AN OVERVIEW OF ATYPICAL BACTERIAL IN CONGENITAL PNEUMONIA

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Abstract

Congenital pneumonia is one of the common causes of respiratory distress at birth with significant morbidity and mortality in infants. Estimates show that neonatal pneumonia including congenital pneumonia contributes to between 750,000 and 1.2 million neonatal deaths every year which accounts for 10% global child mortality. Etiological agents are many and vary but atypical bacterial causes are few. The commonest cause for atypical bacteria is Ureaplasma urealyticum. Congenital pneumonia is often clinically difficult to diagnose owing to poor specificity of clinical signs, with similarities in radiologic presentation with other respiratory conditions of the newborn. Isolation of causative organism(s) by culture from nasopharyngeal aspirates or tracheal aspirates obtained within 8 hours of life is the gold standard of its diagnosis. However, this technique is elaborate and time consuming in identifying atypical bacteria. Development of a more sensitive modality such as polymerase chain reaction (PCR) has dramatically altered the microbiological diagnosis of congenital pneumonia.

Keywords: Congenital pneumonia, Atypical bacteria, Polymerase chain reaction (PCR)

Introduction

Pneumonia is an infection of the lungs, characterized mainly by inflammation of the microscopic air sacs called alveoli. In neonates, pneumonia is classified as congenital or neonatal in origin depending on the time or period of acquisition of infection. The word ‘congenital’ is defined as a condition that is recognized at birth or believed to have been present since birth [1]. It is therefore defined as pneumonia with clinical and/or radiological evidence present within the first 48 hours after birth with a positive identification of the causative organism from either nasopharyngeal aspirates [2-4], tracheal aspirates obtained aseptically within 8 hours of life [5] or gastric aspirates obtained within 1-2 hours after birth [6]. The 3 categories of congenital pneumonia include: true congenital pneumonia which is already established at birth; intrapartum pneumonia which is acquired during passage through the birth canal and postnatal pneumonia in the first 24 hours of life which originates after the infant has left the birth canal.

Congenital pneumonia is one of the common causes of respiratory distress at birth with significant morbidity and mortality in infants. The actual incidence is unknown. Review of the literature showed that no large population studies have reported the incidence of this condition

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Risk Factors and Pathogenesis

The risk factors reported to be associated with congenital pneumonia include maternal chorioamnionitis [12], prolonged rupture of chorioamniont membrane [13], premature prelabour rupture of chorioamniont membrane (PPROM) [14], low socioeconomic status [8, 15] and maternal systemic infection which may be symptomatic in the mother [12]. In a postmortem study of 159 neonates born to mothers with chorioamnionitis, Madan et al. (1988) reported that congenital pneumonia (defined by the presence of polymorphonuclear leukocytes (PNL) in the alveolar spaces) was present in 45% of the cases [12]. Prolonged rupture of membrane without other complications for more than 24 hours before delivery is associated with an increased risk of pathogens ascending the birth canal resulting in neonatal infection. PPROM may occur in response to an untreated urinary tract infection, birth canal infection, previous preterm delivery, uterine bleeding in pregnancy and heavy cigarette smoking during pregnancy [10]. Newborns in developing countries are exposed to external risk factors that put them at greater risk for infection compared with newborns in the industrialized world. According to WHO, only 68% of women in developing countries receive some form of antenatal care and only 35% of mothers in the least developed countries have access to skilled health personnel at delivery [16]. Early investigations of the cause of neonatal deaths in the first 48 hours of life found pneumonia in 20-38% of the cases, with the highest incidence in lower socioeconomic groups [17].

The major route by which the fetus/infant acquires the infection is via perinatally (vertical). Acquisition of congenital pneumonia transplacentally is quite uncommon and is usually part of the systemic infection [18]. Ascending infection from the birth canal and aspiration of infected amniotic fluid are common perinatal mechanisms of acquisition of infection. Infection of the amniotic fluid involves ascending pathogens from the birth canal. It may also result from procedures such as amniocentesis, placement of intrauterine catheters or during pelvic examination. Barton et al. (1999) in an autopsy study of extremely low birth weight infants found that aspiration of organisms in the amniotic fluid during the intrapartum period was the most common mechanism of acquisition of congenital pneumonia [8]. Histology findings of amniotic fluid and/or maternal white blood cells in affected neonatal lungs suggest that congenital pneumonia from infected amniotic fluid or colonization is linked with maternal chorioamnionitis and fetal asphyxia. Asphyxia leads to gasping in the fetus and aspiration of infected amniotic fluid with resultant development of congenital pneumonia [8, 19].

