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Compliance with anti-infective preventive measures: A multicentre survey among paediatric oncology patients

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ABSTRACT

Background: Infections are significant causes of morbidity and mortality among immuno-compromised patients, but little is known about the adherence by the paediatric cancer patients to preventive anti-infective interventions.

Methods: A voluntary and anonymised questionnaire was distributed to all patients, completing intensive anticancer therapy. Compliance was analysed by using a panel of eight commonly recommended preventive interventions and semi-quantitative scoring of adherence by the patient and/or its caretaker. Satisfaction with information and belief in the efficacy of the interventions were similarly assessed. Relationships of these factors to compliance were explored by using an overall compliance score and non-parametric correlation and/or ANOVA and logistic regression, respectively.

Results: In 216 children and adolescents (mean age: 8 years; 94 girls) included in the study, compliance rates were the highest for food restriction (89.3%), the use of topic antimycotics (88.2%) and trimethoprim/sulfamethoxazole (86.6%), and the lowest for the use of face masks (68.8%), antiseptic mouth rinses (67.1%), non-absorbable antibiotic agents (66.5%) and restrictions in social contacts (65.5%). The most frequent reasons for drug non-compliance were forgetfulness and patient refusal. Compliance correlated with haematological malignancy, younger age and belief in its efficacy, but not with the perceived degree of information, burden of interventions and overall satisfaction with quality of information and medical care.

Conclusion: Compliance to recommended anti-infective prophylactic interventions was variable and correlated with haematological malignancy, younger age and belief in efficacy.

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1. Introduction

Infections are important, but to some extent preventable, causes of morbidity and mortality in patients undergoing therapy for cancer. Certain prophylactic anti-infective interventions have been shown to improve overall outcome,^{1,2} and non-adherence to these measures may result in life-threatening or even fatal complications.³ While it has been shown that a relevant fraction of children and adolescents with malignancies do not adequately adhere to their anticancer medication,^{4–6} little is known about the compliance of this patient population to commonly recommended anti-infective interventions. Knowledge about patient compliance and factors influencing adherence to recommendations, however, may help to improve the rate of compliance and may have impact on overall outcome. We conducted a multicentre survey to explore compliance rates to common preventive anti-infective interventions and factors with potential impact on compliance in a large cohort of paediatric patients undergoing therapy for cancer.

2. Patients and methods

During the 12-month-period from December 2003 to November 2004, a standardised structured questionnaire was distributed to all consecutive patients who had completed intensive anticancer chemotherapy within a time frame of three months. All patients had been treated in one of the five participating paediatric cancer centres. All centres were tertiary care centres with a range of 35–100 newly diagnosed cancer patients per year. Four of the centres were located in Germany, one in Austria. The voluntary and anonymised questionnaire captured the basic demographic data, the recommendations and the adherence to common anti-infective measures, and factors that may have impact on adherence. Data collection and handling were reviewed and approved by the local Ethics Committees of the two principal investigators (TL and AHG).

Compliance was assessed using a panel of eight recommended interventions, including the restriction of social contacts, the use of face masks outside home, the consumption of microbiologically safe food items, the use of antiseptic mouth rinses, the use of non-absorbable antibacterial and antifungal agents, *Pneumocystis jirovecii* (PcP) prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX) and the use of systemic antifungal agents. Compliance was assessed and quantified for each individual patient by the patient and/or its caretaker using a four-point semi-quantitative scoring system ('adherence as recommended', 3 points; 'adherence in $\geq 50\%$ of times', 2 points; 'adherence in $< 50\%$ of times', 1 point; 'adherence almost never/never', 0 point).

In addition to the evaluation of reasons for non-compliance, the questionnaire evaluated six factors with potential impact on adherence to recommended anti-infective measures: satisfaction with the information on the rationale of the recommended intervention, satisfaction with the information on the potential adverse effects of the intervention, comprehension of the information obtained, personal belief in the efficacy of the intervention, overall satisfaction with the medical care and the subjective perception of the inter-

vention as a burden. Questions were assessed by a three-way answer option using a semi-quantitative scoring system ('true', 3 points; 'undecided', 2 points; 'not true', 1 point). The relationships of these factors to compliance were explored by means of an overall compliance score (total score normalized to questions with answers). Mann-Whitney U test was used for the correlation of sex and compliance. Kruskal Wallis ANOVA with Dunn's correction for multiple comparisons and with Spearman's rank sum test was used for correlation of subjective perception and compliance. Logistic regression was used for multivariate analysis. For this analysis, compliance was dichotomized (overall compliance score < 2.5 versus ≥ 2.5 ; the latter indicates an overall compliance rate of more than 80%, given the maximum possible score of 3.0). For the factors such as the perceived degree of information, the personal burden, the anticipated benefit, and the overall satisfaction scales being not true and undecided, these factors were combined. Age was classified into < 10 years versus ≥ 10 years. A two-sided P value $< .05$ was considered to be statistically significant.

