Original article

# Pulmonary hypertension in extremely low birth weight infants: characteristics and outcomes

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***Background:*** **To determine the characteristics and outcomes of pulmonary arterial hypertension (PAH) in extremely low birth weight (ELBW) infants.**

***Methods:*** **A retrospective case-control study of all ELBW infants admitted to a level III neonatal intensive care unit (NICU) between January 1, 2003 and December 31, 2010.**

***Results:*** **During the study period, 450 ELBW infants were admitted. 6.4% (29/450) were diagnosed with PAH and were matched to 26 controls. The mean gestational age of infants with PAH and their controls were similar [24.5±1.3 vs. 24.9±1.8 weeks (*P*=0.26)]; however the cases were smaller at birth than were controls [640.7±119.5 vs. 727.0±184.5 g (*P*=0.04)]. The diagnosis of PAH was made at a mean postnatal age of 131.8± 53.7 days. Infants with PAH had a higher rate of intrauterine exposure to illicit maternal drug use [12/29 (41%) vs. 1/25 (4%); *P*=0.001], a longer duration of initial mechanical ventilation [74.9±28.3 vs. 59.1±27.8 days; *P*=0.04)], a higher incidence of severe BPD [23/29 (79%) vs. 13/26 (50%); *P*=0.02], and a greater NICU mortality rate [12/29 (41%) vs. 4/26 (15%); *P*=0.04].**

***Conclusion:*** **PAH in ELBW infants is associated with maternal illicit drug use in pregnancy, longer exposure to mechanical ventilation, severe bronchopulmonary dysplasia and a significant increase in early mortality.**

***World J Pediatr 2014;10(1):46-52***

***Key words:*** **bronchopulmonary dysplasia; echocardiography; illicit drug use; mechanical ventilation; prenatal exposure**

## Introduction

Over the years, the introduction of measures to treat respiratory distress syndrome, including the use of surfactant and more conservative ventilation management, has led to increased survival and reduced morbidity in very small preterm infants.[1,2] This has allowed the emergence of a new spectrum of chronic lung disease marked by abnormal alveolarization, dysregulated angiogenesis and oxygen-mediated chronic lung injury.[3,4] Chronic hypoxia and reduction in effective vascular surface area lead to additional structural remodeling in premature infants[3,5] and development of bronchopulmonary dysplasia (BPD), clinically defined as the requirement of oxygen at 36 weeks after menstrual age.[2,3,6,7]

The pulmonary vasculature in patients with BPD is dysregulated.[8,9] There is also an abnormal distribution of the alveolar blood vessels with variable capillary density in adjacent alveoli, and in vessels situated distant from the air surface.[10,11] There is an accompanied increase in the vascular tone and an overall heightened vasoreactivity to fluctuations in arterial oxygen concentration.[8,12,13] Pulmonary arterial hypertension (PAH) is an end-result. As a disease entity, PAH represents a plexiform pulmonary arteriopathy.[9,10]

Low Apgar scores, oligohydramnios and pulmonary hypoplasia are associated with the development of PAH in premature infants, and several clinical studies have shown that PAH, though rare, contributes significantly to the morbidity and mortality of infants with BPD.[8,13-16] The potential risk factors of BPD-associated PAH in the post surfactant era are not well described and may be population dependent.[3] The diagnosis of PAH in the neonatal intensive care unit (NICU) remains a challenge due to the overlap of symptoms with those related to chronic respiratory failure secondary to BPD.[13] We

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doi: 10.1007/s12519-014-0464-2

hypothesized that patients at risk of developing PAH secondary to BPD have unique characteristics that would help clinicians to determine whether infants are at risk and who may benefit from early screening and intervention. The objective of this study was to determine the potential risk factors associated with PAH in extremely low birth weight (ELBW) infants.

## Methods

### Study design and patient selection

After the approval of the institutional review board at Metro Health Medical Center, we conducted a retrospective case-control study looking at all ELBW infants admitted to our NICU and diagnosed with PAH, and compared to controls who had 2D echocardiography during the course of hospitalization, but they did not have a diagnosis of PAH.

The medical records of all ELBW infants (≤1000 g) who were admitted to our NICU between January 1, 2003 and December 31, 2010 were reviewed to determine who met the criteria for inclusion in the study.

