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Treatment of Community-Acquired Lower Respiratory Tract Infections during Pregnancy

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Abstract

The incidence of lower respiratory tract infection (LRTI) in women of child-bearing age is approximately 64 per 1000 population. The spectrum of illness ranges from acute bronchitis, which is very common, through influenza virus infection and exacerbations of underlying lung disease, to pneumonia, which, fortunately is uncommon (<1.5% LRTI), but can be severe.

Acute bronchitis is generally mild, self-limiting and usually does not require antibacterial therapy. Influenza virus infection in pregnant women has been recently related to increased hospitalization for acute cardiorespiratory conditions. At present, the safety of the newer neuraminidase inhibitors for the treatment of influenza virus

infection has not been established in pregnancy and they are not routinely recommended. In influenza virus infection complicated by pneumonia, antibacterial agents active against *Staphylococcus aureus* and *Streptococcus pneumoniae* superinfection should be used.

There are few data on infective complications of asthma or COPD in pregnancy. The latter is rare, as patients with COPD are usually male and aged over 45 years. Management is the same as for nonpregnant patients.

The incidence and mortality of pneumonia in pregnancy is similar to that in nonpregnant patients. Infants born to pregnant patients with pneumonia have been found to be born earlier and weigh less than controls. Risk factors for the development of pneumonia include anemia, asthma and use of antepartum corticosteroids and tocolytic agents. Based on the few available studies, the main pathogens causing pneumonia are *S. pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae* and viruses. β-Lactam and macrolide antibiotics therefore remain the antibiotics of choice in terms of both pathogen coverage and safety in pregnancy. In HIV-infected pregnant patients, recurrent bacterial pneumonia, but not *Pneumocystis carinii* pneumonia (PCP), is more common than in nonpregnant patients. Trimethoprim/sulfamethoxazole (cotrimoxazole) has not definitely been associated with adverse clinical outcomes despite theoretical risks. Currently it is still the treatment of choice in PCP, where mortality remains high.

In conclusion, there are few data specifically related to pregnant women with different types of LRTI. Where data are available, no significant differences compared with nonpregnant patients have been identified. In considering the use of any therapeutic agent or investigation in pregnant patients with LRTI, safety aspects must be carefully weighed against potential benefit. Otherwise, management strategies should not differ from those for nonpregnant patients. Further research in this area is warranted.

In recent years, much effort has been devoted to improving management strategies in community-acquired lower respiratory tract infections (LRTIs) with emphasis on reducing the inappropriate use of antibacterials and the chance of inducing resistance. For the clinician managing pregnant patients, these public health concerns run alongside the common concern that LRTI in pregnant patients may be more frequent, exhibit atypical features and run a more severe course or may be more difficult to treat than that in nonpregnant patients, in terms of using suitable antimicrobial agents.

1. Changes in Pregnancy

1.1 Physical Changes

The physical changes affecting the respiratory system during pregnancy are well recognized and include elevation of the diaphragm by up to 4cm, splaying of the thoracic cage with a 2cm increase in transverse diameter of the chest and a 5–7cm increase in circumference of the thoracic cage as a result of relaxation of the ligamentous attachments of the ribs due to the enlarging uterus.[1] Functional residual capacity is decreased by 10–25%, the largest reduction occurring in the supine position during the latter stages of pregnancy. Premature airway closure and an increase in lung water and oxygen consumption have also been noted.[2]

1.2 Immune Status

Delicate changes in predominantly the cellular components of the maternal immune system occur to enable survival of the fetus with its complement of 'foreign' paternal antigens. Decreases occur in proliferative antibody responses to soluble antigens, cell-mediated cytotoxicity, numbers of helper T lymphocytes and natural killer cell activity.[3-7]

Soluble factors and hormones, such as progesterone, human chorionic gonadotropin, α-fetoprotein and cortisol, are also present in maternal serum in concentrations that can mediate immunosuppression.[6] Humoral immunity on the other hand appears to be unaffected, with the observed changes in levels of antibodies in later pregnancy probably reflecting the effects of hemodilution.[8]

Taken together, there is a theoretical risk that the physical changes to the respiratory system may adversely affect the mother's ability to clear secretions and increase her vulnerability to respiratory tract infections, while the changes in maternal cellular immunity could potentiate the risk from infection, especially by viral and fungal pathogens. However, robust evidence substantiating these fears is lacking.

2. Use of Antibacterials during Pregnancy

When considering treatment of LRTIs with antimicrobial agents during pregnancy, the following factors should be considered: the severity of the maternal infection; the consequences of

failing to treat the mother; the effect of pregnancy on drug pharmacokinetics; and the potential fetotoxicity of the drugs.

