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Original article

Efficacy and safety of withholding antimicrobial treatment in children with cancer, fever and neutropenia, with a demonstrated viral respiratory infection: a randomized clinical trial

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ABSTRACT

Objectives: To determine efficacy and safety of withholding antimicrobials in children with cancer, fever and neutropenia (FN) with a demonstrated respiratory viral infection.
Methods: Prospective, multicentre, randomized study in children presenting with FN at five hospitals in Santiago, Chile, evaluated at admission for diagnosis of bacterial and viral pathogens including PCR-microarray for 17 respiratory viruses. Children positive for a respiratory virus, negative for a bacterial pathogen and with a favourable evolution after 48 h of antimicrobial therapy were randomized to either maintain or withhold antimicrobials. Primary endpoint was percentage of episodes with uneventful resolution. Secondary endpoints were days of fever/hospitalization, bacterial infection, sepsis, admission to paediatric intensive care unit (PICU) and death.
Results: A total of 319 of 951 children with FN episodes recruited between July 2012 and December 2015 had a respiratory virus as a unique identified microorganism, of which 176 were randomized, 92 to maintain antimicrobials and 84 to withdraw. Median duration of antimicrobial use was 7 days (range 7–9 days) versus 3 days (range 3–4 days), with similar frequency of uneventful resolution (89/92 (97%) and 80/84 (95%), respectively, not significant; OR 1.48; 95% CI 0.32–6.83, p 0.61), and similar number of days of fever (2 versus 1), days of hospitalization (6 versus 6) and bacterial infections throughout the episode (2%–1%), with one case of sepsis requiring admission to PICU in the group that maintained antimicrobials, without any deaths.
Conclusions: The reduction of antimicrobials in children with FN and respiratory viral infections, based on clinical and microbiological/molecular diagnostic criteria, should favour the adoption of evidence-based management strategies in this population. **M.E. Santolaya, CMI 2017;23:173**

Introduction

Children with cancer are exposed to viral, bacterial and fungal infections, especially during the episodes of fever and neutropenia (FN) [1–3]. Episodes of FN during chemotherapy are currently managed within the hospital with broad-spectrum antimicrobial therapy [4,5]. Until recently, the most common aetiological agents reported in FN episodes occurring in children with cancer have been bacterial and fungal pathogens. Viral infections, particularly respiratory viruses, have been increasingly recognized as significant aetiological agents of FN in this population [6,7].

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Respiratory viral infections are a leading cause of morbidity and mortality in immunocompetent children [8,9]. In paediatric patients with cancer, respiratory viruses can be detected in up to 57% of episodes of FN [6,7,10–15]. In a previous study we determined the frequency and clinical outcome of respiratory virus-positive FN episodes [6]. Respiratory viruses were the most common agents detected and clinical outcomes of these episodes were significantly better than episodes with single bacterial infections or viral–bacterial co-infections. Children with respiratory viral infections had fewer days of hospitalization, a lower probability of haemodynamic instability and lower rates of admission to the paediatric intensive care unit (PICU) [6].

For children with FN most research efforts have focused on management of bacterial and fungal infections, mainly in proposing models of risk prediction for invasive bacterial and fungal infections [16–23], improvements in the molecular diagnosis of infections [24,25] and selective antimicrobial management in children with high-risk and low-risk FN episodes [18,26]. In contrast with the increase in studies of bacterial and fungal infections in this population, studies of viral infections are scarce and have been recognized as a research gap in the field [1]. A rational approach towards the management of a potential infection in children with cancer and FN requires a comprehensive analysis of all microbiological agents involved. Implementation of a systematic study and early detection of respiratory viral infection in children with cancer and FN might help to optimize their management by reducing hospitalization and antimicrobial use.

In this study we aim to determine the efficacy and safety of withholding antimicrobial treatment 48 h after admission in children with cancer and FN, with a demonstrated respiratory viral infection and a favourable clinical course.

Patients and methods

Population

From July 2012 to December 2015, a prospective, randomized, multicentre, government-sponsored study was conducted in five participating hospitals in Santiago, Chile, belonging to the National Child Programme of Antineoplastic Drugs network. Children and adolescents with cancer $\leq$18 years of age admitted with an episode of FN were enrolled after parental and child signed informed consent and assent (if older than 8 years of age). Children with haematopoietic stem cell transplants were excluded. This study was approved by the ethics committee of each participating institution.