Our inclusion criteria consisted of all ELBW infants who had an echocardiogram at 28 days of age or later regardless of the presence or absence of PAH. Each patient with PAH was matched to a control patient born prior to or after the birth of a case patient, and who had an echocardiogram (at 28 days of age or later) showing no evidence of PAH. Cases were matched to controls based on gestational age (GA)±one week.

Our exclusion criteria consisted of all infants who were greater than 1000 g at birth, who had a congenital heart disease, or any other congenital malformations that are naturally associated with pulmonary hypertension, such as congenital diaphragmatic hernia, and chromosomal abnormalities.

### Data collection

All medical records were reviewed for patients' demographics including GA at birth (best available estimate), birth weight and birth weight percentiles, being small for gestational age, gender, race, mode of delivery, Apgar scores at 1 and 5 minutes, and severity of illness at birth represented by the score for neonatal acute physiology/perinatal extension (SNAPPE) score.

Medical records were also reviewed for prenatal and maternal characteristics including maternal age, exposure to prenatal steroids, maternal complications of pregnancy and labor [including preterm premature rupture of membranes (PPROM; defined as a rupture of membranes prior to 37 completed weeks GA and before onset of labor), chorioamnionitis, maternal hypertension, multiple gestation, oligohydroamnios, and placental abruption]. Medical records were reviewed for maternal history of use of nicotine, selective serotonin re-uptake inhibitors, and illicit drugs.

Postnatal characteristics of infants with PAH and their controls were reviewed including the need for intubation at birth, duration of initial mechanical ventilation (from birth until extubation), medical or surgical treatment of patent ductus arteriosus, chronologic age at the time of diagnosis, weight at the time (±1 week) of the echocardiogram and BPD. Information on history of pneumothorax and culture proven infections (bacteremia, tracheitis, ventilator associated pneumonia, or urine tract infection) within (before or after) 2 weeks of 2D echocardiography were also documented.

Chorioamnionitis was defined microscopically at the examination of the placenta by a pathologist at the Metro Health Medical Center. Small for gestational age was defined as a birth weight (BW) and/or length at least two standard deviations below the mean for GA. BPD was graded as mild, moderate and severe according to the National Institutes of Health consensus definition.[2,3,6,7]

### Echocardiography

The diagnosis of PAH was made by 2D echocardiography by a pediatric cardiologist who interpreted the test at the time when echocardiography was done on the basis of presence of echocardiographic markers suggestive of elevated right ventricular pressures including tricuspid regurgitation jet velocity, direction of the flow through a foramen ovale or ductus arteriosus, intraventrical septal wall flattening, abnormal right ventricular systolic function, right atrial enlargement, right ventricular hypertrophy, right ventricular dilatation, and pulmonary arterial dilatation.[13,17-21] All echocardiographic results were reviewed by one author of the study.

To enroll patients who have the potential of developing PAH following the development of early BPD (defined as oxygen requirement at 28 days of life), only patients who had echocardiograms obtained at 28 days of life or later were studied.

### Statistical analysis

A bivariate analysis was conducted to compare cases and controls. The Chi-square test and Fisher's exact test were used for categorical variables as appropriate. All quantitative data were expressed as the mean±standard deviation or median with inter-quartile range. A *P* value of ≤0.05 was considered to be statistically significant. The statistical software IBM SPSS Statistics version 19 (SPSS, Chicago, IL) was used for data analysis.

## Results

### Patients' demographics and characteristics

During the study period (from January 2003 to December 2010), 450 ELBW infants were admitted to our NICU. All patients were inborn infants. Fifty-five infants met our inclusion criteria and were enrolled in the study. Twenty-nine of the 450 infants or 6.4% (29/450) had an echocardiogram diagnosis of PAH and were matched to 26 controls (Fig.). The most common indications to obtain an echocardiogram among infants with PAH and their controls were to rule out PAH (*n*=30), congenital heart disease (*n*=9), vegetations (*n*=6), and steroid induced cardiomyopathy (*n*=4). One patient had an echocardiogram as part of the work up of a systemic hypertension, and five patients did not have an indication available in their medical records. Since all ELBW infants did not have a screening echocardiogram at or greater than 28 days of life, a comparison was made between infants with and without an echocardiogram. There were no significant differences between infants who did or did not have an echocardiogram done at or greater than 28 days of life, except that infants who had an echocardiogram had a lower GA and smaller BW than their counterparts (Table 1).