Prompt diagnosis of this condition is often difficult owing to the poor specificity of clinical manifestations and respiratory signs. Chest radiographic appearances are not specific for pneumonia as it may mimic other features in conditions such as respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN) or aspiration syndrome. Routine microbiological culture remains the gold standard in laboratory diagnosis. However, more sensitive tests such as PCR may improve diagnosis in shorter duration [11]. This review focuses on the atypical bacteria U. urealyticum, U. parvum, M. hominis, C. trachomatis and M. pneumoniae, issues in the laboratory diagnosis and management strategies including preventive measures.

Bacteria, virus and fungi are known causative organisms. Atypical bacterial causes include Ureaplasma urealyticum, Ureaplasma parvum, Mycoplasma hominis, Chlamydia trachomatis and Mycoplasma pneumoniae. Although some authors have included Listeria monocytogenes, Mycobacterium tuberculosis and Treponema pallidum as atypical bacterial causes of congenital pneumonia, they will not be discussed in this review.

Acquisition of congenital pneumonia

Based on clearly defined diagnostic criteria. However, estimates show that neonatal pneumonia including congenital pneumonia contributes to between 750 000 and 1.2 million neonatal deaths every year [7]. In a series of extremely low birth weight infants, congenital pneumonia was the predominant type of congenital infection affecting 53.6% of the cases [8]. Barnett and Klein (2001) estimated that congenital pneumonia accounted for 10-38% of stillbirths and 20-63% of liveborns who subsequently die [9]. Mortality caused by congenital pneumonia associated with proven blood-borne infections ranges from 5-10% in full term infants and as high as 30% in very low birth weight infants [10].

Newborns in developing countries are exposed to external risk factors that put them at greater risk for infection compared with newborns in the industrialized world. According to WHO, only 68% of women in developing countries receive some form of antenatal care and only 35% of mothers in the least developed countries have access to skilled health personnel at delivery [16]. Early investigations of the cause of neonatal deaths in the first 48 hours of life found pneumonia in 20-38% of the cases, with the highest incidence in lower socioeconomic groups [17].
Clinical Manifestation

The clinical characteristics of congenital pneumonia are often nonspecific. They may become evident prior to delivery in the form of fetal distress or tachycardia, or at the time of delivery as a low Apgar score or severe respiratory distress. The features of respiratory distress include any of the following: rapid, noisy or difficult breathing, respiratory rate of more than 60 breaths per minute, reccesions, irregular respiration, decreased breath sounds and grunting [19]. However, these features again are not specific to congenital pneumonia as other respiratory disorders such as TTN, meconium aspiration syndrome or RDS mimic such presentation in newborns. Some infants may take a few hours or 1-2 days before respiratory distress or shock manifests. However, some infants may develop nonspecific signs and symptoms such as poor feeding, lethargy, cyanosis, fever or become hypothermic (temperature instability) or constitutional symptoms of unwellness [8]. Presence of lung crackles assists in the diagnosis of congenital pneumonia although detection on physical examination in some infants may be difficult and occasionally absent in neonates even in the presence of florid pneumonia.

Tachypnea appears to be the most consistent sign present in 60-89% of the cases [20]. However, data from some previous studies suggested that tachypnea on its own may not be a very satisfactory indicator of pneumonia [21-23]. Furthermore, variation in the respiratory rate caused by the method and duration of counting, state of infant, fever, and several other factors may also influence its usefulness to predict pneumonia. Singhi and colleagues (1999) determined the clinical signs that predict pneumonia in infants less than 2 months of age. Report generated from their study suggested that the use of a respiratory rate greater than 60 breaths per minute and/or chest indrawing are predictors of pneumonia with sensitivity of 85% and 97% respectively. Their finding further suggested the usefulness of nasal flaring to the criteria for case identification in infants under 2 months of age with this condition [24].

The clinical features of congenital pneumonia are presented in Table 1.