Overall study design

Children were evaluated at admission to characterize the febrile episode, establish their risk for invasive bacterial infection and perform a common protocol for diagnosis of bacterial and viral pathogens. We recorded age, gender, type of cancer, type and date of the last chemotherapy, use of granulocyte colony-stimulating factor, use of antimicrobial prophylaxis, use of central venous catheter, hours of fever before admission, axillary temperature, blood pressure, heart rate, respiratory rate, signs and symptoms indicative of an infectious focus—especially respiratory signs/symptoms, haematological status (absolute neutrophil count (ANC), haemoglobin level, platelet count), biochemical tests, quantitative C reactive protein (CRP), central and peripheral automated blood cultures, other cultures if clinically indicated, and a molecular-based evaluation for respiratory viruses.

After initial evaluation, all children were treated following the Latin American Consensus for a Rational Approach of Children with FN [27] and Guidelines for the management of FN in children with cancer [1]. Briefly, children were hospitalized and low-risk FN episodes were treated with a third-generation cephalosporin (ceftriaxone) whereas children at high risk were treated with an anti-pseudomonal third-generation cephalosporin (ceftazidim) plus amikacin with or without an anti-Gram-positive β-lactam or glycopeptide antimicrobial therapy.

After 48 h of hospitalization (day 3) children with a nasopharyngeal sample positive for a respiratory virus, absence of any positive bacterial culture and with a favourable clinical evolution, were subject to a 1:1 simple randomization by the study coordinator (blinded) using statistical software (GraphPad Prism, version 6.01; GraphPad, San Diego, CA, USA) into two groups: maintenance of antimicrobials until the end of the febrile episode, and the intervention group in which antimicrobials were withdrawn. According to ethical committee requirements, it was possible to randomize each child in only one episode of FN that met the study criteria, for this reason, one randomized episode of FN was equivalent to one randomized patient.

Both groups were monitored daily for clinical and laboratory evolution until fever resolution and ANC $\geq$500/mm^3. Children with a bacterial pathogen or children in whom all studies gave negative results continued their antimicrobial management according to current standard of care. In the antimicrobial withdrawal group, criteria for re-instalment antimicrobial therapy were: resurgence of fever, clinical worsening or new clinical and/or laboratory findings suggesting a bacterial infection. One blinded investigator evaluated all cases after discharge, deciding that outcome was uneventful or not, without access to information about the specific intervention of each child (see Definitions). In children that continued with antimicrobial therapy, the standard duration of therapy was 7 days. Antimicrobials were stopped at day 7 if children had a favourable evolution, with at least a full day without fever and two consecutives CRP values $\leq$40 mg/L. The ANC was not a criterion for stopping antimicrobial therapy.

Study endpoints

The primary endpoint between the group that maintained antimicrobials and the group with antimicrobial withholding was number (%) of episodes with uneventful resolution. The secondary endpoints were (a) number of days of fever, (b) number of days of hospitalization, (c) percentage of episodes that develop a demonstrated or probable invasive bacterial infection, (d) re-instalment of antimicrobial therapy, (e) sepsis during hospitalization, (f) admission to the PICU, (g) death.

Laboratory evaluation

Laboratory tests. Haematological, biochemical and microbiological tests were performed at each hospital according to standard techniques.

Molecular detection for respiratory viruses. Detection was performed on nasopharyngeal samples collected from all children at the time of admission (Copan™ flocked swabs, Brescia, Italy). The swab was inserted into a vial containing viral transport medium (UTM-RT, Copan™), transported to the central laboratory and stored at −80°C until analysis in the next 24 h after admission. Total nucleic acid was extracted (easyMAG NucliSens; BioMérieux, Durham, NC, USA) and tested for 17 respiratory viruses (influenzas A, B, C; parainfluenzas 1, 2, 3, 4a and 4b; respiratory syncytial virus (RSV) A and B; rhinovirus; adenovirus; echovirus; human bocavirus; coronavirus; human metapneumoviruses A and B) by multiplex-PCR low-density microarray, according to the manufacturer's instructions (PneumoVir; Genomica, Madrid, Spain).