Antibiotic use in Greek Pediatric Hematology-Oncology and Bone Marrow Transplantation units

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Abstract

Background: Pediatric hematology-oncology (PHO) and bone marrow transplantation (BMT) units have high use of antimicrobials. Objectives: To survey antimicrobials used in Greek PHO and BMT units before and after an intervention involving education on the 2017 clinical practice guidelines (CPG) for the management of febrile neutropenia in children with cancer and hematopoietic stem cell transplant recipients. Methods: Antibiotic prescribing practices were prospectively recorded between June 2016 and November 2017. In December 2017, education for the CPG took place and antibiotic prescribing practices were followed for one more year. For antibiotic stewardship, days of therapy and length of therapy were calculated. Results: Five of

six PHO units and the single pediatric BMT unit covering >92% of children with hematologic and oncologic diseases in Greece participated. Administration of [?] 4 antibiotics simultaneously and of antibiotics with overlapping activity for [?] 2 days was significantly more common in PHO units located in general compared to pediatric hospitals. Use of at least one antifungal was recorded in approximately 47% of the patients before and after the intervention. De-escalation and/or discontinuation of antibiotics on day 6 of initial treatment increased significantly from 43% to 53.5% (p=0.032). Although the number of patients requiring support in the intensive care unit for sepsis did not change, a significant drop was noted in all-cause mortality after the intervention (p=0.008). Conclusion: Our surveillance was able to accurately document the antibiotic prescribing practices of Greek PHO and BMT units. Moreover, it identified areas in immediate need for improvement in antibiotic stewardship.

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List of abbreviations

Abbreviation	Meaning
ANC	Absolute Neutrophil Count
ASP	Antibiotic Stewardship Program
BMT	Bone Marrow Transplantation
CLEO	Center for Clinical Epidemiology and Outcomes Research
CPG	Clinical Practice Guideline
DOT	Days of Therapy
FN	Febrile neutropenia
HSCT	Hematopoietic Stem Cell Transplantation
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IFD	Invasive Fungal Disease
IQR	Interquartile range
LOT	Length of Therapy
PHIG	Preventing Hospital Infections in Greece
PHO	Pediatric Hematology-Oncology
TMP/SMX	Trimethoprim/sulfamethoxazole (cotrimoxazole)

ABSTRACT Background: Pediatric hematology-oncology (PHO) and bone marrow transplantation (BMT) units have high use of antimicrobials.**Procedure:** To survey antimicrobials used in Greek PHO and BMT units before and after an intervention involving education on the 2017 clinical practice guidelines (CPG) for the management of febrile neutropenia in children with cancer and hematopoietic stem cell transplant recipients. Antibiotic prescribing practices were prospectively recorded between June 2016 and November 2017. In December 2017, education for the CPG took place and antibiotic prescribing practices were followed for one more year. For antibiotic stewardship, days of therapy and length of therapy were calculated.**Results:** Five of six PHO units and the single pediatric BMT unit covering >92% of children with hematologic and oncologic diseases in Greece participated. Administration of [?] 4 antibiotics simultaneously and of antibiotics with overlapping activity for [?] 2 days was significantly more common in PHO units located in general compared to pediatric hospitals. Use of at least one antifungal was recorded in approximately 47% of the patients before and after the intervention. De-escalation and/or discontinuation of antibiotics on day 6 of initial treatment increased significantly from 43% to 53.5% (p =0.032). Although the number of patients requiring support in the intensive care unit for sepsis did not change, a significant drop was noted in all-cause mortality after the intervention (p =0.008).

Conclusions : Our surveillance was able to accurately document the antibiotic prescribing practices of Greek PHO and BMT units. Moreover, it identified areas in immediate need for improvement in antibiotic stewardship.