3. Results

The study population comprised 216 children and adolescents (122 boys, 94 girls) with a mean age of 8 years (median, 7.5 years; range, 1 month to 27 years). Hundred-and-forty-eight patients had leukaemia/lymphoma [acute lymphoblastic leukaemia (ALL; 91) acute myeloid leukaemia (AML; 16) leukaemia not further specified by the patient/caretaker (10), Hodgkin's disease (16), and non-Hodgkin lymphoma (15)], whereas 63 patients had a solid tumour as underlying malignancy [including rhabdomyosarcoma (10), neuroblastoma (6), Ewing sarcoma (13), osteosarcoma (9) and brain tumour (14)]. No information on the underlying disease was given in 5 patients. Of the total 300 questionnaires distributed in the centres, 216 (72%) had been returned.

3.1. Recommended interventions and compliance rates

During the course of intensive chemotherapy, the vast majority of patients received the recommendation for PcP prophylaxis with TMP/SMX (100%), to consume only microbiologically safe food items (95.3%), to restrict social contacts (94%) and to use non-absorbable antibacterial agents (92.6%) (Fig. 1). Less frequently, the use of face masks outside home (77.3%), the use of antiseptic mouth rinses (69%) and the use of topical antimycotic agents (74.5%) were recommended as prophylactic measures (Fig. 1). Notably, prophylactic systemic antifungal were prescribed only in few patients considered to be at high risk (16.7%), e.g. in patients with high-risk ALL or with AML.

When analysing those patients who received the recommendation for a particular anti-infective prophylactic measure, the highest compliance rates (defined as 'adherence $\geq 50\%$ of times') were reported for food restriction (89.3%), the use of topical antimycotics (88.2%) and the use of TMP/SMX (86.6%) (Fig. 1). Considerably fewer patients reported adherence to recommendations to use face masks (68.8%), regular antiseptic mouth rinses (67.1%), non-absorbable anti-

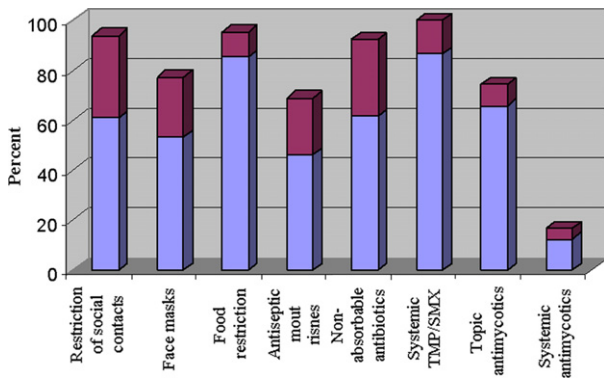


Fig. 1 – The percentage of patients receiving the recommendation for a specific prophylactic intervention. The light part of the column represents the percentage of patients who adhered to this recommendation. TMP/SMX, trimethoprim/sulfamethoxazole.

bacterial agents (66.5%) and to limit social contacts (65.5%). The overall reported adherence to the use of systemic antifungal agents was 73.9%, and was higher in those patients using fluconazole (29/36; 80.5%) as compared to those who received itraconazole (5/10; 50%).

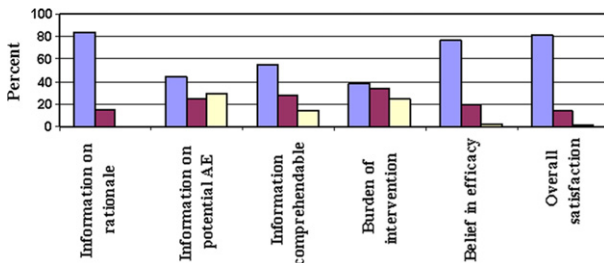


Fig. 2 – The perceived degree of information, subjective burden, anticipated benefit and overall satisfaction with medical care. The left column (grey) represents the percentage of positive answers, the central column (dark) the percentage of undecided answers and the right column (white) the percentage of negative answers. (For interpretation of the references to colour, the reader is referred to the web version of this article.)