*Table 1: Clinical features of congenital pneumonia

<table>
<thead>
<tr>
<th>Clinical signs present in most cases</th>
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<tr>
<td>Tachypnea</td>
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<td>Recession</td>
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<td>Grunting</td>
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<td>Nasal flaring</td>
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<th>Non-specific clinical signs present in some cases</th>
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<td>Poor feeding</td>
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<td>Cyanosis</td>
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<td>Abdominal distention</td>
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<td>Lethargy</td>
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<td>Temperature instability</td>
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Atypical Bacteria Causes

Ureaplasma urealyticum

Ureaplasma urealyticum (U. urealyticum) is a eubacteria that have evolved from clostridia-like gram-positive cells by gene deletion [25]. It belongs to the class Mollicutes known as the smallest free-living organisms. Its genome is comprised of 947kbp with 711 genes. All serovars lack cell walls but are bounded by cell membrane, are resistant to β-lactam antibiotics, have small genome size, mucosal association in the human host and limited biosynthetic abilities [26]. Recently, Ureaplasma was split into 2 separate species and 14 serovars. U. parvum, known as biovar 1, contains serovars 1, 3, 6, and 14 while U. urealyticum biovar 2 contains the remaining serovars 2, 4, 5, and 7-13 [27]. U. urealyticum exists as normal commensal flora in the reproductive tract of adults especially women. It can be isolated from the vagina of 40-80% of sexually active asymptomatic women [28]. Colonization occurs as a result of sexual activity especially with multiple partners, younger age, low socioeconomic status, black ethnicity and oral contraceptive usage [29]. Routes of transmission from an infected mother to the fetus are before birth (in utero) or during birth via passage through a colonized birth canal [28, 30]. The major virulence factor for adherence to human cells is adhesins. Cleavage of protease IgA may enable ureaplasmas to colonize and invade the cervix and upper genital tract of pregnant women [31].

Early work on the possible role of Ureaplasma spp. as a pathogen in neonatal respiratory infections arose in the mid-1970s, when Tafari and colleagues (1976) described the isolation of these organisms from lungs of stillborn infants with pneumonitis [32]. Recovery of U. urealyticum from the lower respiratory tract of newborn infants has been linked to pneumonia and persistent pulmonary hypertension [33]. Crouse et al. (1993) further isolated U. urealyticum from endotracheal aspirates of newborn infants in the absence of other respiratory pathogens and was significantly associated with radiographic pneumonia [34]. In a study of 100 low birth weight infants, congenital pneumonia was evident in three of seven infants with positive U. urealyticum tracheal aspirate culture [35]. In another series of autopsies involving 159 neonates, U. urealyticum was one of the most common isolates (9%) and congenital pneumonia was a major outcome [12]. Panero et al. (1995) reported isolation of U. urealyticum from 16 (55.2%) tracheal aspirates and/or blood specimens of 29 neonates with acute respiratory disease. Pneumonia was diagnosed more frequently in U. urealyticum positive infants compared to those who were negative. Their findings suggested that U. urealyticum can induce an inflammatory response in selected individuals who presented with clinical, radiological or histological features of pneumonia [36].

Culture is the gold standard for diagnosis of U. urealyticum infections. However it is elaborate, takes too long to yield, usually within 2-5 days, expensive and not available in most centers. Furthermore, reports on culture studies have shown detection rates to be 80% in typical clinical laboratory conditions, but, research laboratories report higher sensitivities [37].

Although Quinn et al. (1986) suggested that type-specific antibody response greater than or equal to 1:32 against certain Ureaplasma serovars occurs in infants with respiratory disease and in women with pregnancy wastage compared with control patients, there is a need for more studies to fully appreciate the value for antibody determination in this population [38]. Microimmunofluorescence test (MIF), metabolic inhibition and enzyme immunoassay (EIA) are serological tests that have been used for Ureaplasma spp. but, only in research setting. No assays for genital mycoplasmas have been standardized and made commercially available in the United States [39].

Recently, great attention has been given to the application of PCR assay in the primary detection of Ureaplasma perinatal infections because PCR assay is fast, does not necessarily require viable organisms and rate of detection is better than culture. Blanchard et al. (1993) compared results of culture and PCR analysis of 95 endotracheal aspirates of newborn infants and found 99% agreement between culture and PCR [37]. Other reports have shown greater sensitivity of PCR in comparison to culture [40-44]. Real-time PCR has been reported to have higher sensitivity and specificity than culture and conventional PCR. Xiao et al. (2010) compared real-time PCR with conventional PCR and culture in the detection of human ureaplasmas. They reported that real-time PCR had a diagnostic sensitivity of 96.6% and specificity of 99.1% for U. urealyticum [45]. Compared to culture and traditional PCR, Xiao et al. (2010) and Cao et al. (2007) concluded that real-time PCR is the most sensitive assay for the detection of Ureaplasma spp. [45, 46].
**Ureaplasma parvum**

