**Problem-Solving in Clinical Practice: Persisting respiratory distress in a premature infant**

**Corresponding author:**

**Dr Sanjay Patel**

Paediatric Infectious Diseases and Immunology, University Hospital Southampton NHS Foundation Trust, Southampton, Hampshire, UK

Email: Sanjay.patel@uhs.nhs.uk

**Authors:**

**Dr Daniel R. Owens**

1. NIHR Southampton Clinical Research Facility and NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, UK

**Dr Michelle Medalla**Department of Child Health, Hampshire Hospitals NHS Foundation Trust,
Basingstoke, Hampshire, UK

**Dr Kelly N. Brown**

Department of Neonatal Medicine, University Hospital Southampton NHS Foundation Trust, Southampton, UK

**Dr Kishani Wijewardena**

Department of Child Health, Hampshire Hospitals NHS Foundation Trust,
Basingstoke, Hampshire, UK

**Dr Claire P. Thomas**
Department of Clinical Microbiology/Infection, Hampshire Hospitals NHS Foundation Trust, Basingstoke, Hampshire, UK

**Dr Mildred A. Iro**

1. Paediatric Infectious Diseases and Immunology, University Hospital Southampton NHS Foundation Trust, Southampton, UK
2. Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, UK

 **Dr Christine E. Jones**

1. NIHR Southampton Clinical Research Facility and NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK
2. Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, UK

**Professor Saul N. Faust**

1. NIHR Southampton Clinical Research Facility and NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK
2. Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, UK

**Dr Sanjay V. Patel**

Paediatric Infectious Diseases and Immunology, University Hospital Southampton NHS Foundation Trust, Southampton, UK

Word count (excluding title page, abstract, references, figures and tables): 2555 words

**Acknowledgements:**

Dr Mildred Iro is funded as an NIHR Clinical Lecturer.

**Keywords:** Infectious Disease, Neonatology

**Problem-Solving in Clinical Practice: Persisting respiratory distress in a premature infant**

**Summary:** The deterioration of a previously stable preterm infant is a common scenario on the neonatal unit. The commonest bacterial causes of deterioration are nosocomial infections, such as *coagulase negative Staphylococcus* and *Staphylococcus aureus*. Non-infective conditions such as pulmonary haemorrhage, anaemia of prematurity and necrotising enterocolitis may also cause preterm infants to deteriorate. This case chronicles the unusual diagnostic journey of an infant born at 27+1 weeks who deteriorated at 26 days of life and did not respond to antimicrobial therapy as anticipated**.**

**A female infant was born to non-consanguinous Indian origin parents in a UK district general hospital at 27+1 weeks gestation weighing 1Kg. The antenatal course was unremarkable with normal antenatal screening results. The parents had a previous infant born at full term in 2015. The patient was intubated at birth and given surfactant. She was ventilated for one day then received 2 days of Continuous Positive Airway Pressure (CPAP) and 15 days of high flow oxygen therapy.**

**On day 26 of life the patient was breathing in air and fully enterally fed but then acutely deteriorated with increased oxygen requirement and a raised C-Reactive Protein (CRP) of 145mg/L.**

When a premature infant with a previously uncomplicated course deteriorates acutely, the commonest cause is infection (Box 1). Bloods, including full blood count, CRP and blood cultures should be taken and antibiotic treatment for late-onset sepsis (LOS) commenced. Microbiological investigations should be performed to look for common infective causes of deterioration. If the infant has raised inflammatory markers or positive blood cultures a lumbar puncture should usually be performed. Respiratory secretions should be sent for bacterial culture and respiratory virus testing.

|  |
| --- |
| Box 1: Causes of late-onset deterioration in a preterm infantInfective causes*Bacterial:** Pneumonia
* Central line sepsis
* Meningitis
* Urinary Tract Infection

*Viral:** Bronchiolitis (RSV or other respiratory virus)
* Neonatal HSV
* Enterovirus
* Cytomegalovirus
* Parechovirus
* HIV-associated infections

