Respiratory Syncytial Virus in Children with Influenza-like Illness

Respiratory Syncytial Virus (RSV) is a major cause of acute respiratory tract infection among children. It is documented that by age of three years, virtually all children are infected by RSV, and re-infection occurs throughout life [1]. The World Health Organization (WHO) estimates global RSV burden as 64 million cases and about 160,000 deaths annually [2]. The clinical presentation of RSV and influenza is similar, but the antiviral treatment is different. This study aimed to detect the positivity for RSV in hospitalized children (≤2 years) suspected of influenza-A (H1N1) pdm 09 infection during the 2009 influenza pandemic.

The samples (throat swab, nasopharyngeal swab or lung aspirates) were referred to Virus Research and Diagnostic Laboratory of Regional Medical Research Centre for Tribals, Jabalpur, India following the Government of India guidelines [3]. A total of 2549 samples (Oct 2009-Dec 2012) consisting of 398 (16%) samples of age group ≤2 years were received and processed for diagnosis of influenza by WHO recommended qRT-PCR [4]. Part of the samples was stored at -70ºC. From the aforesaid age group, 54 (14%) samples were found to be positive for Influenza A. From remaining 344 samples, 75 cases were randomly selected for RSV testing. Viral RNA extraction was done (Qiagen, Germany) followed by RT-PCR as described by Stockton, *et al*. [5] with minor modifications. The study was approved by our Centre's ethical committee.

Out of 75 samples, 33 (44%) were positive for RSV, of which 25 (76%) and 8 (24%) were positive for RSV-A and RSV-B, respectively (***Table* I**). There was no significant difference observed in clinical features (fever, cough, sore throat, nasal catarrh, shortness of breath, and pneumonia and/or pneumonia like symptoms) of RSV and Influenza. Studies from developing countries have reported that RSV is responsible for 27-96% of hospitalized cases of acute respiratory tract infections, and it has higher positivity than any other respiratory virus in pediatric age group [6-8]. When RSV positivity was compared with contemporary Influenza A positivity, the children (≤2 years) were at significantly higher risk of RSV (P<0.001). During the recent Influenza A (H1N1) pdm09 pandemic, majority of severe cases with influenza like illness might have been labelled and treated for influenza, though most of the children (≤2 years) probably had RSV infection. Oseltamivir that was used as a frontline antiviral drug for Influenza A (H1N1) pdm09 has known psychological and neuropsychiatric side-effects in children, and has also been shown to prolong RSV shedding [9]. We suggest that samples from age group ≤2 years in children with influenza like illness should be tested simultaneously for RSV in order to rationalize antiviral treatment.

TABLE I DISTRIBUTION OF RSV CASES BY AGE

Age group	*Tested for RSV*	*Positive for RSV*
≥01 mo	9	2 (RSV-A=2; RSV-B=0)
02-06 mo	23	13 (RSV-A=12; RSV-B=1)
07-12 mo	20	7 (RSV-A=6; RSV-B=1)
13-24 mo	23	11(RSV-A=5; RSV-B=6)
Total	75	33 (RSV-A=25; RSV-B=8)

RSV-Respiratory syncytial virus.

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REFERENCES

1. Empey KM, Peebles RS Jr, Kolls JK. Pharmacologic advances in the treatment and prevention of respiratory syncytial virus. Clin Infect Dis. 2010; 50:1258-67.
2. Initiative for Vaccine Research (IVR). Respiratory Syncytial Virus and Parainfluenza Viruses Disease Burden. WHO Geneva, Switzerland. Available from: *http://www.who.int/vaccine_research/diseases/ari/en/index2.html.* Accessed January 15, 2013.
3. Guidelines for Sample Collection and Handling of Human Clinical Samples for Laboratory Diagnosis of H1N1 Influenza. Available from: *http://www.mohfw.nic.in.*