Introduction

The overuse of antimicrobials, the emergence of antimicrobial resistance worldwide, and increasing healthcare associated costs have shown the importance of maximizing the application of antibiotic stewardship programs (ASP) in order to maintain the efficacy of currently existing antibiotics along with substantial cost savings.[1,2]This issue is particularly important when it comes to children with cancer, who frequently require antibiotics during periods of febrile neutropenia (FN) associated with the administration of cytotoxic chemotherapy or with their underlying disease.[3,4] FN is a condition where evidence-based antibiotic prescribing is not frequently followed, as shown by a retrospective cohort study of audits performed during an ASP.[1]

In pediatric hematology-oncology (PHO) units, evidence-based use of antibiotics and antibiotic de-escalation strategies have the potential to decrease unnecessarily prolonged use of broad-spectrum antimicrobial agents,[5] but such measures have not been studied extensively, especially on a national level.[6] Studies in both adults and children have shown that in hematology-oncology units, antibiotic de-escalation and discontinuation can be safely implemented, i.e., without increasing the number of infectious deaths or Intensive Care Unit (ICU) admissions.[7-10] For example, an open-label, randomized, controlled phase 4 clinical trial in six academic hospitals in Spain showed that in adults with hematological malignancies, high-risk FN and negative blood cultures, empirical antimicrobial therapy can be safely discontinued after 72 hours of apyrexia and clinical recovery irrespective of the absolute neutrophil count (ANC).[11]

In Greece, nearly 300 pediatric oncology patients aged 0 to 14 years are diagnosed annually, out of a national population of approximately 11 million people. Additionally, approximately 12 children with non-malignant diseases such as immunodeficiencies, homozygous beta-thalassemia, aplastic anemia, and other conditions require hematopoietic stem cell transplantation (HSCT) annually. Currently, there are six PHO units located in Greece: three units in Athens; two units in Thessaloniki, and one unit in Heraklion, Crete. In addition, there is a single pediatric bone marrow transplantation (BMT) unit located in Athens. The two PHO units in Thessaloniki and the PHO unit in Crete are in general university hospitals, while all units in Athens, including the BMT unit are in Aghia Sophia Children's Hospital and P. and A. Kyriakou Children's Hospital.

The Center for Clinical Epidemiology and Outcomes Research (CLEO) is an non-governmental, not-profit organization in Greece that surveils the most common hospital-acquired infections, with emphasis on improving prevention strategies and promoting and monitoring the judicious use of antibiotics.[12] Since 2016, as part of the project Preventing Hospital Infections in Greece (PHIG), CLEO has been monitoring the use of an-

timicrobials in Greek PHO units with the goals of promoting the implementation of evidence-based insertion and maintenance bundles for central lines and encouraging implementation of international evidence-based guidelines for management of FN in children with cancer and HSCT recipients.[13]

The goal of this study is to describe the use of antibiotics in hospitalized children with cancer or children requiring HSCT in Greece and to evaluate the impact of a simple multifaceted intervention on prescribing practices. The results of PHIG intervention regarding central line-associated bloodstream infections will be the subject of a separate report.

Patients and Methods

In end of June 2016, 5 out of 6 Greek PHO units and the country's single pediatric BMT unit participated in this collaborative, and prospectively recorded the first 15 children per month admitted to their units, who required the initiation of new antibiotics for treatment or prophylaxis. Ethics approval was obtained from the institutional review boards of all participating hospitals. Individual informed consent was not considered necessary to be obtained in any of the hospitals.

Data collection

Children receiving only prophylactic antibiotics were included, while children who were already on intravenous antibiotics for a previous infection the day before the initiation of the new antibiotic regimen were excluded. Administration of any antifungal therapy in a child with FN was recorded as empirical therapy. No pediatric patient was recorded twice within the same month, and the form was completed for the first seven days of antibiotic administration.

Data recorded included age and sex, presence of central lines, type of underlying disease (hematologic malignancy, solid tumor, or other disease), ANC and its relation to the first day of antibiotic therapy, antibiotics used and their indication (empirical or targeted therapy, perioperative or other prophylaxis), cultures obtained, and pathogens isolated, presence or absence of invasive fungal disease (IFD), and clinical outcome (hospital discharge, ICU admission, or death).