*Fungal:** *Candida spp.*

Other causes:Evolving Chronic Lung DiseaseAnaemia of prematurity* Patent Ductus Arteriosus or other cardiac causes
* Pulmonary Haemorrhage
* Necrotising enterocolitis
 |

**Bacterial causes of LOS**

The commonest bacterial cause of LOS in preterm infants on the neonatal unit is *coagulase negative Staphylococcus* (CONS)followed by *Staphylococcus aureus.*(1, 2)Other causes include Group B *Streptocococcus* (GBS), *Pseudomonas, Klebsiella* and *Enterobacter spp.* LOS on the neonatal unit is predominantly nosocomial whereas early onset sepsis (EOS), most commonly caused by GBS, is usually secondary to perinatal vertical transmission. CONS is a skin commensal that can invade the blood especially when the skin is immature, there are low levels of endogenous bacterial flora and intravenous lines are present. Whilst not generally as virulent as other pathogens, resistant strains of CONS are on the rise which underlines the importance of good infection control measures and antimicrobial stewardship.(3)

In Western Europe, the most commonly used antibiotics for LOS are Flucloxacillin (or Ampicillin) and Gentamicin. This combination of antibiotics cover between 95-97% of pathogens causing LOS in the United Kingdom.(1) Cephalosporins are not recommended for LOS due to resistance patterns seen in common pathogens such as non-*E.Coli* organisms,including *Enterobacter cloacae,* and *Pseudomonas aeruginosa*. They also exert selection pressure leading to higher rates of antimicrobial resistance (AMR). Another key aspect of good antimicrobial stewardship is safely minimising the course duration. If cultures are negative at 36-48 hours and there is clinical improvement, then antibiotics should be discontinued.

One challenge in LOS is the diagnostic accuracy of current microbiological investigations. Blood cultures are of relatively low sensitivity, especially when a small blood volume is taken.(4) Although Polymerase Chain Reaction (PCR) tests are being developed which may offer results from small blood volumes, they are associated with a risk of false positive results from contaminants and do not provide antibiotic sensitivities.(3) Further work is on the horizon to develop fast, reliable diagnostic methods which provide antibiotic sensitivities.

**Fungal causes of LOS**

The rate of fungal sepsis in premature infants varies geographically but in the United Kingdom is reported as 2.4/1000 neonatal admissions, although there is wide variation even among tertiary neonatal units.(5) The commonest cause of fungal sepsis is *Candida albicans* which accounts for 69% of cases.(5) Risk factors for fungal sepsis include birthweight of <1000g, recent courses of antibiotics, invasive ventilation, central venous catheters and parenteral nutrition. The clinical presentation is indistinguishable from bacterial sepsis. Due to the variation in fungal sepsis rates, the use of fungal prophylaxis remains a decision for individual neonatal units. Serum markers such as Beta-D-glucan, and fungal PCR are available but not in routine use.(6)

**Viral causes of LOS**

Although often overlooked, viruses also may cause rapid deterioration in the preterm infant.Disseminated herpes simplex virus (HSV) is an uncommon but potentially catastrophic cause of LOS with high morbidity and mortality. The estimated incidence in the UK has risen to 17.5/100,000 live births which likely reflects higher rates of maternal infection.(7) Presentation is variable but abnormal liver function tests and coagulopathy may differentiate it from other causes of sepsis. A low threshold for investigation in blood, CSF and surface swabs (eye, mouth, stool) by PCR and consideration of empirical treatment with aciclovir is warranted especially given the rise in incidence. Other causes of viral sepsis include enterovirus, cytomegalovirus, and parechovirus.