*Ureaplasma parvum* (*U. parvum*) is part of the normal genital bacterial flora of both men and women. It is more common than *U. urealyticum* as a colonizer of the male and female urogenital tracts [47]. Their occurrence in pregnant women provides a reservoir for transmission to the fetus and neonate. *U. parvum* is associated with the development of chorioamnionitis, funisitis and preterm delivery. It also causes neonatal sepsis, bronchopulmonary dysplasia in premature babies, meningitis or even death [48]. There is little knowledge about the pathogenicity of *U. parvum* in term newborn infants. Morioka and colleagues (2010) reported the first and only case of *U. parvum* being implicated in the pathogenesis of congenital pneumonia with sepsis in a human term newborn [49].

*U. parvum* can be identified by culture, serology and PCR. Culture technique for detecting *U. parvum* requires special media and expertise that is not widely available [50] while serological tests are mainly used as research tools and not recommended for routine diagnostic purposes. PCR is the most suitable diagnostic tool. Morioka and colleagues (2010) detected *U. parvum* from blood by multiplex PCR and samples from placenta and umbilical cord by conventional PCR.

**Mycoplasma hominis**

*Mycoplasma hominis* (*M. hominis*) is an intracellular pleomorphic bacterium which belongs to the class Mollicutes and the genus *Mycoplasma*. Analysis of the genome indicates that this *Mycoplasma* has undergone horizontal gene transfer with *Ureaplasma* spp. It is the second smallest known self-replicating free-living organism behind *Mycoplasma genitalium* with 665 kbp and 527 protein-coding genes [51]. *M. hominis* like other mycoplasmas lacks cell walls and exists in association with eukaryotic cells, mainly colonizing mucosal surfaces of the respiratory and urogenital tracts [52].

*M. hominis* is one of the most common organisms isolated from the vagina of asymptomatic sexually active women with a colonization rate of 20-53%. Occurrence in the male urethra is lower [50]. Factors linked to colonization are similar to those of *U. urealyticum* and *U. parvum*. Henrich and colleagues (1997) used homologous antibodies to prevent adherence of mycoplasmas to HeLa cells thus suggesting that specific proteins may be involved in the adherence process [53]. Variable adherence-associated (Vaa) adhesin which is a major protein with adhesive properties may undergo antigenic modification and assists *M. hominis* in evading host defenses [54].

*M. hominis* is often present concurrently with *Ureaplasma* spp. and can be transmitted vertically from mother to the developing fetus in utero or to the neonate at the time of delivery via passage through a colonized birth canal [55]. In newborn infants, *M. hominis* is associated with conditions such as bacteremia, meningitis, and abscesses. Although Waites et al. (2011) [48] stated that *M. hominis* may cause congenital pneumonia in neonates, reports implicating this organism as an etiological agent of this condition are lacking.

**Chlamydia trachomatis**

*Chlamydia trachomatis* (*C. trachomatis*) is a member of the phylum Chlamydiae which are obligate intracellular bacteria. They were thought to be viruses for many years but later discovered to have the characteristics of bacteria except the lack of energy-production mechanism [56].

*C. trachomatis* is a genital pathogen and considered one of the most prevalent sexually transmitted bacterium. It is found with increased frequency among young individuals, more often nonwhites, individuals with low socioeconomic status and multiple sexual partners [56]. The actual incidence of cervical infection caused by this bacterium is unknown. About 80% of cases are symptomatic. *C. trachomatis* species is currently divided into 19 serovars. Serovars D to K have been generally isolated from the genital tract [57].

Infants born to women with untreated chlamydial infection are at high risk of infection. Neonatal chlamydial infections are acquired during vaginal delivery, although reports of intrauterine chlamydial infections causing fetal death or pneumonia in infants delivered by caesarean sections have been reported [58, 59]. *C. trachomatis* pneumonia acquired perinatally is mostly seen between 4–11 weeks, and is responsible for 25–45% of all pneumonia cases in infants less than 6 months of age [60]. The most frequent site of infection is the nasopharynx and only about 30% of infants with nasopharyngeal infection develop Chlamydial pneumonia [28]. Most infants with Chlamydial pneumonia become symptomatic before the eighth week of life with the insidious development of nasal obstruction and/or discharge, tachypnea, staccato cough, without fever or wheezing. Chest X-ray findings reveal hyperinflation and diffuse bilateral
infiltrates. Some infants may have symptoms as early as the second week of life, initially involving the upper respiratory tract. Typically, the infants have been symptomatic for 3 or more weeks before presentation. Most of them are only moderately ill and are afebrile [60]. The estimated risk of C. trachomatis pneumonia developing in an infant whose mother is colonized is 7% [61]. Two large cohort studies of infants exposed to C. trachomatis reported pneumonia incidences of 3% and 16% [62].