In December 2017, a meeting between CLEO representatives and the directors of all PHO units took place, where baseline data analysis was presented along with the main conclusions. Finally, the goal of implementing the recently updated at that time clinical practice guidelines (CPG) for the management of FN in children with cancer and HSCT recipients by the International Pediatric Fever and Neutropenia Guideline Panel was also discussed.[13] The timeframe and the goals of the PHIG intervention are shown in **Figure 1** . For FN, the definition of the Infectious Diseases Society of America (IDSA) was used.[17]

PHIG intervention

The surveillance of antibiotic use and the educational intervention about the implementation of the CPG started in December 2017 for five of the units; one started in March 2018 due to local resource restrictions, while one of the units participated in data collection only during the pre-intervention period (June 2016 to December 2017) due to limited resources. The same demographic and clinical data were recorded in the post-intervention two-year period (January 2018 to December 2019), to compare antimicrobial use before and after implementation of the guidelines for the management of FN in children with cancer and HSCT recipients.[13]

Data analysis

For the purposes of antibiotic stewardship, we calculated days of therapy (DOT) and length of therapy (LOT).[18,19] One DOT represents the administration of a single antibiotic on a given calendar day, even if multiple doses are given on that day. LOT is the number of days a patient is receiving antibiotics regardless of the number of different agents administered. We compared administration of [?] 4 antibiotics simultaneously, use of antibiotics with overlapping antimicrobial activity for [?]2 days, de-escalation/discontinuation with negative cultures by day 6, start of antibiotics without obtaining cultures, antibiotic initiation without a clear source or fever and with ANC>500/μl, use of standard versus other non-standard regimens for empirical

therapy (defined as cephalosporins without anti-*Pseudomonas* activity such as ceftriaxone and cefotaxime, ceftazidime monotherapy, colistin, metronidazole, and others), early use of antifungals before day 4 of fever, number of patients admitted for sepsis to ICU, and number of deaths before and after PHIG intervention. In all participating units, a feedback report was sent every six months throughout the study period to inform them about their specific progress with respect to implementation of the CPG.

Statistical analysis

Nominal variables are presented with absolute and relative (%) frequencies, whereas continuous variables are presented with medians and interquartile ranges (IQR). To evaluate differences between units and the effect of intervention, chi-square tests of independence and Mann-Whitney U tests were performed, as appropriate. Stratified analysis by unit and type of unit (PHO units located in pediatric compared to general hospitals) was also performed. All reported p values were based on two-sided tests, and statistical significance was set at$p$ <0.05. All statistical analyses were performed with STATA v.13.0 software (StataCorp., College Station, TX, USA).

Results

Cohort characteristics

Demographic (age, gender), and clinical characteristics (underlying disease) of recorded cases by PHO unit and location in a pediatric or general hospital are shown in **Table 1** . Patients hospitalized in PHO units located in general hospitals were significantly younger than patients hospitalized in PHO units located in pediatric hospitals [(pediatric hospitals: median 7.5 years (IQR 3.6-12.3) versus general hospitals: median 5.4 years (IQR 3.1-8.5), p =0.001]. In addition, significantly more female patients were hospitalized in PHO units located in general hospitals.

Antibiotic use

Patient and antibiotic days, LOT per 1000 patient days, DOT/LOT ratios, and most commonly used antibiotics during the study period by PHO unit and by type of hospital (pediatric versus general) are shown in**Table 2.** Ceftazidime was commonly used in PHO units located in general hospitals, while piperacillin/tazobactam monotherapy was commonly used in the BMT unit. After intervention, ceftazidime use decreased in the two PHO units located in general hospitals (from 19% to just 1.1%) and remained low in units located in pediatric hospitals throughout the surveillance period (0.2% before and 0.4% after intervention). Regarding the use of glycopeptides, their use remained high and essentially unchanged after intervention. More specifically, their use was 30.4%, both prior to and after the intervention in PHO units located in general hospitals, and slightly increased after the intervention from 24.9% to 27.2% in PHO units located in pediatric hospitals.