|  |
| --- |
| **Despite treatment with 1 week of intravenous flucloxacillin and gentamicin, she continued to deteriorate and was intubated, ventilated and transferred to a tertiary neonatal unit. There were widespread interstitial changes on chest radiograph (Figure 1).****Her antibiotics were switched to clarithromycin and meropenem to empirically treat resistant gram negatives and atypical bacteria. A non-bronchoscopic bronchoalveolar lavage (BAL) was performed as she deteriorated despite broad spectrum antibiotic treatment. Bacterial cultures were negative. She subsequently improved, was extubated and transferred back to the district general hospital after 6 days on high flow oxygen therapy to complete her planned antibiotic course.(6)** |

When the clinical condition does not respond to first line antibiotics, atypical causes of bacterial LOS should be considered such as *Ureaplasma, Mycoplasma* and *Acinetobacter* as well as the possibility of resistant organisms and non-infectious causes.(8, 9) Testing for *Ureaplasma* and *Mycoplasma* in neonates is by PCR. Consideration should be given to broadening the antibiotic cover to treat for atypical infection following consultation with a Paediatric Infectious Diseases team. The role of *Ureaplasma* in pathological processes in premature infants is controversial, it is thought to cause pneumonia, septicaemia and meningitis and could be considered in infants not responding to standard therapy.(8) Although found frequently in amniotic fluid and the respiratory tract of preterm infants its role in the pathogenesis of preterm birth and chronic lung disease is unclear and the role of eradication treatments with macrolides is debated.(8)

BAL can be performed in ventilated infants with LOS and it may provide useful microbiological information to direct antibiotic therapy, however a raised BAL white cell count is hard to interpret in infants ventilated for >48 hours as ventilation itself causes inflammation.(9)

**On day 14 following her BAL cultures grew *Mycobacterium* spp. and subsequent PCR on the positive culture confirmed *Mycobacterium tuberculosis.* Further investigations were performed to look for evidence of dissemination; abdominal ultrasound showed renal, ovarian and splenic lesions; cranial ultrasound and cerebrospinal fluid examination were normal. Quadruple therapy was commenced (isoniazid, rifampicin, ethambutol and pyrazinamide), along with pyridoxine. HIV PCR was negative.**

Tuberculosis (TB) should be considered in an unwell newborn infant, who has not responded to conventional antibiotic therapy and has negative standard microbiological investigations. Risk factors for TB should be sought, and TB considered when the mother is from an area of high TB prevalence. TB remains one of the leading causes of death worldwide with an estimated 1.3 million deaths in 2017, of which 10% of cases are in children. However it is rarely reported in the newborn period, possibly reflecting difficulty in diagnosis.(10)

For optimal management of TB, the diagnosis needs to be considered early and discussed with microbiology. Appropriate samples including respiratory secretions (ideally BAL), for urgent smear for acid fast bacilli, mycobacterial culture and PCR. Gastric lavage, blood, liver and lymph node biopsies can also be used for diagnostic testing. Examination of the cerebrospinal fluid for cell count, biochemistry, TB smear, culture and PCR may be warranted. (10)

Conventional diagnostic approaches such as the Tuberculin Skin Test (TST) and Interferon Gamma Release Assays (IGRAs) are less helpful in the diagnosis of neonatal TB.(11) These investigations may support the diagnosis but their sensitivity is thought to be low in neonates. Rapid nucleic acid amplification testing in the form of the *Xpert MTB/RIF assay* is increasingly being used and is recommended by the World Health Organisation (WHO) a first line investigation for diagnosing TB and rifampicin resistance if culture is unavailable.(12) It remains less sensitive than culture but is rapid and easily implemented.(12) HIV testing should be performed on both the mother and infant, infants should be tested with HIV PCR, and the mother evaluated by a respiratory or infectious disease physician.

