Use of Ambroxol and Treatment of *Klebsiella ozaenae* in Extremely Low Birth Weight Preterm: Case Report and Literature Review

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**Keywords:** Respiratory distress syndrome; Ambroxol, *Klebsiella ozaenae*; Extremely low birth weight; Cefoperazone sulbactam

**Abstract**

**Introduction:** Respiratory distress syndrome (RDS) is the most common respiratory complication occurring in preterm newborns due to deficiency of endogenous pulmonary surfactant. Ambroxol, is a promoter of fetal lung maturity and indicated as secretolytic therapy in bronchopulmonary diseases. *Klebsiella ozaenae*, whose antibiotic susceptibility data is limited, is associated with ozena; a primary atrophic rhinitis (AR), RTIs, cerebral abscess, meningitis, UTIs, and is one of the leading cause of (ICU) acquired pneumonia. This case study reports the use of post-natal intravenous amroxol to treat RDS, and use of cefoperazone sulbactam to treat *Klebsiella ozaenae* and *Pseudomonas aeruginosa*.

**Case Presentation:** A Chinese preterm, extremely low birth weight female (birth weight was 750 grams) was delivered by emergency caesarian section to a pregnancy-induced hypertensive G2P2 mother at 27 weeks’ gestational age and was admitted in the pediatric ward because of severe dyspnoea with grunting respiration, tachypnoea, cyanosis and crackles in the lung fields. A working diagnosis of RDS was made and she was placed in incubator and neonatal continuous positive airway pressure (NCPAP) was applied immediately. She was managed with ambroxol for RDS and cefoperazone sulbactam for *Klebsiella ozaenae* and *Pseudomonas aeruginosa* bacteria and was successfully treated by 3 days’ intravenous gamma globulin therapy and 10 days’ antibiotics administration. On 67th day of hospitalization, baby was discharged with a body weight of more than 2100 grams.

**Conclusions:** The early application of NCPAP and ambroxol reduced the severity of this disease in preterm neonate and improved the clinical course of RDS. The combination of cefoperazone and sulbactam is effective against both of *K. ozaenae* and *Pseudomonas aeruginosa* bacteria.

**Keywords:** Respiratory distress syndrome; Ambroxol, *Klebsiella ozaenae*; Extremely low birth weight; Cefoperazone sulbactam

**Introduction**

Respiratory distress syndrome (RDS) is the most common respiratory disease of preterm neonates caused by deficiency of endogenous pulmonary surfactant needed for alveolar stability [1,2]. Although exogenous surfactant therapy has enhanced survival from RDS, chronic lung disease still is a potential cause of mortality and morbidity, thus there is a great need of newer treatments that may decrease lung injury in premature neonates [3]. Although glucocorticoids are effective in the prevention of RDS and in the treatment of chronic lung disease, the repetition of their dose causes aggregated side effects [4]. The studies show that repeated antenatal doses could lead to growth retardation, decreased fetal brain size and affected neuronal development [5]. Ambroxol, is a relatively new promoter of neonatal lung maturity and increasing number of studies described its role in the prevention of RDS [6]. The effectiveness of postnatal intravenous ambroxol in the treatment and the prevention of RDS need concern and more research [7]. This case is reported to study the role of post-natal intravenous ambroxol in the treatment of RDS and its effects on the course and severity of the disease.

The genus *Klebsiella* comprises of non-motile, aerobic and facultatively anaerobic, Gram negative rods [8]. At the time of writing, the genus *Klebsiella* includes *K. pneumonia*, *sub specie pneumoniae*, *K. pneumoniae* sub specie *sauzae*, *K. pneumoniae* sub specie *rhinoscleromatis*, *K. oxytoca*, *K. ornithinolytica*, *K. planticola*, and *K. terrigena* [9]. *K. pneumoniae* are amongst the most common causes of community-acquired and hospital-acquired infections [10]. *K. pneumoniae* is followed by *K. oxytoca*, *K. ozaenae* and *K. rhinoscleromatis* are rare, but can cause serious clinical syndromes (ozena and rhinoscleroma, respectively) [11]. The in vitro data on antibiotic susceptibility of *K. ozaenae* is very limited. The first report of plasmid mediated resistance to broad-spectrum cephalosporins was of an isolate of *K. ozaenae* [12,13]. There have been no succeeding reported isolates of ESBL producing *K. ozaenae* and no randomized trials in the treatment of *K. ozaenae* infections have been reported [14]. This case study reports the successful treatment of *Klebsiella ozaenae* accompanied with *Pseudomonas aeruginosa* in an extremely low birth weight neonate.