Infants with PAH had a lower birth weight and a higher Apgar score at 1 minute of life than their controls (Table 2). There were no other differences in patients' demographics and characteristics between infants with PAH and their controls.

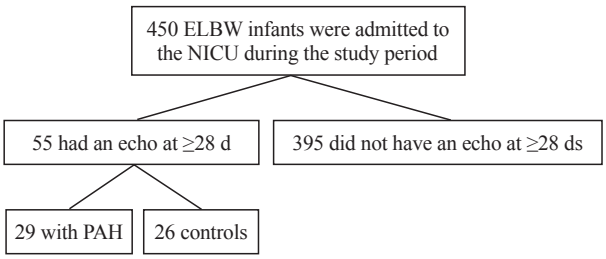


**Fig.** Flow chart of all ELBW infants who were admitted to the NICU during the study period. ELBW: extremely low birth weight; NICU: neonatal intensive care unit; PAH: pulmonary arterial hypertension; echo: echocardiogram.

**Table 1.** Characteristics of all extremely low birth weight infants with and without an echocardiogram (done at or greater than 28 days of life)

| Variables | With echocardiogram (*n*=55) | Without echocardiogram (*n*=395) | *P* values |
|---|---|---|---|
| GA* (wk) | 24.6±1.5 | 25.9±2.2 | <0.01 |
| Birth weight* (g) | 681.6±158.3 | 738.3±157.5 | 0.01 |
| SGA† (%) | 7/55 (13%) | 89/395 (22%) | 0.09 |
| Male (%) | 31/55 (56%) | 206/395 (52%) | 0.55 |
| Caucasian (%) | 15/55 (27%) | 125/395 (32%) | 0.51 |
| African American (%) | 36/55 (65%) | 232/395 (59%) | 0.34 |
| Other race (%) | 4/55 (7%) | 37/395 (9%) | 0.65 |
| Cesarean section (%) | 35/55 (64%) | 262/395 (66%) | 0.69 |
| Apgar 1 min‡ | 4 (2-6) | 4 (2-6) | 0.51 |
| Apgar 5 min‡ | 7 (6-8) | 7 (6-8) | 0.45 |
| SNAPPE score* | 48.9±14.4 | 45.1±16.2 | 0.07 |

*: data expressed in means±standard deviations; †: small for GA (less than 10th percentile birth weight for GA); ‡: data expressed as medians and inter-quartile ranges. SNAPPE: score of Neonatal Acute Physiology Perinatal Extension; GA: gestational age.

**Table 2.** Neonatal demographics and characteristics of extremely low birth weight infants with pulmonary arterial hypertension (PAH) and their controls

| Variables | PAH (*n*=29) | Controls (*n*=26) | *P* values |
|---|---|---|---|
| GA* (wk) | 24.5±1.3 | 24.9±1.8 | 0.26 |
| Birth weight* (g) | 640.7±119.5 | 727.3±184.5 | 0.04 |
| SGA† (%) | 4/29 (14%) | 3/26 (11%) | 1.00 |
| Male (%) | 18/29 (62%) | 13/26 (50%) | 0.36 |
| Caucasian (%) | 6/29 (21%) | 9/26 (35%) | 0.24 |
| African American (%) | 22/29 (76%) | 14/26 (54%) | 0.08 |
| Other race (%) | 1/29 (3%) | 3/26 (11%) | 0.33 |
| Cesarean section (%) | 18/29 (62%) | 17/26 (65%) | 1.00 |
| Apgar 1 min‡ | 4 (3-7) | 3 (1-5) | 0.054 |
| Apgar 5 min‡ | 7 (6-8) | 7 (5-8) | 0.18 |
| SNAPPE score* | 50.4±14.1 | 47.4±15.0 | 0.44 |

*: data expressed in means±standard deviations; †: small for GA (less than 10th percentile birth weight for GA); ‡: data expressed as medians and inter-quartile ranges. SNAPPE: score of Neonatal Acute Physiology Perinatal Extension; GA: gestational age.

