isolation wards as compared to 50% in the ordinary wards.

Overshoes were mainly employed in isolation wards (60%). Gloves use did not substantially differ regardless the type of wards. In the isolation wards, nurses took care of the patient’s hygiene exclusively in 40% of cases; sterile water was used in 20% and antiseptic soap and sterile sheets in 50% of cases.

In need of patient transfer, masks were used in 80% of cases, independently of ward type and FFP2/FFP3 type were employed in 30% of isolation ward patients only.

Disposable material and chlorine-containing agents were used for room cleaning 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 (donning 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 population have been published.

Furthermore, scant data have been reported and no guidelines on antimicrobial prophylaxis have been outlined for this patient group.

Moreover, empirical therapies have been assessed in 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, consistently with relevant pediatric studies 8-9. Furthermore we observed that 80% of HR patients undergo an antifungal prophylaxis, and 47% of LR patients also receive such prophylaxis. Differently from adult patients 10-11, no well designed clinical trials evaluating antifungal prophylaxis in children have been performed, and limited evidence of benefit has been provided by few prospective and retrospective studies.

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. Notwithstanding, our data show that, in addition to HSV-positive patients, also the majority of HSV-negative subjects received antiviral prophylaxis.

Anti-PCP prophylaxis resulted widely used in all patient categories.

This survey has shown that the most commonly used antibiotic for first-line empiric treatment in pediatric neutropenic patients is represented by third 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 (about one half of the patients).

The rationale for the use of combination therapy is the rapidly 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 empiric 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 publications15-16. In the HSCT patient group (both autologous and allogeneic), combination therapy is less frequently used (55% for autologus and 67% for allogeneic transplants), as compared to LR and HR groups (57% on LR and 81% on HR), probably due to a better management of HSCT patients on the basis of more recent evidences. Addition of a glycopeptide, such as teicoplanin or vancomycin, to the empiric therapy has generated a heated debate on the risk of development of resistance, especially concerning enterococci.

Our survey showed that 64 to 76% of our different patient categories receive a glycopeptide at the beginning of the empirical therapy or within 48 hours; 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 events17. Their empirical use is currently recommended only in case of clinical suspicion of a catheter-related infection, skin and soft tissue infections, bone and joint infection, and severe mucositis18-19. 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 were controlled with nil or placebo20-21. A recent Italian randomized study indicated empirical antifungal therapy clearly not to be necessary in LR patients (D. Caselli in press). This results confirm the need of a different approach, made possible by recent improvement of diagnosis, with the use of pre-emptive antifungal therapy, aimed at treating a fungal disease when suggestive but not definitive diagnosis is present.

Many drugs have been tested for this indications, and this heterogeneity was reflected in our survey; only a recent pediatric study was published on liposomal Amphotericin B vs Caspofungin20. The nursing survey confirmed that Standard Precautions are applied in the majority of centers (protocols are used in 80% of them), 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 what reported in literature so far. As far as empirical antifungal therapy is concerned, its use in LR category is still high, despite adult guidelines and pediatric studies do not recommend it in this setting. This survey confirms the absolute need of 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

Cagliari, Ospedale Regionale per le Microcitemie, Adele Sanna; Padova, Dipartimento di Pediatría Università di Padova, Simone Cesaro; Verona, Policlinico “G.B: Rossi”, Pierluigi Marradi Bolzano, Ospedale Regionale, Laura Battisti; Tricase, Ospedale Card. G. Panico, Adele Civino Milano, Policlinico San Raffaele, Sarah Marktel; Milano, Ospedale Niguarda, Fedeli Catanzaro, Ospedale Pugliese-Ciaccio, Caterina Consarino; Pescara, Ospedale Civile, Giuseppe Fioritoni; Udine, Policlinico Universitario, Agostino Nocerino; Pisa, Azienda Ospedaliero Universitaria Pisana, Claudio Favre; Bologna, Policlinico Sant’Orsola Malpighi, Arcangelo Prete Varese, Ospedale Filippo Del Ponte, Silvana Binda Napoli, Ospedale Cardarelli, Fiorina Casale Napoli, Ospedale Santobono, Nicoletta Marra Rimini, Ospedale Infermi, Roberta Pericoli Ancona, Ospedale Salesi, Pierani Cosenza, Ospedale Annunziata, Carpino Novara, Azienda Ospedaliera Maggiore della carità, only nursing Pesaro, Ospedale San Salvatore, Guiducci Lecce, Ospedale Vito Fazzi.