Tissue culture for C. trachomatis remains the “gold standard” for diagnosis in nasopharyngeal specimens. Bekler et al. (2011) reported greater sensitivity of tissue culture over direct immunofluorescent testing (DIF) for detecting C. trachomatis, thus demonstrating the diagnostic superiority of tissue culture tests [63]. Microimmunofluorescence testing is useful in diagnosing chlamydial infection in neonates. The microimmunofluorescence test developed by Wang and Grayston (1975) is the current method of choice for serodiagnosis of chlamydial infection. A high level of IgM antibody in neonates is associated with the disease. An acute microimmunofluorescence serum titer of C. trachomatis specific IgM of 1:32 or greater is diagnostic of infection. Level of IgG is not diagnostic of infection because passively transferred maternal antibody may persist at high titers for months [64]. PCR, ligase chain reaction (LCx), transcription mediated amplification (TMA) and strand displacement amplification (SDA) are nucleic acid amplification assays currently used to detect C. trachomatis in clinical specimens. However, only PCR is often used in neonatal chlamydial infections. Namazaki et al. (2003) used both PCR and enzyme immunoassay (EIA) to detect C. trachomatis in nasopharyngeal specimens of newborns with Chlamydia pneumonia and reported equal sensitivity for both methods [65].

**Mycoplasma pneumoniae**

*Mycoplasma pneumoniae* (M. pneumoniae) is different from other Mollicutes because of its ability to ferment glucose to lactic acid as its means of generating ATP. *M. pneumoniae* adheres to host cells respiratory tract by the P1 adhesin and other accessory proteins. This is followed by induction of chronic inflammation [66].

*M. pneumoniae* is one of the most common causes of community acquired pneumonia and has been implicated in 40% of the cases [67]. This organism is an uncommon cause of pneumonia in children less than 5 years of age and greatest among school-age children. In neonates, it may cause severe respiratory illness such as pneumonia. Colonization of infants by genital mycoplasmas usually occurs during passage through an infected birth canal [50].

*M. pneumoniae* is a rare cause of congenital pneumonia. Attempts to isolate this organism from two neonatal populations have failed [68]. Although in 1970, Miller and Enborn, isolated *M. pneumoniae* from a newborn infant but no signs or symptoms of respiratory tract infection were present until the age of 4 months [69]. To date, only two cases of congenital pneumonia caused by this organism have been reported. Ursi et al. (1995) [70] and Srinivasjois et al. (2008) [71] detected *M. pneumoniae* from nasopharyngeal aspirates and placenta of newborn infants with radiologic evidence of pneumonia respectively.

Culture for *M. pneumoniae* is the gold standard for diagnosis but, it has little analytical sensitivity. On the other hand, PCR and serology are considered as better methods. Disadvantages of the use of serological analysis for diagnosing *M. pneumoniae* in neonatal infections include the requirement of acute and convalescent serum samples that are tested simultaneously for IgM and IgG for seroconversion and the need to wait 1 to 2 weeks from onset of infection until detectable antibody develops. PCR offers better detection ability for *M. pneumoniae* in neonates. Ursi et al. (1995) [70] reported PCR as a better diagnostic tool compared to culture in the detection of *M. pneumoniae* while Srinivasjois et al. (2008) [71] detected *M. pneumoniae* by real-time PCR.