**Case Presentation**

A Chinese preterm, extremely low birth weight female (birth weight was 750 grams) was delivered by emergency caesarian section to a pregnancy-induced hypertensive G2P2 mother at 27 weeks’ gestational age, having normal placenta and umbilical cord with clear amniotic fluid. She had no birth asphyxia and had spontaneous breathing at birth (APGAR scores were 8 in one minute and 10 in 5 minutes). She
developed moaning, frothing and peri-oral cyanosis with decreased reactivity, and was admitted in the pediatric ward. Examination revealed severe dyspnoea with grunting respiration, tachypnoea, cyanosis and crackles in the lung fields. She also had tachycardia and tender hepatomegaly. Heart rhythm was regular with no audible murmur. Muscle tone was reduced and neonatal reflexes were not elicited. Chest X-ray showed hyperinflation, right lower zone patchy consolidation with increased lung markings and obliteration of the costophrenic angle. Echocardiography was normal. AmnioStat-FLM test was negative. She was placed in incubator and neonatal continuous positive airway pressure (NCPAP) was applied immediately. She was managed with ambroxol 30 mg/kg/d, divided in three intravenous doses and theophylline therapy for 3 days which gradually resulted in smooth breathing. Intravenous nutrition therapy was started 2nd day after admission and the adjuvant naso-gastric tube feeding was started with preterm children formula on the fifth day. During the first 10 days of admission daily milk feeding was 20 ml/d and body weight dropped to 685 grams, until the 14th day of hospitalization when milk feeding was increased gradually to 80 ml/d and weight correspondingly increased to 900 grams. The 14th day, child became cyanosed with poor response and fever, transcutaneous oxygen desaturation (TCSO₂) dropped to 60%, WBC raised to 12.26 × 10⁹/L, neutrophils 0.60, Hemoglobin 127 g/L and CRP 21 mg/L. 16th day and 18th day throat swab bacterial cultures were reported as *Klebsiella ozaenae* and *Pseudomonas aeruginosa* bacteria and was successfully treated by 3 days’ intravenous gamma globulin therapy and 10 days’ antibiotics administration (cefoperazone sulbactam). She was transfused with oral feeding was started and daily milk feeding was increased to 360 ml/d with body weight 1900 grams. On 67th day of hospitalization, baby was discharged with a body weight of more than 2100 grams. The follow up visit after 2 years revealed height being 85 cm and weight 10 kg with normal nervous system development including hearing, vision and language skills. 3rd year follow-up showed height 90 cm and weight 11 kg with normal intelligence level (Figure 1).

**Discussion**

Respiratory distress syndrome, RDS, occurs in up to 83.0% of extremely low birth weight premature neonates and is one of the leading causes of child mortality [15]. Complicated RDS can cause pneumopericardium, patent ductus arteriosus, pulmonary hypertension and heart failure. Distressed breathing in children causes endothelial dysfunction, which is an early marker of atherosclerosis [16]. These cardiac conditions can later cause adult cardiovascular disease. It has been reported that cardiovascular mortality is higher among former preterm adults than those born at term which may be related to preterm RDS. This condition is referred to as cardiovascular perinatal programming [17]. Ambroxol is a secretolytic agent used in the treatment of respiratory diseases associated with viscous or excessive mucus [18]. This is a mucoactive drug with secretolytic and secretomotoric properties that maintains clearance mechanisms of the respiratory tract, and plays an important role in the body’s natural defence mechanisms. It stimulates type II pneumocytes for the synthesis and release of surfactant [19]. Surfactant acts as an anti-glue factor by decreasing the adhesion of mucus to the bronchial wall. Ambroxol is indicated as secretolytic therapy in bronchopulmonary diseases associated with abnormal mucus secretion and impaired mucus transport [20]. It facilitates expectoration and productive cough. Although in this case, before admission treatment was given to promote lung maturity but because of the low gestational age and the pregnancy-induced hypertensive mother, child developed RDS after admission to the hospital. The early application of NCPAP and ambroxol treatment, avoided the use of pulmonary surfactant (PS). In this work, the RDS at 24 hours of administration was successfully treated in the neonate with Ambroxol. This preventive effect coincides with earlier reports [21]. The need for CPAP was used as an index for severity (morbidity of RDS). Ambroxol reduced the need for CPAP and its mean pressure. Moreover, Ambroxol reduced the need for the initiation of mechanical ventilation during the course of illness. This coincides with the results of Wauer et al. [22].

