Outpatient *Versus* Inpatient IV Antibiotic Management for Pediatric Oncology Patients With Low Risk Febrile Neutropenia: *A Randomised Trial*

Source Citation: **Orme LM, Babl FE, Barnes C, Barnett P, Donath S, Ashley DM. Pediatr Blood Cancer. 2014;61:1427-33.**

Summary

This randomized controlled trial (RCT) [1] compared outpatient *versus* inpatient antibiotic therapy in a group of children presenting with low risk febrile neutropenia against a background of hematological malignancies. The investigators focused on Quality of Life (QoL) using a 13-point scale, and efficacy of treatment. Children (1-21 y) receiving chemotherapy for acute leukemia or solid tumors at a tertiary care hospital in Melbourne, who presented with fever (defined appropriately) were administered one dose of intravenous cefipime pending the neutrophil count. Those with confirmed neutropenia (<500/mm^3) and a low-risk status (defined as absence of septic shock or comorbidities requiring hospitalization) were randomized to receive outpatient or inpatient intravenous cefipime 12 hourly until a positive blood culture became available or the clinical condition warranted change in management. Parents and children in the outpatient arm had better QoL scores for almost all items (although many did not achieve statistical significance), and no significant difference in treatment duration, fever duration, microbiologically proven infection, identified focus of infection, or complications. Six episodes in the outpatient arm required readmission to hospital.

Commentaries

Evidence-based-medicine Viewpoint

*Relevance***:** Febrile neutropenia is a fairly common experience in clinical settings providing chemotherapy for childhood malignancies. In most settings (including India), empiric antibiotic therapy pending confirmation of diagnosis, is the practical approach [2-4]. Considering the clinical situation, relatively immune-compromised status, and logistic difficulties, most physicians opt for hospitalization and intravenous antibiotic therapy. Therefore, outpatient therapy (albeit intravenous) appears attractive for patients, families and hospitals.

Critical appraisal: The investigators elucidated eligibility criteria and provided reasons for children who were excluded at presentation. There was appropriate generation of the allocation sequence using blocks of variable sizes, and stratification by age and disease type. However, allocation concealment was not described and outcome assessors were unblinded, raising the risk of bias. All randomized subjects completed the trial as per protocol, and all pre-defined outcomes were reported. Sample size was calculated *a priori* but focused only on the QoL score. The absence of statistically significant differences in efficacy suggests that the small sample size lacked power to detect such differences. The fact that 6 of 19 (32%) outpatient episodes required hospitalization points to this possibility. Ideally, a non-inferiority design to compare efficacy of the two interventions should have been used.

Also, the scale used to measure QoL was not validated for the purpose. Several items in the scale are oriented in favour of home-based management, hence may not be appropriate for comparison against hospital-based treatment. The QoL questionnaire was administered multiple times, and it is unclear which readings were used for analysis. The investigators chose to compare scores using mean (SD) rather than median (IQR).

Applicability: The findings in this trial raise several challenges for application in our setting. The health-care system (in this RCT) was geared to detect and manage any untoward event occurring at home. The tertiary center functioned in a hub-and-spoke fashion; hospital staff trained to work in the community visited children's homes for clinical monitoring, administering treatment and taking samples for investigations. In the Indian context, home-based care often revolves around parental efforts at the individual level, with or without support from local physicians/nurses, who are otherwise not part of the management team. In other words, these professionals

may assist with implementing prescribed therapy, but may not take responsibility for events that follow. The tertiary level health care system in our country does not include a hub-and-spoke pattern, or a shared-care delivery model; hence the intervention described in this RCT is difficult to administer. Further, a high level of parental understanding, cooperation, education and responsibility (in a single word, empowerment) is crucial for the success of such interventions. This can be very variable in our setting, even when education and finances are not constraints [5]. A simple example is that most children in the RCT had central venous access, even at home. The third issue is that the febrile neutropenia episodes in the RCT were rarely associated with positive blood cultures or an identified focus of infection (about 10% in each arm). This frequency is much lower than reported in developed and developing countries [6-8] suggesting that most febrile neutropenia episodes were not related to infection (hence not requiring antibiotics in the first place, but detailed clinical evaluation to rule out infection). In our context, febrile neutropenia patients are likely to be exposed to infection more often [9-12].