Accessed January 15, 2013.
4. CDC Protocol of Real-time RTPCR for Influenza A (H1N1). Available from: *http://www.who.int*. Accessed January 24, 2013.
5. Stockton J, Ellis JS, Saville M, Clewley JP, Zambon MC. Multiplex PCR for typing and subtyping influenza and respiratory syncytial viruses. J Clin Microbiol. 1998;36:2990-95.
6. Rudan I, Boschi-pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ. 2008;86:408-16.
7. Griffin MR, Coffey CS, Neuzil KM, Mitchel EF Jr, Wright PF, Edwards KM. Winter viruses: Influenza- and respiratory syncytial virus-related morbidity in chronic lung disease. Arch Intern Med. 2002;162:1229-36.
8. Singh AK, Jain A, Jain B, Singh KP, Dangi T, Mohan M, *et al*. Viral aetiology of acute lower respiratory tract illness in hospitalised paediatric patients of a tertiary hospital: one year prospective study. Indian J Med Microbiol. 2014;32:13-8.
9. Moore ML, Chi MH, Zhou W, Goleniewska K, O'Neal JF, Higginbotham JN, *et al*. Cutting Edge: Oseltamivir decreases T cell GM1 expression and inhibits clearance of respiratory syncytial virus: potential role of endogenous sialidase in antiviral immunity. J Immunol. 2007;178:2651-4.

Tenofovir in Indian Children

We describe our experience with tenofovir-based antiretroviral therapy in seven HIV-infected children after failure of first line antiretroviral drugs, or due to adverse effects to other antiretrovirals. For follow-up period of average 3.4 years, none had adverse effects or failure of treatment, indicating that tenofovir has good renal and gastrointestinal safety profile in HIV-infected Indian children and adolescents.

Keywords: *Antiretroviral treatment, HIV infection, Renal dysfunction*.

Tenofovir Disoproxil Fumarate (TDF) is an orally bioavailable prodrug of tenofovir. In March 2010, the US FDA approved TDF for use in patients ≥12 years, and in January 2012, this approval was extended to children aged ≥2 years [1]. However response of TDF-based antiretroviral therapy (ART) in Indian children is not known.

Seven children (4 males) aged 6 to 16 years with mean (SD) age of 13.1 (3.5) years were started on TDF-based regimen. We used TDF, available as 300 mg tablet, in dosage of 8 mg/kg/dose once daily along with other antiretroviral drugs. At each visit, these children were evaluated for gastrointestinal symptoms and clinical evidence of rickets or pathological fractures. Serum creatinine, blood urea nitrogen, glomerular filtration rate, urinary proteins and blood gases were estimated trimonthly during the follow-up. Calcium and phosphorus levels in the serum were estimated trimonthly. Details of these patients are described in ***Table* I**.

Mean (SD) age for starting ART was 7.6 (4.2) years, and mean (SD) duration of for receiving TDF-based regimen was 3.4 (2.7) years. No patient suffered from renal dysfunction, urinary abnormalities or acidosis during the follow-up. Serum calcium and phosphorus levels in the serum remained normal. None of them had clinical evidence of gastrointestinal symptoms, rickets, or pathological fractures.

Adverse effects of TDF include lactic acidosis, besides nausea, diarrhea, vomiting, and flatulence [2]. While fatal lactic acidosis has been reported when TDF was added to a regimen that also contained didanosine, the effect was probably because TDF increases didanosine concentrations which causes significant mitochondrial toxicity [3]. None of our patients had lactic acidosis. Two small studies [4,5] in children reported reduction in bone mineral density (BMD) following TDF use. In these studies, BMD was measured by dual-energy *X*-ray absorptiometry (DEXA) scan. We could not do BMD in our patients on TDF-based regimen. A decrease in renal function and hypophosphataemia occur over time in HIV-infected children and adolescents on TDF-based ART [6]. Hypophosphatemia is significantly more common with recent TDF exposure, but is generally reversible if TDF is stopped [7]. A prospective study of 40 children, who had received at least six months of TDF, observed no change in creatinine clearance, but serum phosphate levels showed a significant decrease over the duration of follow-up [8]. Another study in 27 Italian children who received two years of TDF treatment found no evidence of impaired glomerular or tubular renal function [9]. We observed no adverse effect or failure of treatment in our case series, indicating that TDF has good renal and gastrointestinal safety profile in HIV-infected Indian children and adolescents. Reports based on larger number of patients are required to confirm our findings.

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