Authorship and Disclosures

SL originated the study and designed the questionnaire, SL, GP, LF, GMM and AS provided input into design of questionnaire, built the electronic database, contributed to the interpretation of data; SL, GP, LF wrote the paper; GMM, EC, SC, MRR, AB, GZ, FN, ML, RDS, OZ, MC, DC answered to the surveys, gave comments, and approved the manuscript.

The authors reported no potential conflicts of interest.

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References


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

<table>
<thead>
<tr>
<th></th>
<th>antibacterial (%)</th>
<th>antimycotic (%)</th>
<th>antiviral (%)</th>
<th>anti-PCP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR (neutrophil count &lt; 10 days)</td>
<td>40</td>
<td>47</td>
<td>20</td>
<td>85</td>
</tr>
<tr>
<td>HR (neutrophil count &gt; 10 days)</td>
<td>63</td>
<td>81</td>
<td>28</td>
<td>91</td>
</tr>
<tr>
<td>autologous transplant</td>
<td>78</td>
<td>91</td>
<td>62</td>
<td>100</td>
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<tr>
<td>allogenic transplant</td>
<td>78</td>
<td>94</td>
<td>95</td>
<td>100</td>
</tr>
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</table>

### Table 2. Empirical antimicrobial therapy,

<table>
<thead>
<tr>
<th></th>
<th>combination therapy (%)</th>
<th>monotherapy (%)</th>
<th>empirical glycopeptides¹ (%)</th>
<th>empirical antimycotic² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR (neutrophil count &lt; 10 days)</td>
<td>57</td>
<td>43</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>HR (neutrophil count &gt; 10 days)</td>
<td>81</td>
<td>19</td>
<td>71</td>
<td>81</td>
</tr>
<tr>
<td>autologous transplant</td>
<td>55</td>
<td>45</td>
<td>71</td>
<td>73</td>
</tr>
<tr>
<td>allogenic transplant</td>
<td>67</td>
<td>33</td>
<td>76</td>
<td>78</td>
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</tbody>
</table>

¹ at start of treatment or after 48h
² after 5-7 days of antibiotic treatment

### Table 3. Nursing prevention/precautionary rules.

<table>
<thead>
<tr>
<th></th>
<th>% centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of protocols</td>
<td>80</td>
</tr>
<tr>
<td>Hand washing before/after the contact with the patient</td>
<td>90</td>
</tr>
<tr>
<td>• Use of antiseptic soap</td>
<td>80</td>
</tr>
<tr>
<td>Use of cap, disposable overall, mask</td>
<td>90</td>
</tr>
<tr>
<td>• Isolation ward</td>
<td>90</td>
</tr>
<tr>
<td>• Ordinary hospitalization</td>
<td>50</td>
</tr>
<tr>
<td>Use of overshoes in isolation ward</td>
<td>60</td>
</tr>
<tr>
<td>Patient’s hygiene procedures in isolation ward</td>
<td></td>
</tr>
<tr>
<td>• Nurse care</td>
<td>40</td>
</tr>
<tr>
<td>• Sterile water</td>
<td>20</td>
</tr>
<tr>
<td>• Antiseptic soap and sterile sheets</td>
<td>50</td>
</tr>
<tr>
<td>Use of mask during patient’s transport</td>
<td>80</td>
</tr>
<tr>
<td>Room cleaning with disposable material and chlorine by-products</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Pharmacy-centralized preparation</td>
<td></td>
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<tr>
<td>• Chemotherapy</td>
<td>50</td>
</tr>
<tr>
<td>• Parenteral nutrition</td>
<td>80</td>
</tr>
<tr>
<td>Prepacked individual meal</td>
<td>80</td>
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</table>