**Diagnosis**

**Radiologic Diagnosis**

Chest roentgenogram is the most helpful tool in the diagnosis of pneumonia. Chest radiographic presentation of congenital pneumonia shows abnormal findings which include nodular or coarse patchy infiltrates, diffuse haziness or granularity, air bronchogram signs and lobar or segmental consolidation [9]. These features vary depending on the mode of transmission of infection. Diffuse reticulogranular infiltrates that resemble the ground-glass pattern of respiratory distress syndrome are suggestive of a hematogenous transmission, though it could also be a result of aspiration of infected fluid. Patchy
irregular infiltrates of the normal margin suggest an antepartum or intrapartum aspiration, peribronchial thickening indicating bronchopneumonia may be present while patchy irregular densities concentrated on the right side suggests postnatal aspiration. Presence of generalized over inflation with patchy infiltrates may indicate partial hindrance of the airways from inflammatory debris. Air bronchograms (single or multiple) with 2 or more generations beyond the mainstream bronchi indicate dense pulmonary parenchyma. In a retrospective analysis of the chest films of 30 infants with pneumonia, the most common abnormality was bilateral alveolar densities (77%). Other abnormal presentations include dense bilateral with air bronchograms (33%), less dense but bilateral and confluent (24%), bilateral patchy segmental densities (10%), generalized pulmonary over inflation (17%) and pleural fluid (10%) [72].

Chest radiographic findings of congenital pneumonia caused by atypical bacteria are the same as described in the paragraph above. However, there are some features particular to some atypical bacteria. Tipple et al. (1979) [60] reported that chest roentgenograms of 81% infants with Chlamydia pneumonia showed bilateral and symmetrical interstitial-type pulmonary infiltrates together with hyperinflation while others had scattered areas of density believed to represent both atelectasis and alveolar infiltrates. Interstitial infiltrates were also present in the case report by Srinivasjois et al. (2008) [71] while Ursi et al. (1995) [70] reported that the chest radiography of their case report showed pleural effusion and alveolisation on Day 1 of life, pneumothorax and pneumomediastinum on Day 2 and reticulonodular infiltrates with small amount of pleural fluid on Day 3. Both cases reported M. pneumoniae as etiology of congenital pneumonia.

Laboratory Diagnosis

Culture technique
Nasopharyngeal aspirates or tracheal aspirates obtained aseptically before 8 hours of life are appropriate specimens that are cultivable on microbiological media. Sherman and coworkers (1980) used tracheal aspirate obtained aseptically within 8 hours of life in diagnosing congenital pneumonia. The culture result yielded growth of bacteria from the tracheal aspirates of infected infants [5]. However, conventional bacteriological culture is not useful in the recovery of atypical bacterial pathogens of congenital pneumonia. The cultures of genital mycoplasmas require different microbiological processing and media for cultivation. Culture for C. trachomatis involves isolation of the organism in tissue culture and confirmation of microscopic identification of the characteristic inclusions, by staining with a fluorescein-conjugated, species-specific monoclonal antibody [73].

Blood culture is useful in identifying the causative organisms, but not all cases of congenital pneumonia are associated with a positive blood culture. In a study by Sherman et al. (1980), blood culture was positive in 56% of 25 neonates with congenital pneumonia [5]. However, it is not useful in isolating or identifying atypical bacteria. Quantitative culture technique of bronchoscopic alveolar lavage (BAL) which reportedly has specificity of >80%, is difficult to use on newborn infants and data for its use in neonates are sparse. The use of culture for the diagnosis of atypical bacteria is limited since it is elaborate, quite expensive, time consuming and not available in most centres. Other techniques that may help overcome these limitations include serological tests, antigen detection, nucleic acid probes and PCR assays.

Serological tests
The use of serological tests to establish diagnosis have limited use, however, it may offer some insight. Serological tests for genital mycoplasma infections in infants remain problematic and used only in research settings. Although a number of serological test have proven useful in the diagnosis of C. trachomatis infections in neonates and infants, issues of sensitivity and specificity limit their uses. Though lacking well-defined sensitivity, direct fluorescent antibody tests (DFA) are FDA-approved test for the use in pharyngeal specimens. However, it has high specificity if a C. trachomatis specific strain is used. ELAs are not recommended for use in pharyngeal specimens due to lack of specificity. Microimmunofluorescence test which uses elementary bodies as antigen is the test of choice which results in lesser occurrence of cross reaction between the various chlamydia species [74].

Nucleic Acid Amplification Tests
Nucleic acid amplification techniques (NAATs) have the potential to produce rapid, sensitive, and specific results, allowing early appropriate antibiotic therapy. Among the nucleic acid amplification tests, PCR was the first to be utilized. It is still the commonest and the most frequently
applied nucleic acid-based test. PCR testing has increased the sensitivity of detection of many organisms, such as *C. trachomatis* and Mycoplasmas. PCR assay showed a greater sensitivity than culture method in detecting *Ureaplasma* spp. in endotracheal aspirate or nasopharyngeal fluid samples from neonates [40]. In multiplex PCR, several independent amplifications are carried out simultaneously in one tube with a mixture of primers. Studies have indicated that increase in the number of targets in one reaction resulted in reduced or loss of sensitivity [75].