**Table 3.** Prenatal characteristics of extremely low birth weight infants with pulmonary arterial hypertension (PAH) and their controls

| Variables | PAH (*n*=29) | Controls (*n*=26) | *P* values |
|---|---|---|---|
| Maternal age (y) | 27.5±6.6 | 28.3±6.5 | 0.68 |
| Prenatal steroids (%) | 18/27 (67%) | 22/26 (85%) | 0.13 |
| Oligohydramnios (%) | 4/29 (14%) | 7/26 (27%) | 0.31 |
| Maternal HTN (%) | 14/29 (48%) | 8/26 (31%) | 0.18 |
| Chorioamnionitis (%) | 14/29 (48%) | 10/26 (38%) | 0.46 |
| Placental abruption (%) | 6/29 (21%) | 5/26 (19%) | 0.90 |
| Multiple gestations (%) | 9/29 (31%) | 3/26 (11%) | 0.11 |
| Maternal PPROM (%) | 8/29 (28%) | 10/26 (38%) | 0.39 |
| Maternal nicotine use (%) | 13/29 (45%) | 11/26 (42%) | 1.00 |
| Maternal SSRI use (%) | 4/29 (14%) | 5/26 (19%) | 0.72 |
| Maternal drug use (%) | 12/29 (41%) | 1/25 (4%) | 0.001 |

HTN: hypertension; PPROM: prolonged premature rupture of membranes; SSRI: selective serotonin re-uptake inhibitors.

**Prenatal characteristics**

Infants with PAH had a higher percentage of prenatal drug exposure than their controls (Table 3). Thirteen infants had an intrauterine exposure to illicit drugs either by maternal history or by a screening of positive urine toxicology. One infant in the control group was exposed to marijuana. Twelve infants in the PAH group were exposed to multiple drugs including marijuana (9/12), cocaine (4/12), opiates [methadone, unclassified; (2/13)] and alcohol (2/12). None of the controls versus 17% (5/29) of the PAH patients had multiple drug exposure ($P$=0.053). Overall, 58% (32/55) of all mothers had a screening of urine toxicology and 62% (18/29) in the PAH group vs. 54% (14/26) in the control group ($P$=0.53).

There were no other significant differences in prenatal characteristics between the PAH and the control groups.

**Postnatal characteristics and potential risk factors**

Infants with PAH had a longer duration of mechanical ventilation at birth and had a higher percentage of severe BPD than their controls (Table 4). There was an association between the development of PAH and severe BPD [odds ratio (OR)=3.8, 95% CI=1.2-12.0, $P$=0.02]. Infants with PAH were also more likely to have been re-intubated at the time of their 2D echocaridography. [16/27 (59%) vs. 6/25 (24%), OR=4.6, 95% CI=1.4-14.6; $P$=0.01]. Six patients with PAH received sildenafil during their NICU stay, whereas none of the control group received sildenafil.

There were no other significant differences in postnatal characteristics between infants with PAH and their controls.

**Echocardiogram and cardiac catheterization**

A measurable tricuspid regurgitation (TR) was present in 72% (21/29) of the time. Right ventricular dilatation and hypertrophy were present in 86% (25/29) and 83% (24/29) of the time, respectively. Septal wall flattening was present in 69% (20/29), and right atrial dilatation was present in 69% (20/29) of time. In patients with PAH, 48% (14/29) had septal wall flattening with measurable TR; and 62% (18/29) had right ventricular hypertrophy with measurable TR. In patients, PAH was diagnosed at a mean postnatal age of 131.8±53.7 days, and in controls echocardiogram was obtained at a mean postnatal age of 89.1±41.7 days ($P$=0.002). Three infants underwent cardiac catheterization that confirmed the diagnosis after completion of their 2D echocardiography.

**Table 4.** Postnatal characteristics of extremely low birth weight infants with PAH and their controls

| Variables | PAH ($n$=29) | Controls ($n$=26) | $P$ values |
|---|---|---|---|
| Initial intubation at birth (%) | 29/29 (100%) | 25/26 (96%) | 0.47 |
| Initial mechanical ventilation (d)* | 74.9±28.3 | 59.1±27.8 | 0.04 |
| Severe BPD (%) | 23/29 (79%) | 13/26 (50%) | 0.02 |
| PDA treatment (%) | 26/29 (90%) | 22/26 (85%) | 1.00 |
| PDA medical treatment | 4/26 (15%) | 6/22 (27%) | 0.47 |
| PDA surgical treatment | 22/26 (85%) | 16/22 (73%) | 0.47 |
| Age at PDA closure (d) | 11.0±14.2 | 12.7±10.6 | 0.18 |
| Pneumothorax (%) | 7/28 (25%) | 6/24 (25%) | 1.00 |
| Culture proven infections (%) | 15/29 (52%) | 13/26 (50%) | 1.00 |

*: data expressed in means±standard deviations. BPD: bronchopulmonary dysplasia; PDA: patent ductus arteriosus; PAH: pulmonary arterial hypertension.