Redundant antibiotic use

Results of PHIG intervention in relation to other study goals are summarized in **Table 3.** Overall, the administration of [?] 4 antibiotics simultaneously remained unchanged at 4.1% before and after the intervention. However, it changed from 2.2% to 0.9% in units located in pediatric hospitals and from 8.2% to 11.2% in units located in general hospitals. Both the pre- and post-comparison of the simultaneous use of [?] 4 antibiotics between units by type of hospital was highly significant (p =0.001 for both). The overall administration of antibiotics with overlapping activity for [?]2 days did not change significantly (4.5% before and 5.4% after the intervention,p =0.39). It decreased from 3.5% to 2.1% in units located in pediatric hospitals, while it increased from 6.7% to 12.5% in units located in general hospitals. Again, the pre- and post-intervention comparison of the administration of antibiotics with overlapping activity for [?]2 days between units by type of hospital was highly significant (p =0.034 and p =0.001, respectively).

Antibiotic use for FN

Antibiotic use on day one of FN before and after PHIG intervention is shown in **Table 4** . Major differences in practice existed between different PHO units prior to intervention. In units 1 and 2, triple antibiotic

therapy (i.e., an antipseudomonal beta-lactam, a second Gram negative agent and a Gram-positive agent) was commonly practiced; in the BMT unit monotherapy with an antipseudomonal beta-lactam was more commonly used; in unit 5, double Gram-negative coverage was used; and in unit 6, triple antibiotic therapy and other non-standard regimens were frequently used. Significant improvements in appropriateness of antibiotic prescribing were noted after the intervention (p =0.005). For all units combined, antibiotic therapy was started without obtaining cultures less frequently after the intervention (9.8% versus 14.1% before, p =0.006). This practice was more frequent in PHO units located in general compared to pediatric hospitals before (25.5% compared to 9%) and after intervention (18.2% compared to 5.8%), and this difference was highly significant (p =0.001 for both comparisons).

De-escalation of antibiotic therapy

In cases of negative blood cultures in patients receiving antibiotics with Gram-positive coverage and/or a second antibiotic with Gram-negative coverage, de-escalation and/or discontinuation of antibiotics on day 6 in all units significantly increased from 43% to 53.5% (p =0.032). More specifically, it increased from 53.1% to 60.2% in units located in pediatric hospitals and from just 15.1% to 28.3% in units located in general hospitals.

Antibiotic initiation without a clear infectious source or fever and with ANC>500/μl occurred during the pre-and post-intervention period in 4.1% and 3% of antibiotic courses, respectively (p =0.198). In PHO units located in pediatric hospitals, it tended to drop from 3.7% to 3% and in PHO units located in general hospitals from 5% to 3%.

Use of non-standard antibiotic regimens

The overall use of non-standard antibiotic regimens was not significantly different after the intervention (11.9% before versus 12.7% after). However, it was significantly more frequent in PHO units located in general versus pediatric hospitals prior to intervention (p =0.001) and remained so post-intervention (p =0.001). Triple antibiotic therapy decreased in units 1 and 2, monotherapy with an antipseudomonal beta-lactam decreased in the BMT unit, and triple antibiotic therapy and non-standard antibiotic combinations decreased in unit 6.

Antifungal use

Use of antifungals in PHO units before and after PHIG intervention is shown in **Table 5** . Overall, 47.4% of patients before and 46.9% after the intervention received at least one antifungal (p =0.893). Almost all patients treated in the BMT unit were receiving at least one antifungal at the time of data collection. Almost two thirds of children treated in units located in general hospitals were receiving at least one antifungal compared to approximately one fourth of patients treated in units located in pediatric hospitals. In unit 6, antifungal use significantly increased after intervention (p =0.044). Overall, use of at least one antifungal was significantly more common in PHO units located in general versus pediatric hospitals before the intervention (66% compared to 40.9%,p =0.001) and remained so after the intervention (73% compared to 36.2%, p =0.001).