General principles of prescribing during pregnancy are to consider the period of gestation, avoid new drugs, use the lowest effective dose of drug and minimize the treatment period, and use a single drug if possible. A gradual increase in renal function and an increased volume of distribution during pregnancy can give rise to decreased plasma drug concentrations.[9] Conversely, protein binding falls, thereby increasing the free (active) fraction of the drug.

As regards reports of teratogenicity, these need to be compared against a background incidence of major malformations in the general population of 2–3%.[10] Drugs and chemicals are thought to account for only 4–6% of these malformations. The period of maximum susceptibility for most structural defects is the first 10 weeks after conception (i.e. up to 12 weeks pregnancy).

3. Antibacterial Use in Breast-Feeding Mothers

Three potential problems exist for the infant when nursing mothers are treated with antibacterials. These consists of modification of bowel flora, direct effects on the infant (e.g. allergy or sensitization) and interference with the interpretation of culture results if a workup for fever in the neonate is required.[6] Neonates (particularly premature infants) are at greatest risk from accumulation of drugs in the breast milk because of their immature excretory functions.

4. Non-Pneumonic Lower Respiratory Tract Infection (LRTI)

There is currently no consistent and widely accepted definition of LRTI.[11] In its broadest sense, LRTI is characterized by an acute illness with cough as its cardinal symptom, which is not attributable to an underlying distinct illness such as asthma. This loose description embraces terms such as acute bronchitis,[12,13] middle respiratory tract infection,[14] lower respiratory tract illness[15] and lower respiratory tract infection.[16] Community-acquired pneumonia (CAP) can be readily distinguished from non-pneumonic LRTI by the presence of shadowing, consistent with infection on a chest x-ray and is therefore discussed separately.

4.1 Incidence

Visits by adults to primary-care physicians for cough in the US are very common and have increased from 5.5 million office visits in 1980 to 10.2 million in 1994.[17] Most of these patients are women (60%) and 75% are younger than 65 years of age. Acute bronchitis accounts for approximately 42% of these visits, about 75% of ambulatory antibacterial prescriptions and about 11% of total antibacterial prescriptions for adults in the US.[18,19] In a British study, using a standard definition for acute lower bronchitis or lower respiratory tract illness, the incidence of lower respiratory tract illness in women aged 16–39 years was found to be 64 per 1000 population, almost twice the incidence in men of a similar age group (36 per 1000 population).[15] The clinical burden of community-acquired LRTI and its contribution to antibacterial use is therefore enormous, with CAP requiring hospital admission representing only the tip of the iceberg.[20]

4.2 Etiology

There have been few robust studies examining the pathogens associated with non-pneumonic LRTI. Viruses are generally considered the main pathogens in acute bronchitis.[21,22] Rhinoviruses, coronaviruses, influenza viruses, adenoviruses, parainfluenza viruses and respiratory syncytial virus have all been implicated.[23,24] The exact role of atypical pathogens, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae,* and of *Streptococcus pneumoniae* is unclear. In some studies, these pathogens have been implicated in 6% or less of patients.[25] On the other hand, in a series of studies performed in Nottingham, UK,[15,16,26,27] using comprehensive microbiological tests in well defined cohorts of patients representing the spectrum of community-acquired LRTI, *S. pneumoniae*, *C. pneumoniae* and *M. pneumoniae* were identified with similar frequency in non-pneumonic LRTI and pneumonia (figure 1). Distinguishing between secondary bacterial infection, colonization and primary infection is difficult and is reflected in the uncertainty concerning the role of identified bacterial pathogens in non-pneumonic LRTI.

4.3 Outcome

Acute bronchitis is generally a self-limiting disease. Verheij et al.[13] reported that at presentation, 33% of patients were staying in bed because of symptoms, 35% had stopped daily work and 69% had problems with physical activity. Corresponding percentages 2 weeks later were 4%, 15% and 29%, respectively. Reconsultation rates in the UK are high, with one in every five patients arranging to see their general practitioner again for the same illness.[15] However, severe disease is unusual. In one analysis of LRTI in England and Wales, only 1.4% of patients required hospital admission.[28]

Clinical studies, randomized, controlled trials and subsequent meta-analyses examining the role of antibacterials in patients with acute bronchitis have found them to be of little meaningful clinical benefit.[29,30] A recent Cochrane review which included over 750 patients aged 8 years and older from nine trials found that, at follow-up, patients who received antibacterials for acute bronchi-