3.2. Reasons for drug non-compliance

The most frequently provided explanations for drug non-compliance were forgetfulness (56 patients; 25.9%), refusal of the patient to take the scheduled medication (55; 25.5%) and the previous experience of adverse events (24; 11.1%). Less frequently, concerns about potential adverse events (6; 2.8%) and inadequate supply of prescribed medication (3; 1.4%) were given as the reasons for drug non-compliance.

3.3. Perceived degree of information, personal burden, anticipated benefit and overall satisfaction with medical care

Most patients/caretakers perceived that the degree of information on the rationale of the prophylactic anti-infective measure was sufficient (83.3%) (Fig. 2). In addition, most patients/caretakers believed in the efficacy of the recommended intervention (76.9%) and were satisfied with the overall medical care in the hospital where they were treated (81.9%). In contrast, there were apparent deficits in the comprehension of medical information and in the information on potential adverse effects of the recommended intervention (undecided and unsatisfied patients/caretakers 41.7% and 54.6%, respectively) (Fig. 2). Similar percentages of patients/caretakers perceived and did not perceive the recommended interventions as burden (38.9% and 33.8%, respectively) (Fig. 2). The use of topical antimycotics and the restriction of social contacts were perceived as the greatest subjective burden (each 14.8%, choice of two items possible).

3.4. Correlation of overall compliance with demographic features and subjective perception

Compliance as assessed by the overall compliance score significantly correlated with younger age ($r = -.2247$; $P = .0009$), haematological malignancy as underlying disease ($P < .0001$; ANOVA, Table 1) and the belief in the efficacy of the recommended measures ($r = .4153$; $P < .0001$) (Table 2). In contrast, no correlation was observed with sex, the satisfaction with the information on the recommended measures and the perceived burden of the prophylactic intervention (Table 2). Of note, there was no correlation between the overall compliance score and the number of recommended interventions [$r = .065$ (95% CI .072–.020); $P = .78$].

Table 1 – The correlation of overall compliance and underlying diagnosis

Leukaemia	Lymphoma	CNS tumours	Solid tumours	P-value (Kruskal Wallis)
2.67 ± .39 ^a .75 – 3.0 ^b	2.65 ± .37 1.4 – 3.0	1.97 ± .62 .85 – 3.0	2.2 ± .74 .4 – 3.0	<.0001 ^c
Kruskal Wallis (ANOVA) and Dunn's correction for multiple comparisons.				
a Mean ± SEM.				
b Range.				
c $P < .001$ leukaemia versus CNS tumours, $P < .01$ leukaemia versus solid tumours and lymphoma versus CNS tumours (Dunn's correction for multiple comparisons).				

Table 2 – The correlation of overall compliance as assessed by the overall compliance score with subjective perceptions

Variable tested	Spearman correlation	P-value
Sufficient information on rationale	-.05	.51
Sufficient information on potential AE	+.10	.13
Perceived level of comprehension	+.08	.27
Perceived burden of interventions	-.04	.58
Belief in efficacy of interventions	+.42	<.0001
Overall satisfaction with medical care	+.01	.94

AE, adverse event.

Using multivariate analysis, the belief in the efficacy of the recommended measures ($P < .0001$) and underlying diagnosis (haematological malignancy versus other, $P = .0002$) were the statistically significant variables with an impact on compliance.

4. Discussion

Our study shows that in paediatric cancer patients, adherence to commonly recommended prophylactic anti-infective measures is variable and correlates with underlying diagnosis, age and with the belief in the effectiveness of the prophylactic intervention. As some preventive anti-infective interventions have been shown to reduce morbidity and mortality in cancer patients,^{1,2} adherence may play a critical role in clinical practice and information on frequency and reasons of non-compliance may ultimately help to improve outcome. On the other hand, the efficacy of a number of frequently recommended interventions, such as wearing face masks or the consumption of microbiologically safe food items, has not been demonstrated to date and remains a matter of controversy.^{7,8}