Outcomes (ICU admissions and deaths)

The number of patients requiring ICU support for sepsis did not change significantly (18 or 2.13% before intervention compared to 23 or 2.33% after intervention, p =0.781), while a significant drop was noted in the recorded number of deaths in all PHO units combined (36 deaths or 4.29% before intervention compared to 21 deaths or 2.13% after intervention, p =0.008).

Discussion

We prospectively recorded the inpatient antibiotic use of pediatric oncology patients and HSCT recipients hospitalized in five of six PHO and one BMT units in Greece. These six units treat >92% of children with

hematologic and oncologic diseases in the country, hence the resulting data are highly representative of the country as a whole. The distribution of underlying diseases was significantly different by unit, and this is mainly because patients with diagnoses other than hematologic malignancies and solid tumors were almost exclusively treated in units located in Athens, predominantly the BMT unit.

The first goal of this study was to document the use of antibiotics in PHO units throughout Greece. The second goal was to educate the medical personnel of all PHO units on the evidence-based management of FN in children with cancer and HSCT recipients, as updated in 2017 by the International Pediatric Fever and Neutropenia Guidelines.[13]

In this study, LOT per 1000 patient days slightly decreased after the intervention from 517 to 501. During the same period, we noted a highly significant decrease in the number of deaths in all PHO units combined, while the number of patients requiring ICU support for sepsis did not change significantly. In short, although the recorded changes in antibiotic prescribing practices were not always appropriate, there was a significant drop in the number of deaths during the surveillance period. However, it is unclear to what extent this can be attributed to our intervention. Better care and gain of expertise with the implementation of current international disease-specific oncology protocols may be the main reason for the drop in overall mortality.

The use of ceftazidime dropped after intervention, especially in units located in general hospitals. It is of note that most Greek hospitals harbor multi-resistant *Pseudomonas aeruginosa* with decreased susceptibility to ceftazidime.[20,21] The goal of decreasing the use of glycopeptides was not achieved, as vancomycin and teicoplanin use represented 25-30% of antibiotic DOT before and after the intervention.

The IDSA and the Society for Healthcare Epidemiology of America have published guidelines for developing an institutional program to enhance antimicrobial stewardship.[22] Based on these guidelines, there are insufficient data to recommend combination antibiotic therapy as routine to prevent the emergence of resistance, although empirical combination therapy is important for critically ill patients at risk of infection with multidrug-resistant pathogens. In addition, de-escalation and/or discontinuation of empirical antimicrobial therapy based on culture results, and the elimination of redundant combination therapy are highly recommended and can result in decreased antimicrobial exposure and substantial cost savings.[22] As a result, a goal of the PHIG intervention was to minimize redundant combination antibiotic therapy. This goal was partially achieved. More specifically, administration of [?] 4 antibiotics simultaneously and redundant combination therapy decreased in units located in pediatric hospitals but increased in units located in general hospitals.

The reasons for these inconsistent changes are unclear. We speculate that involvement of pediatric infectious diseases specialists was likely higher in units located in children's hospitals. Another possible explanation is that on-call physicians treating patients with FN in general hospitals are more likely to choose more aggressive antibiotic therapies than those needed for lower-risk patients with FN. The latter was shown to be the case in the management of adult patients with FN in an urban tertiary-care teaching hospital in United States that provides emergency and inpatient services to a large comprehensive cancer center.[23] It could be argued that unit antibiograms show higher rates of resistance in units situated within general hospitals compared to ones in pediatric hospitals. However, to our knowledge no such data exist, as PHO units are not typically located within general hospitals outside Greece. A final possible explanation is that general hospitals likely harbor more resistant bacteria, necessitating more aggressive empirical antibiotic therapy. In fact, this is something that has been shown for uropathogens in USA and Greece.[24,25]

Of note, the BMT unit used more piperacillin/tazobactam monotherapy, an evidence-based strategy, than any of the PHO units. Although the risk of infections in allogeneic-HSCT patients is higher than in PHO patients and their outcomes tend to be worse,[26] a systematic review of randomized trials showed that monotherapy for high-risk FN is an effective strategy.[27]

The prompt de-escalation and/or discontinuation in case of negative blood cultures increased in all units but remained low after intervention to just 28.3% in units located in general hospitals. Regarding antibiotic initiation without a clear infectious source or fever and with ANC>500/μl, no significant change was noted after the intervention, but this practice, which is not recommended, was relatively rare to begin with.