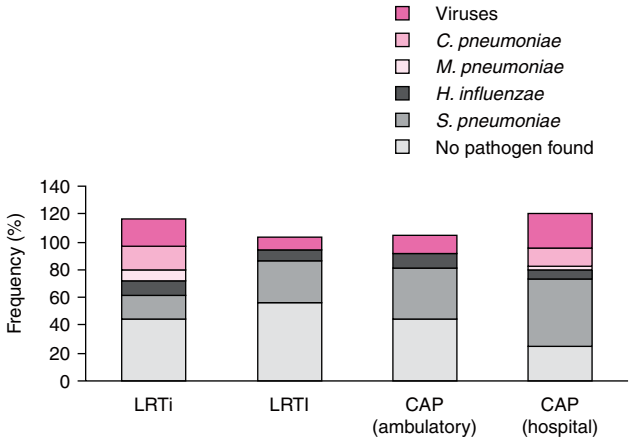

Fig. 1. Frequency of selected pathogens across the spectrum of lower respiratory tract infection (LRTI) from studies performed in Nottingham, UK. Totals are greater than 100% because of the identification of more than one pathogen in some individuals. Tests for *Chlamydiae pneumoniae* were not performed in studies on patients with LRTI and in ambulatory patients with community-acquired pneumonia (ambulatory CAP). CAP (ambulatory)[26] patients showed symptoms of LRTI with focal chest signs; CAP (hospital)[27] patients showed symptoms of LRTI with radiographic confirmation of pneumonic shadowing; LRTi[15] was defined as an acute illness in a previously well patient with cough as the cardinal symptom and at least one other lower respiratory tract symptom and LRTI[16] was defined as the presence of productive cough associated with another symptom or sign of LRTI plus constitutional symptoms and prescription of antibiotics for the illness.

tis were less likely to have a cough (relative risk [RR] 0.64, 95% CI 0.49–0.85) or abnormal lung findings (RR 0.48, 95% CI 0.26–0.89).[31] However, there were no significant differences between treated and non-treated groups for presence of night cough, productive cough or activity limitations at follow-up or in the mean duration of activity limitations. Significantly more adverse effects such as nausea, vomiting, headache, skin rash or vaginitis were reported by patients treated with antibacterials (RR 1.48, 95% CI 1.02–2.14).

4.4 Treatment of Pregnant Patients with LRTI

No studies have specifically addressed the issue of LRTI in pregnancy. In the absence of conflicting data, management strategies that have been developed for non-pregnant patients should be applied equally to pregnant patients.

In line with published guidelines, we do not recommend the use of antibacterials for most patients with acute bronchitis.[32,33] In our opinion, any modest benefit accrued from their use is outweighed by the disadvantages in relation to the promotion of antibacterial resistance, their adverse effects and their safety in pregnancy. Instead, we recommend the adoption of specific behavioral and multifactorial strategies aimed at educating patients regarding the normally self-limiting nature of acute bronchitis.[23] This is not to say that antibacterials are never indicated in the treatment of acute bronchitis.[34] There will be a proportion of patients, about 20%, where the physician is confident that antibacterials are indicated, usually because of the presence of factors such as focal chest signs, older age of patient and coexisting disease and generally how ill the patient appears.[35,36]

Some pregnant patients may wish to avail themselves of over-the-counter cough suppressants for symptom control even though there is currently no good evidence for their effectiveness.[37] Dextromethorphan, an active ingredient in many antitussive remedies, has been hypothesized, in a study in chick embryos, to be associated with neural tube defects. However, this risk has not been substantiated by a recent case-control study involving 184 pregnant women, 128 of whom were exposed to dextromethorphan in the first trimester.[38] There were six (3.2%) major malformations in the study group compared with five (2.7%) in the control group. No cases of neural tube defects were reported in the study group. This study had 80% power to detect a 3.5-fold increase in the rate of malformations. Other theoretical concerns regarding postnatal neurodevelopment have been raised but as yet remain untested. Therefore, based on current knowledge, there is no good evidence to either support or discourage the routine use of cough suppressants for symptom control in non-pneumonic LRTI in pregnant patients.

5. Influenza Virus Infection

Influenza is characterized by the abrupt onset of fever, headache, generalized myalgia, extreme malaise, nonproductive cough, sore throat and rhinitis. When influenza virus is circulating in a community, approximately two-thirds of persons with relevant signs and symptoms have been found to have laboratory-confirmed influenza virus infection.[39] Of adult patients with influenza-like symptoms, fewer than half seek medical attention, and time taken off work ranges from 0.8 to 4 days.[40] Uncomplicated influenza virus infection is usually self-limiting, and in previously healthy adults, alleviation of all major symptoms occurs in about 5 days.[41] When complicated by pneumonia, fulminant respiratory failure may develop. Secondary bacterial infection by *Staphylococcus aureus* and *S. pneumoniae* is well recognized.