An important problem in the assessment of compliance is the lack of uniformly accepted evaluation end-points. Evaluating the rate of adherence by indirect methods such as the physician's estimate, clinical outcome or counting pills is fraught with problems: Physicians tend to overestimate drug compliance,⁹ and measuring compliance by clinical outcome presumes a direct association between recommended intervention and achievement of treatment target, which is not always predictable.¹⁰ The major limitation of counting pills, which can be performed electronically, is the assumption that each pill not returned has been ingested. This, however, may not be justified since discarding unused medication is well described and results in an overestimation of compliance.^{6,11,12} Direct methods, such as the quantitative analysis of drug or drug metabolites in blood and urine, usually provide only an indication of recent medication adherence, and are limited by genetic variants accounting for inter-individual variation of pharmacodynamics and pharmacokinetics.^{9,13} We chose to assess the adherence to anti-infective measures in the form of retrospective self-reporting, as it is inexpensive and, therefore, suitable for a large cohort of patients, which decreases the risk of biased results associated with analysing selected small patient groups. The approach of retrospective self-reporting has been found to reasonably correlate with laboratory-based objective measures of compliance,^{4,14} and avoids potentially false high rate of compliance due to a Haw-

thorne effect.¹² However, we recognize that the accuracy of our data is limited since patients might not exactly remember adherence to the various recommendations and medication administration over a number of weeks or months, or they wish to conceal non-adherence to medication. Another limitation of our approach is the fact that the questionnaire does not identify whether the patient and/or the caretaker was reporting, which might be important in targeting specific interventions and making them age-appropriate.

There are few published data on the adherence rate to prophylactic anti-infective measures in children and adolescents undergoing intensive anticancer treatment. In addition, most of these studies are limited by small patient samples. A retrospective chart review of 54 paediatric transplant recipients revealed that more than half of the patients had significant adherence problems to oral antibiotic medications.¹⁵ Surprisingly, this study reported the lowest rates of compliance in younger children while compliance was greater in adolescents. In our study population consisting of 216 patients receiving chemotherapy for cancer, we found a considerably higher overall rate of compliance. Since adherence rates seem to decrease over time,^{16,17} the observed difference in compliance could be due to the duration of treatment, which is usually longer in transplant recipients compared to patients undergoing chemotherapy. Although only significant in the univariate analysis, we observed higher rates of non-compliance in adolescents compared to younger children, a finding which has been reported for anticancer drugs in paediatric patients receiving therapy for leukaemia or lymphoma.^{6,18,19} It is common belief that the complex age-specific developmental factors in adolescents, which are often marked by rebellious behaviour and disagreement with parents and authority figures, account for the lower rates of compliance in this age group as compared to younger patients who usually may receive their medication under the control of parents.^{4,18} The positive correlation of compliance with underlying haematological malignancy was unexpected. Since forgetfulness was the most frequently provided explanation for drug non-compliance, the observed correlation might be explained, at least in part, by the usually more regular clinical visits of patients with haematological malignancies compared to those with solid tumours.

Interestingly, in our survey, the burden perceived by the recommended anti-infective measure did not influence compliance. Our data also corroborate the previous data that information of both the disease and treatment regimen is not a prerequisite for adherence.²⁰ In contrast, the belief of the patient/caretaker in the efficacy of the recommended

measure strongly improves the rate of compliance, a phenomenon that has also been observed for treatment with anticancer drugs in paediatric patients.^{4,21} Similar to other studies, forgetfulness, refusal of the child and previous experience of side-effects were the most frequently reported reasons of missed medication in our survey.^{5,22,23}

In conclusion, our survey demonstrates that adherence to anti-infective measures should never be taken for granted, not even in paediatric oncology where patients/parents are generally thought to be highly motivated by the severity of the disease. There is an obvious need to improve compliance, and research programmes have to clarify the types of measures that are most likely to improve adherence in paediatric cancer patients. This is particularly important in the special subgroup of patients, such as in patients with non-haematological malignancies and in adolescents who showed the lowest rates of adherence in our survey. The fact that compliance significantly correlates with factors such as the belief in the effectiveness of the recommended measure underlines the importance to positively address factors which are associated with a higher rate of compliance. At the same time, professionals have to evaluate prophylactic measures and to find a uniformly accepted agreement in order to convince patients and families of the efficacy of a recommended intervention.

Conflict of interest statement

None declared.

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