**Outcomes**

Infants with PAH, in comparison to their controls, had a similar percentage of growth failure (defined as a weight below the 3rd percentile for corrected GA) at the time of their echocardiographty [69% (18/26) vs. 67% (14/21); $P$=0.85]. However, they had a higher percentage of mortality prior to discharge from the NICU [41% (12/29) vs. 15% (4/26); $P$=0.04)]

## Discussion

As a screening tool, 2D echocardiography is commonly used to assess PAH in adults and children.[17-20] Through a case series of 10 infants with BPD, Fouron et al[17] demonstrated, as early as 1980, that serial echocardiography could reliably be used to assess pulmonary vasculature in neonates. Lazarani et al[18,19] found that, in adults with heart failure, 2D echocardiography can estimate right-sided pressures comparably to cardiac catheterization done around the same time, and can classify patients with the presence or absence of PAH. Skinner et al[20] reported similar findings when they performed serial analyses of pulmonary arterial pressures in neonates with persistent pulmonary hypertension of the newborn. In a study of infants with both pulmonary hypertension and chronic lung disease, who subsequently underwent cardiac catheterization, Mourani et al[21] found that echocardiography often identifies pulmonary hypertension in young children with chronic lung disease. In our study, 2D echocardiography was helpful in identifying infants with PAH when there was a high index of suspicion by their treating physicians; however we did not perform a routine 2D echocardiography for all infants to screen PAH, nor we did a cardiac catheterization for all infants with 2D echocardiographic findings of PAH to confirm the diagnosis.

Low Apgar scores are thought to be associated with pulmonary hypertension.[22] In our study, we did not find any significant difference in Apgar scores at

5 minutes between the PAH and control groups, most probably because the majority of our patients had a good Apgar score at 5 minutes of age (the Apgar score's lower quartile for the PAH and control groups were 6 and 5, respectively). Oligohydramnios is also associated with pulmonary hypertension.[22] Again, this association was absent in our study, probably because our study was small and not powered to show a significant difference. Oligohydramnios and low Apgar scores are associated with acute PAH in the newborn period due to failure of normal postnatal pulmonary vasodilatation. In contrast, "late PAH", associated with BPD, is due to chronic postnatal structural changes in the pulmonary vasculature, which most likely accounts for the lack of association between PAH and oligohydramnios/Apgar in our study. The use of selective serotonin re-uptake inhibitors during pregnancy is also associated with the development of persistent pulmonary hypertension in the immediate newborn period.[23] We did not find any difference in maternal use of selective serotonin re-uptake inhibitors between infants with PAH and their controls, most probably because the rate of use of selective serotonin re-uptake inhibitors was low in our studied population, in both the PAH and control groups.

Also of interest, there has been no previously reported association between maternal use of illicit drugs and the development of PAH in ELBW infants as we have seen in our patients. However, one of the pulmonary complications of illicit drug use in adult patients is pulmonary arterial hypertension.[24] The use of illicit drugs, mainly stimulants, such as amphetamines and cocaine is found to be associated with idiopathic pulmonary hypertension in adults. Adult patients with idiopathic PAH are more likely to use stimulants including amphetamines and cocaine than patients with other forms of pulmonary hypertension with a known risk factor.[25] Since there has been no previously reported association between maternal drug use and PAH in ELBW infants, we can only speculate about co-related potential mechanisms for this association. For instance, maternal use of illicit drugs might have been a marker of other maternal psychosocial factors such as malnutrition, unhealthy diet and life style that would have had an impact on the development of fetus pulmonary vasculature.

It has been advocated to screen for PAH in infants with BPD who are either extremely premature, that is, less or equal to 25 weeks GA, extremely small, BW less or equal to 600 g, who are small for gestational age, have a history of prolonged mechanical ventilation, prolonged $O_2$ requirement out of proportion to the severity of lung disease and poor growth despite adequate caloric intake.[13,26] Our findings are consistent with the previous recommendations, since our ELBW patients who had PAH were smaller than their controls with a mean BW of 640 g despite the efforts of controlling and matching for gestational age between the two groups. In our study, however, the rate of SGA was not different between the groups, probably because the rate of small gestational age was elevated in both the PAH and the control groups.