**Infection control**

**The TB result was immediately communicated to the local hospital and a risk assessment conducted to establish if transmission had occurred on the Neonatal Unit (NNU).**

**During their admission to the NNU, the baby was managed within an enclosed incubator with occasional ‘kangaroo’ care. She had received CPAP via an open circuit and had been regularly suctioned. It was decided that the period of infectivity was from the initial clinical deterioration at day 26 of life to the point at which the diagnosis was made and adequate infection control measures were initiated. The highest risk of transmission was deemed to be during aerosol generating procedures such as out of incubator suctioning and receipt of CPAP.**

**An initial meeting was held with all families by the NNU consultant to provide information regarding TB. Due to the small environment of the NNU, clear communication whilst maintaining confidentiality was important, especially as infection control measures were now clearly visible.**

**Screening was offered to all babies in the same room as the index case and to family members who had been present during the period of infectivity. Screening was performed by TB IGRA and TST. Symptomatic babies, defined as cough and poor weight gain, were also offered a chest radiograph. Prophylaxis with 6 months of isoniazid and pyridoxine was commenced for all exposed infants with monthly follow up. Staff were offered screening if they worked on the unit or were present at the delivery. No linked cases were found amongst patients or staff.**

In the event of a possible TB outbreak, it is important to collect accurate information on the movement of patients and staff during the period of infectivity in order to identify at risk individuals. When screening at risk contacts, consider individuals who have been cumulatively exposed for >8 hours within 2 metres of the index case. Infectivity depends on the potential for aerosolization and the extent of pulmonary and laryngeal TB, especially if miliary or cavitatory lung disease is present.

**After the diagnosis, the patient’s mother was investigated. A chest radiograph showed a right-sided pleural effusion but sputum and BAL were negative for TB. The placenta was examined and showed granulomatous inflammation. An MRI brainshowed 2 ring enhancing lesions and she was commenced on anti-TB therapy with dexamethasone and has responded well. The patient’s father and sibling were also screened with Interferon Gamma Release Assay (IGRA) and chest radiograph; both were found to be negative.**

TB in an infant can be congenital or acquired postnatally. *Cantwell et al.* established the following criteria for a diagnosis of congenital TB.(13)

Proven tuberculosis lesions in the infant plus one of the following:

* Onset of lesions in the first week of life
* Primary hepatic complex or caseating hepatic granulomas
* Tuberculosis infection of the placenta or maternal genital tract
* Exclusion of the possibility of postnatal transmission

According to these criteria, the findings in our patient confirmed a diagnosis of congenital TB.

Congenital TB is extremely rare and therefore firm data on its incidence is lacking. One small study in a high incidence area (South Africa) demonstrated a vertical transmission rate of 16%.(14) This suggests that the incidence of congenital TB in low risk areas is extremely low. Symptoms are non-specific (reduced feeding, irritability, fever, failure to thrive, cough and respiratory distress), and present at a median age of 24 days of life.(13) Signs include organomegaly, lymphadenopathy and abdominal distension.(13) Congenital TB is usually disseminated with liver, lymph node, spleen, renal and CNS involvement. Patients may partially improve on antibiotics, in this case Meropenem and Clarithromycin were used, which have have anti-mycobacterial activity and may explain the initial clinical improvement.

The WHO advises treating as for postnatally acquired TB with the following first line treatments:(12)

* Isoniazid with pyridoxine
* Rifampicin
* Pyrazinamide
* Ethambutol

HIV negative children living in areas of low HIV and isoniazid resistance prevalence can be treated with a 3 drug regimen (Isoniazid, Rifampicin and Pyrazinamide) for 2 months followed by 4 months of Isoniazid and Rifampicin, although in the UK, the general consensus is to treat with a 4 drug regimen during the intensive phase. Dosing data in infants is limited so close monitoring is needed for evidence of toxicity. If there are concerns around adequate absorption, serial serum blood testing for rifampicin levels should be performed.