While conventional PCR measures the end PCR product using gels or other method, real-time PCR uses fluorogenic probes which allows amplification and detection to occur simultaneously [76]. Traditional PCR assays are gradually being replaced by real-time formats in which the same targets may be used. Sensitivity and specificity of real-time PCR has been reported to be identical to that of conventional PCR for *M. pneumoniae* [77, 78], however Xiao et al. (2010) [45] and Cao et al. (2007) [46] reported the test as superior for the detection of *U. urealyticum* and *U. parvum*. Although PCR is sensitive, this assay is not easily affordable and available as diagnostic tool especially in developing countries. Moreover, it is not a standardized test. This can prevent confirmation of diagnosis of congenital pneumonia caused by atypical bacteria.

**Treatment**

**Antibiotic and Supportive Care**

A positive isolation of organisms by culture or PCR assay from a normally sterile site in newborn infants with evidence of infectious inflammation is justified for treatment [28]. Antibiotics are a vital part of managing newborns with pneumonia. Except for *C. trachomatis*, making specific recommendations in terms of dosage and duration for treating genital mycoplasma (including ureaplasma and mycoplasma) infections in neonates is particularly difficult in view of the fact that the spectrum of the disease in this population has not been fully described and there are very few clinical studies indicating in vivo efficacy of antibiotics [79]. In general, macrolides, fluoroquinolones and tetracyclines are drugs of choice for atypical infections. However, fluoroquinolones and tetracyclines are not allowed in neonatal and pediatric settings due to potential toxicity [29]. Duration of antimicrobial treatment depends on the clinical, radiological and microbiological response of the infants, varying between 5 days to 2 weeks [79].

Congenital pneumonia caused by *C. trachomatis* is treated with a macrolide orally. Oral erythromycin or ethylsuccinate 50mg/kg/day in 4 divided doses for 14 days is recommended [79]. A failure rate of about 20% has been reported in infants with Chlamydia pneumonia treated with oral erythromycin, thus, requiring a second course of therapy [80]. To date, fluoroquinolones or clarithromycin are alternatives to erythromycin. Compliance and tolerance with erythromycin in newborns are a frequent problem. In the event of intolerance, oral sulfisoxazole at a dose of 150mg/kg/day in 4 divided doses is sufficient after the immediate newborn period [81]. For ureaplasmal respiratory infections in neonates, erythromycin and new-generation macrolide such as azithromycin and clarithromycin are effective, but treatment failures are known to occur [50, 81]. On the other hand, *M. hominis* is generally, susceptible to tetracylines, fluoroquinolones and clindamycin [82].

Equally important in the management of congenital pneumonia are supportive measures. Respiratory insufficiency is often linked to infants with congenital pneumonia, hence, the need for ventilatory support. The use of ventilator support requires precautions to ensure that the airway pressure required to attain alveolar stability interfere as little as possible with alveolar perfusion, myocardial function and venous return. Other supportive measures include appropriate use of inotropes, meticulous fluid therapy to ensure electrolyte balance and nutrition by proper breast feeding. Surfactant therapy could be useful in preterm infants since lung effluents has been reported to have disturbed surface properties despite the presence of surfactant in sufficient amount [83].

**Prevention**

A major preventive measure for congenital pneumonia is active management of premature rupture of maternal chorioamnionotic membranes. In a review of 14 randomized controlled trials, administration of antibiotics after premature rupture of membranes was associated with a delay in delivery, reduction in maternal infection, chorioamnionitis and neonatal infections [84]. Prenatal screening and treatment of pregnant women, especially those ages <25 years which are at high risk is the most effective strategy for preventing neonatal chlamydidal infections [85].
Conclusion

Congenital pneumonia is a common cause of significant morbidity and mortality in neonates, especially among preterm infants. Congenital pneumonia should be suspected in any newborn infant with clinical features such as respiratory distress present at birth or shortly after birth and/or a chest radiographic presentation indicative of pneumonia. Atypical bacteria are not common causes of the condition and should be suspected in infants with persistent pneumonia not responding to WHO recommended first line antibiotics. Consequently, appropriate antibiotic administration including supportive care should be started while proper techniques to identify these organisms are performed.

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