Conclusion: This RCT suggests that children with low-risk febrile neutropenia receiving outpatient antibiotic therapy have better quality of life scores than those receiving inpatient therapies, in a developed country, tertiary-care setting. However, failure to demonstrate equivalence in terms of clinical efficacy, and extendibility issues limit application in our setting.

JOSEPH L MATHEW
Department of Pediatrics, PGIMER, Chandigarh, India.
dr.joseph.l.mathew@gmail.com

Pediatric Hematologist's Viewpoint

Febrile neutropenia – which can frequently occur in a child with cancer on myelosuppressive treatment – necessitates prompt assessment and intravenous antibiotic therapy, generally as an inpatient. The management reflects the seriousness of the condition but these hospitalizations also lead to interruptions in the daily activities of the child and their family, and affect their quality of life. By delivering the antibiotics, in this case intravenous cefepime 50 mg/kg 12-hourly, at home (*versus* inpatient) in low risk febrile neutropenia, Orme, *et al*. have demonstrated significant QoL benefits to parents and children without compromising on safety [1]. This study confirms what logic would suggest that treatment at home is less disruptive than treatment in the hospital.

Delivery of non-inpatient intravenous antibiotics in low risk febrile neutropenia is a common practice in India, particularly in the hospitals in the public sector. This practice is driven by a paucity of inpatient beds rather than impact on QoL. Moreover, this non-inpatient intravenous antibiotic therapy is delivered by several daily visits to the outpatient clinic with its own QoL issues, and not delivered at home as in this study. The current community health-based infrastructure in India cannot provide home-based intravenous antibiotic treatment, and hence this intervention would have very limited application in our context. An additional issue would be the appropriateness of use of cefepime monotherapy due to the high level of antibiotic resistance in India consequent to widespread irrational antibiotic use in primary care.

An area of greater need for research in India is to find solutions to the considerable time lag seen between onset of fever and reaching the hospital to receive the first dose of antibiotic therapy [5]. Health education and establishment of network of shared care units where tertiary care facilities are limited is very desirable. Another area of greater relevance would be delivery of oral (rather than intravenous) antibiotic therapy for low risk febrile neutropenia. There is evidence to recommend this approach for a select group of patients with certain caveats like availability of infrastructure for monitoring and follow-up and child's tolerability and acceptability of oral antibiotics [13]. The results from another study from India [14] appear promising but more research is needed.

RAMANDEEP SINGH ARORA
Department of Medical Oncology,
Max Super-Speciality Centre, New Delhi, India.
childhoodcancer@gmail.com

Pediatric Infectious Disease Specialist's Viewpoint

Managing children with febrile neutropenia is a challenging task. One would usually opt to treat outpatients with oral antibiotic but this RCT opted to evaluate intravenous antibiotic in domiciliary management of children with febrile neutropenia. The authors carefully selected the outpatient group after verifying all the risk factors. The authors chose Cefepime which is a good drug for monotherapy in low-risk group. The concept of comparing QoL scores between the inpatient and outpatient group is again a new concept. Although the sample size is small, the study proves that outpatient management of low-risk children with febrile neutropenia is safe and convenient to the parents and the children.