Ambroxol also reduced the oxygenation index (OI) which shows a better gas exchange, a lower mean airway pressure (MAP) and a lower fraction of inspired oxygen (FIO2) endorsing earlier studies [23,24]. This reflects a reduced peak inspiratory pressure (PIP) and peak expiratory end pressure (PEEP), as well as reduced inspiratory time, reflecting a reduced peak inspiratory pressure (PIP) and peak expiratory end pressure (PEEP), as well as reduced inspiratory time, verifying the already reported study by Elsayed [25]. Ambroxol efficacy is probably dependent not only on lung pathology, but also on the dose administered and the duration of administration. Our choice of 30 mg/kg/day was the dose already reported yet, larger doses could also be used safely [26]. The Ambroxol used in this study was safe and caused no complications which is in accordance to the reported researches [27]. Moreover, its administration is simple in comparison with surfactant administration and is cheaper.

Biggest tool in treating premature children is infection, particularly hospital-acquired infections which are also one of the main reasons of death [28]. Signs of infection must be closely monitored and timely treated [2]. *Klebsiella ozaenae* is associated with ozena; a primary atrophic rhinitis (AR), RTIs, cerebral abscess and meningitis, and...
UTIs. Sources for clinical samples of *Klebsiella ozaenae* are respiratory tract (RT; nasopharyngeal samples), urinary tract (UT) and blood [29] and the spectrum of disease caused by this organism is very extensive [30]. *Klebsiella ozaenae* is one of the leading cause of (ICU) acquired pneumonia. The in vitro data on antibiotic susceptibility of *K. ozaenae* is very limited and there have been no randomized trials in the treatment of *K. ozaenae* infections so, treatment is said to be based on antibiotic susceptibility results and the site of infection. The use of ciprofloxacin, intravenous aminoglycosides, trimethoprim/sulfamethoxazole and piperacillin are already reported for the treatment of *K. ozaenae* [31,32] but in case of neonates, the side effects may limit the selection of antibiotics. In this report, on the 14th day of hospital admission the patient developed cyanosis with poor responses, fever of 38, TCSO2 dropped to 60% and increased blood WBC and CRP. 16th day and 18th day throat swab bacterial cultures were reported as *Klebsiella ozaenae* and *Pseudomonas aeruginosa* bacteria. The culture and sensitivity was confirmed with multiple laboratory analysis and thus according to the susceptibility, intravenous cefoperazone sulbactam and gamma globulin therapy was given. Cefoperazone is a third generation cephalosporin antibiotic and Sulbactam is an irreversible inhibitor of β-lactamase [33,34]. In the combination of cefoperazone and sulbactam, cefoperazone exerts its bactericidal effect by inhibiting the bacterial cell wall synthesis, and sulbactam acts as a beta-lactamase inhibitor, to increase the antibacterial activity of cefoperazone against beta-lactamase-producing organisms. The outcome was successful against both of the cultured bacteria i.e. *Klebsiella ozaenae* and *Pseudomonas aeruginosa*. Early postnatal protein deficiency could affect the development of cell differentiation and myelination of the brain, resulting in irreversible cognitive, motor and behavioral abnormalities [35,36]. The caloric requirements of the neonate during the disease process were fulfilled initially as total parenteral nutrition and later partial parenteral nutrition respectively.

The purposes of this report is to sensitize practitioners about the early diagnosis and management of the unusual organism *K. ozaenae*, and to validate the use of postnatal I.V ambroxol for the management of RDS.

**Conclusion**

Early administration of intravenous ambroxol can produce a positive efficacy for the prevention of RDS in preterm infants. The early application of NCPAP and Ambroxol reduced the severity of this disease in preterm neonate and improved the clinical course of RDS and in turn prevented future cardiac complications. The combination of cefoperazone and sulbactam is effective against both of *K. ozaenae* and *Pseudomonas aeruginosa* bacteria. The arrangement of symptomatic, supportive and specific treatment, with enthusiastic clinical and nursing care, is the key to successful rescue of the extremely low birth weight preterm neonates.

**References**