**Due to ongoing high flow oxygen therapy requirement and poor growth, she was transferred back to the tertiary centre and started on Non-Invasive Ventilation. The patient’s chest radiograph is shown in figure 2. 14 days after transfer the patient deteriorated significantly with a respiratory acidosis requiring intubation and transfer to the Paediatric Intensive Care Unit where she remained ventilated for 5 days. Drug levels showed adequate absorption of rifampicin, there was no evidence of secondary bacterial infection and repeat PCR demonstrated no evidence of rifampicin resistance. A bronchoscopy showed bilateral airway granulomas and subtotal obstruction of the left main bronchus.**

When a patient on TB treatment deteriorates, the following should be considered: inadequate treatment secondary to poor absorption or adherence, intercurrent bacterial infection or development of multi-drug resistance TB. TB-Immune Reconstitution Inflammatory Syndrome (TB-IRIS) should also be considered. TB-IRIS is a paradoxical reaction in which a patient on tuberculosis treatment deteriorates following initial improvement and no other cause is found.(15)

The pathogenesis of TB-IRIS in HIV negative patients is poorly understood. It is proposed that the high bacillary load, as seen in active military TB or congenital TB, is associated with an initial secondary immunodeficiency. This resolves during treatment leading to an inflammatory reaction during recovery of the immune system and accounts for the clinical findings.(16)

In HIV negative patients, presentation is usually 2-3 months after initiation of treatment.(17) The most commonly affected sites are the lymph nodes and lung, however it can affect the brain, muscle, bone, pleura and pericardium.(15) 25-30% of patients will develop new lesions in sites that were unaffected at presentation.(16, 18) TB-IRIS of the lung and lymph nodes presents as fever, enlarged lymph nodes and respiratory distress but symptoms vary depending on age and the affected site.(16)

TB-IRIS may occur in up to 10% of immunocompetent children, with younger age and absence of BCG vaccine being risk factors for its development, however these numbers should be taken with caution in view of the paucity of data and variation in criteria used to define TB-IRIS.(19) To our knowledge this the first case of congenital TB-IRIS described in an extremely premature infant.(20, 21)

There is no clear standard treatment for TB-IRIS but anti-tubercular therapy should continue; some cases may resolve with no additional therapy.(22) Corticosteroids are the only treatment studied with a randomised controlled trial in TB-IRIS and were shown to reduce hospital stay, improve symptoms and reduce medical intervention.(17) In this case steroids were also indicated due to airway obstruction.

The overall prognosis is good but data is lacking in children. In adults with TB-IRIS, all-cause mortality is 7% and TB-IRIS attributable mortality is 2%.(23) 2 previous case report of congenital TB-IRIS had good outcomes.(20, 21)

|  |
| --- |
| **The infant was commenced on prednisolone (1mg/kg/day) for 4 weeks. Following this she improved clinically and was discharged a month after transfer on low flow oxygen and nasogastric feeds.**  |

Summary

In the event of deterioration despite adequate treatment with broad spectrum antibiotics, unusual infections such as TB should be considered and treated. Infection control implications for an NNU are likely to be complex however early multi-disciplinary planning are key to a good outcome.

Funding: Not applicable

Competing interests: None

**References**

1. Muller-Pebody B, Johnson AP, Heath PT *et al.* Empirical treatment of neonatal sepsis: are the current guidelines adequate? *Arch Dis Child Fetal Neonatal Ed.* 2011;96(1):F4-F8.

2. Cailes B, Kortsalioudaki C, Buttery J *et al*. Epidemiology of UK neonatal infections: the neonIN infection surveillance network. *Arch Dis Child Fetal Neonatal Ed.* 2018;103(6):F547-f53.

3. Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. *Arch Dis Child Fetal Neonatal Ed.* 2015;100(3):F257-F63.

4. Connell TG, Rele M, Cowley D *et al.* How reliable is a negative blood culture result? Volume of blood submitted for culture in routine practice in a children's hospital. *Pediatrics*. 2007;119(5):891-6.

5. Oeser C, Vergnano S, Naidoo R *et al*. Neonatal invasive fungal infection in England 2004–2010. *Clin Microbiol Infect*. 2014;20(9):936-41.