Previous studies[27,28] have shown that PAH is common among ELBW infants ranging between 17.9% and 37%. In a retrospective cohort study of ELBW infants, Slaughter et al[27] found that 37% of ELBW infants who had an echocardiogram after 4 weeks of life had evidence of PAH. In contrast, a prospective study[28] of ELBW infants found that 17.9% of all ELBW infants who were screened for PAH had echocardiographic findings of PAH. Our study is a retrospective case-control study that was not designed to determine the incidence of PAH in ELBW infants. Hence the rate of PAH was 6.4% among ELBW infants who had an echocardiogram, a rate that is lower than previously reported rates.

To determine if the group of infants who had a 2D echocardiography was representative of our population, we compared all the patients who had an echocardiogram performed at or greater than 28 days of life with other ELBW infants who were admitted to our NICU and did not have an echocardiogram. The comparison showed that infants who required an echocardiogram (if deemed necessary by their treating physicians) at or greater than 28 days of life, were smaller and younger at birth than their counterparts, which is consistent with previous recommendations advocating screening extremely premature and small infants for PAH.[27,28]

The increasing severity of lung disease has been described as a risk factor for the development of pulmonary hypertension which is consistent with our findings.[22,26] In our study, infants with PAH had more days of mechanical ventilation and a higher rate of severe BPD than their controls.

PAH is potentially fatal in preterm infants. Our patients with PAH were three times more likely to die before discharge home than their controls. Other studies[13,22,27] have documented similar findings. A study[13] of 42 premature infants found that premature infants with BPD and severe PAH had a high mortality of 36% during the first 6 months after their diagnosis of PAH. A retrospective cohort study[27] of ELBW with BPD requiring prolonged mechanical ventilation showed that infants with PAH are four times more likely to die than their controls.

In summary, in this study we found that PAH in ELBW infants is associated with maternal use of illicit drugs during pregnancy, longer exposure to mechanical

ventilation, and severe BPD. We also found that PAH in ELBW infants is associated with a significant increase in early mortality.

Contrary to other studies, we did not find an association between PAH and an increased rate of growth failure in our population.[13,22] This may suggest a multifactorial etiology for poor growth.

There are several limitations to our study, a small retrospective case-control study from a single institution. The population in this study has a high socio-economic demographic risk, and may not necessarily reflect the general population. We did not screen PAH in every single ELBW infant with severe BPD. The detection rate of 6.5% was lower than the reported (17%-37%) in ELBW infants despite the similar rates of BPD.[13,28] The lack of screening might have been responsible for missing cases of PAH that might have resolved uneventfully and be missed. Thus, our study did not allow us to determine the prevalence of PAH in our population. Over the duration of the study, there was a significant change in practice, with a tendency towards gentler ventilation and earlier extubation. A change in the management of ELBW may have affected the percentage of PAH over the years; however we attempted to counteract this problem by enrolling contemporary controls to our patients. Another limitation of our study is related to the diagnostic limitations of echocardiography in assessing PAH. The diagnosis of PAH in our study was made by echocardiography, and since PAH may be difficult to diagnose and to quantify especially without evidence of TR jet or PDA, we might have missed patients with PAH who did not have echocardiographic findings of PAH and misclassified them under controls. Also, since infants in the control group had their echocardiography done earlier than the PAH group, it is possible that some of the control infants had their echocardiogram too early to detect PAH.

In conclusion, severe BPD, the need for lengthy mechanical ventilation, with a history of maternal illicit drug use should alert physicians to screen ELBW infants for PAH. 2D echocardiography could be a useful non-invasive screening tool in infants suspected to have PAH secondary to chronic lung disease. Future studies are needed to determine highly sensitive risk markers of PAH in ELBW infants.

**Funding:** There are no financial disclosures or disclaimers related to this manuscript.
**Ethical approval:** The study was approved by the institutional review board at Metro Health Medical Center.
**Competing interest:** None.
**Contributors:** Waruingi W was responsible for data collection, data entry and writing the manuscript. Mhanna MJ was responsible for data analysis, and editing the manuscript.

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*Received November 20, 2012*
*Accepted after revision March 5, 2013*