The use of antifungals on days 1-4 of fever is contrary to international guidelines published by major scientific societies and organizations,[13,28,29]; but almost two thirds of children treated in units located in general hospitals received at least one antifungal compared to approximately one fourth of patients treated in units located in pediatric hospitals, and this practice did not change much after intervention. We believe that apart from HSCT patients, such widespread and early use of antifungals, i.e., prior to day 4 of FN, is unjustified. Apart from children with acute myeloid leukemia, high-risk acute lymphoblastic leukemia (i.e., with refractory or relapsed disease), Burkitt lymphoma, and exposure to high-dose corticosteroids,[30-32] none of whom were overrepresented in our sample, most children with cancer do not require prophylaxis or therapy with antifungal agents. A multicenter randomized controlled trial in Italy showed that empirical antifungal therapy was of no advantage in terms of survival without fever and IFD in children who were defined as low risk for systemic fungal disease.[33]

Our study has strengths, but also has several limitations. This was the first study to prospectively collect a large amount of data regarding antibiotic use in Greek PHO units. The limited resources for stewardship programs in almost all units involved did not prevent us from accurately documenting antibiotic prescribing practices in children with cancer and HSCT recipients. Although one PHO unit did not participate, and another did not collect data during the post-intervention period, our data are representative of the inpatient antibiotic prescribing practices for children with cancer and HSCT recipients treated in specialized units in Greece. One limitation of the study is that only hospital-wide and not unit-specific antibiotic susceptibility data for bacterial pathogens were available in the participating units during the surveillance period. Hence, we can only speculate about the reasons for the considerably different antibiotic prescribing practices among units. Lower susceptibility rates of microbial pathogens may be the reason for the more aggressive use of antibiotics in PHO located in general hospitals, but this issue needs further research. Finally, lack of antimicrobial dosing data is another limitation of our study, as is the limited duration of data collection for each patient, and the inability to separate all-cause from infectious mortality.

CONCLUSION

In this study, we performed surveillance of antibiotic prescribing practices in hospitalized children with cancer and HSCT recipients in Greece. Our surveillance data allowed comparisons among units, identified areas necessitating improvement and provided useful information on antibiotic prescribing to physicians in each PHO unit. As a next step, an active intervention with designated antibiotic stewardship physicians and prospective audit and feedback recommendations at each Greek PHO unit is needed. Ideally, future accurate capturing of unit-specific antibiotic susceptibility data for all bacterial pathogens is needed along with more dedicated personnel exclusively involved with antibiotic stewardship. Finally, further research in this area is required to reduce the use of broad-spectrum antimicrobials and antifungals safely and substantially in this susceptible patient population.

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514 **FIGURE 1** Timeframe and goals of the PHIG intervention in five Greek PHO and one BMT units.

- To promote adequate coverage for virulent hospital-acquired organisms, while minimizing exposure to unnecessary antibiotics, such as ceftazidime in cases of concerns for Gram-positive or resistant Gram-negative infections.
- To minimize unjustified addition of glycopeptides and to promote their prompt discontinuation.[14]
- To reduce the concurrent use of antibiotics with overlapping activity, such as second antibiotic therapy against Gram negative pathogens (redundant combination therapy).[15]
- To promote prompt de-escalation and/or discontinuation of antibiotic therapy in case of negative blood cultures along with signs of recovery of bone marrow function.[4,16]
- To discourage antibiotic initiation without obtaining appropriates cultures, and in the absence of neutropenia without a clear source of infection, and finally,
- to discourage initiation of antifungals prior to day 4 of FN.[3,13]

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