6. Ramos JT, Villar S, Bouza E *et al*. Performance of a Quantitative PCR-Based Assay and Beta- D -Glucan Detection for Diagnosis of Invasive Candidiasis in Very-Low-Birth-Weight Preterm Neonatal Patients (CANDINEO Study). *J Clin Microbiol*. 2017;55(9):2752-64.

7. Batra D, Davies P, Manktelow BN *et al.* The incidence and presentation of neonatal herpes in a single UK tertiary centre, 2006-2013. *Arch Dis Child.* 2014;99(10):916-21.

8. Waites KB, Katz B, Schelonka RL. Mycoplasmas and Ureaplasmas as Neonatal Pathogens. *Clin Microbiol Rev.* 2005;18(4):757-89.

9. Mackanjee HR, Naidoo L, Ramkaran P *et al.* Neonatal bronchoscopy: Role in respiratory disease of the newborn - A 7 year experience. *Pediatr Pulmonol*. 2019;54(4):415-20.

10. King AMQ, Lefkowitz EJ, Mushegian AR *et al*. Changes to taxonomy and the International Code of Virus Classification and Nomenclature ratified by the International Committee on Taxonomy of Viruses (2018). *Arch Virol*. 2018;163(9):2601-31.

11. Sun L, Tian J-l, Yin Q-q *et al*. Performance of the Interferon Gamma Release Assays in Tuberculosis Disease in Children Five Years Old or Less. *PloS One*. 2015;10(12):e0143820-e.

12. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2014. World Health Organisation. 2nd edition. Accessed 30 August 2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/112360/9789241548748\_eng.pdf;jsessionid=F7222165A56C9EE5FB28D30B51B2AA25?sequence=1.

13. Cantwell MF, Shehab ZM, Costello AM *et al*. Congenital Tuberculosis. *N Engl J Med*. 1994;330(15):1051-4.

14. Pillay T, Sturm AW, Khan M, et al. Vertical transmission of Mycobacterium tuberculosis in KwaZulu Natal: impact of HIV-1 co-infection. *Int J Tuberc Lung Dis*. 2004;8(1):59-69.

15. Geri G, Passeron A, Heym B *et al.* Paradoxical reactions during treatment of tuberculosis with extrapulmonary manifestations in HIV-negative patients. *Infection*. 2013;41(2):537-43.

16. Cheng V, Ho P, Lee R *et al.* Clinical Spectrum of Paradoxical Deterioration During Antituberculosis Therapy in Non-HIV-Infected Patients. *Eur J Clin Microbiol Infect Dis.* 2002;21(11):803-9.

17. Meintjes G, Wilkinson RJ, Morroni C *et al.* Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS.* 2010;24(15):2381-90.

18. Cheng VC, Yam WC, Woo PC *et al.* Risk factors for development of paradoxical response during antituberculosis therapy in HIV-negative patients. *Eur J Clin Microbiol Infect Dis.* 2003;22(10):597-602.

19. Olive C, Mouchet F, Toppet V *et al*. Paradoxical reaction during tuberculosis treatment in immunocompetent children: clinical spectrum and risk factors. *Pediatr Infect Dis J.* 2013;32(5):446-9.

20. Park JA, Park SS, Park SE. A paradoxical reaction during antituberculosis therapy for congenital tuberculosis. *Int J Infect Dis.* 2009;13(5):e279-e81.

21. Chakraborty S. A Rare Complication of a Common Disease. *C61 Tuberculosis Case Reports*. 2017;195(A6000).

22. Cho O-H, Park K-H, Kim T *et al*. Paradoxical responses in non-HIV-infected patients with peripheral lymph node tuberculosis. *J Infect*. 2009;59(1):56-61.

23. Namale PE, Abdullahi LH, Fine S *et al.* Paradoxical TB-IRIS in HIV-infected adults: a systematic review and meta-analysis. *Future Microbiol*. 2015;10(6):1077-99.

**Figures**

Figure 1 - Chest radiograph prior to transfer on day 41 of life
Figure 2 Chest radiograph at 123 days of age prior to transfer to Paediatric Intensive Care Unit