JANANI SANKAR
Department of Pediatrics
Kanchi Kamakoti Childs Trust Hospital, Chennai, India.
janani.sankar@yahoo.com

REFERENCES

1. Orme LM, Babl FE, Baversus inpatient IV antibiotic management for pediatric oncology patients with low risk febrile neutropenia: A randomised trial. Pediatr Blood Cancer. 2014;61:1427-33
2. Livadiotti S, Milano GM, Serra A, Folgori L, Jenkner A, Castagnola E, *et al.* A survey on hematology-oncology pediatric AIEOP centers: prophylaxis, empirical therapy and nursing prevention procedures of infectious complications. Haematologica. 2012;97:147-50.
3. Oberoi S, Suthar R, Bansal D, Marwaha RK. Febrile neutropenia: outline of management. Indian J Pediatr. 2013;80:138-43.
4. Pakakasama S, Surayuthpreecha K, Pandee U, Anurathapan U, Maleewan V, Udomsubpayakul U, *et al*. Clinical practice guidelines for children with cancer presenting with fever to the emergency room. Pediatr Int. 2011;53:902-5.
5. Oberoi S, Trehan A, Marwaha RK, Bansal D. Symptom to door interval in febrile neutropenia: perspective in India. Support Care Cancer. 2013;21:1321-7.
6. Hakim H, Flynn PM, Knapp KM, Srivastava DK, Gaur AH. Etiology and clinical course of febrile neutropenia in children with cancer. J Pediatr Hematol Oncol 2009;31:623-9.
7. Stabell N, Nordal E, Stensvold E, Gammelsrud KW, Lund B, Taxt A, *et al.* Febrile neutropenia in children with cancer: A retrospective Norwegian multicentre study of clinical and microbiological outcome. Scand J Infect Dis. 2008;40:301-7.
8. Arnello LM, Quintana BJA, Barraza CP. Febrile neutropenia in children with cancer in a medical center of Santiago, Chile. Rev Chilena Infectol. 2007;24:27-32.
9. Bothra M, Seth R, Kapil A, Dwivedi SN, Bhatnagar S, Xess I. Evaluation of predictors of adverse outcome in febrile neutropenic episodes in pediatric oncology patients. Indian J Pediatr. 2013;80:297-302.
10. Ghosh I, Raina V, Kumar L, Sharma A, Bakhshi S, Thulkar S, *et al*. Profile of infections and outcome in high-risk febrile neutropenia: Experience from a tertiary care cancer center in India. Med Oncol. 2012;29:1354-60.
11. Bakhshi S, Padmanjali KS, Arya LS. Infections in childhood acute lymphoblastic leukemia: An analysis of 222 febrile neutropenic episodes. Pediatr Hematol Oncol. 2008;25:385-92.
12. Mathur P, Chaudhry R, Kumar L, Kapil A, Dhawan B. A study of bacteremia in febrile neutropenic patients at a tertiary-care hospital with special reference to anaerobes. Med Oncol. 2002;19:267-72.
13. Lehrnbecher T, Phillips R, Alexander S, Alvaro F, Carlesse F, Fisher B, *et al*. International Pediatric Fever and Neutropenia Guideline Panel. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. J Clin Oncol. 2012;30:4427-38.
14. Gupta A, Swaroop C, Agarwala S, Pandey RM, Bakhshi S. Randomized controlled trial comparing oral amoxicillin-clavulanate and ofloxacin with intravenous ceftriaxone and amikacin as outpatient therapy in pediatric low-risk febrile neutropenia. J Pediatr Hematol Oncol. 2009;31:635-41.

EDITOR'S NOTE

Call for Experts to Contribute to Journal Club

Indian Pediatrics has started this section "Journal Club" that comprises a short summary of a current publication (from any reputed journal or other public access source), in any area of child health, followed by commentaries from 2-4 experts in different domains of the related field(s). These commentaries include discussion on the focus and validity of the research findings, issues related to statistical analysis, and potential applicability in the public and private settings in Indian scenario. We invite readers interested to contribute to this section – as an expert – to send their names, contact details, brief curriculum vitae (maximum 200 words) and area(s) of expertise, to the Editor in Chief at *jiap@nic.in*. Selected experts will be invited from time to time to contribute their commentaries on publications identified for the Journal Club.