Historically, influenza virus infection in pregnant patients has been associated with more severe disease. During the worldwide pandemic of 1918, maternal mortality was 30%, rising to 50% when complicated by pneumonia. In the Asian flu epidemic of 1957–58, almost half of the women of child-bearing age who died in Minnesota and New York, USA, were pregnant. In New York, this represented 10% of all influenza deaths.[42,43] Mortality was highest in women in the third trimester. Post-mortem studies

showed that pregnant women most commonly died of fulminant primary viral pneumonia, whereas nonpregnant patients died of secondary bacterial infection.[44] Subsequent to 1958, excess mortality during interpandemic periods have not been documented. An epidemiological study measuring hospitalizations for or death from acute cardiopulmonary conditions during influenza seasons found that women aged 15–44 years in their third trimester of pregnancy were 3–4 times more likely to be hospitalized than postpartum controls.[45] In a seroepidemiological study, Irving et al.[46] used a 4-fold rise in antibody titer to determine infection with the influenza virus and identified intercurrent influenza virus infection in 182 (11%) of 1659 women in the second and third trimesters of pregnancy. In that study, no significant increase in specific medical complications was observed, but overall there was a significantly greater number of fetal, medical and obstetric complications than in the controls. Together these data suggest that influenza virus infection is common during pregnancy, and while there does not appear to be the same magnitude of risk of mortality as noted in earlier epidemics, hospital admission is more likely, particularly in the late stages of pregnancy.

Transplacental passage of influenza A virus has been reported but does not appear to be common.[43] In the study by Irving et al.,[46] none of 138 samples of cord sera from patients infected with influenza virus during pregnancy was positive for influenza A virus-specific IgM. The authors concluded that transplacental transfer of influenza would be a rare outcome of maternal infection in the second or third trimester. Whether influenza virus can cause congenital malformations is under debate, but seems unlikely. Although circulatory defects and central nervous system malformations have been described, a review of the literature could not find convincing evidence for a definite association with pregnancy.[47]

5.1 Treatment of Influenza Virus Infection in Pregnancy

The efficacy and safety of the M2 ion channel inhibitors (amantadine and rimantadine) and of the newer neuraminidase inhibitors (zanamivir and oseltamivir) in pregnancy have not been clearly established. There are several case studies of congenital abnormalities following exposure to amantadine in pregnancy. These include cardiac anomalies (e.g. single ventricle with pulmonary atresia, tetralogy of Fallot) and tibial hemimelia.[48-50] Levy et al.[51] reported one woman who gave birth to two normal infants while on treatment with amantadine. There are no published reports of the use of rimantadine, zanamivir or oseltamivir during human pregnancy. In pregnant rats and rabbits treated with high oral doses of oseltamivir, maternal toxicity and an increase in minor skeletal variations were noted.[52]

Based on the above evidence, the routine use of amantadine, rimantadine and the newer neuraminidase inhibitors for the treatment of influenza virus infection in pregnancy cannot be recommended. Indeed, restriction of the use of these agents to the third trimester may be reasonable in view of the relatively higher influenza mortality during this period compared with the first and second trimesters.

In influenza virus infection complicated by pneumonia, the use of antibacterial agents with activity against the likely pathogens that cause secondary bacterial infection is recommended. Antiviral agents may be considered although they are of unproven benefit. Two instances of the use of amantadine to treat influenza virus infection in pregnant women have been reported.[53,54] However, the potential teratogenicity of the M2 inhibitors (amantadine and rimantadine) in contrast to the relative lack of any teratogenicity or reproductive toxicity of the neuraminidase inhibitors (zanamivir and oseltamivir) in laboratory animals make the latter agents the preferred choice where indicated.[55] In all instances, the uncertain benefit must be weighed against the concerns regarding safety.

5.2 Prevention

In the UK, influenza virus vaccine is not recommended for pregnant women who would not otherwise qualify for immunization according to Departments of Health guidelines.[56] In contrast, in the US, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention recently broadened their recommendations for vaccination against influenza virus infection to include women who will be in the second or third trimester of pregnancy during the influenza season.[57] This change was influenced by the recent report of increased rates of hospital admissions for acute cardiopulmonary complications in pregnant women, similar to that in nonpregnant women with a high-risk condition.[58] The influenza vaccine currently available in the US contains three strains (two type A and one type B). The vaccine is made from highly purified, egg-grown viruses that have been inactivated (i.e. made noninfectious) and is considered to have a good safety profile during any stage of pregnancy. A study involving over 2000 pregnant women demonstrated no adverse fetal effects associated with the vaccine.[59] However, additional data are still needed, and in the meantime, avoidance of the first trimester where possible seems prudent.

6. Community-Acquired Pneumonia

6.1 Incidence

There are few studies on treatment of pneumonia during pregnancy. Most studies are retrospective in design and include few

Table I. Incidence and mortality of pneumonia in pregnancy (reproduced from Lim et al.[67] Thorax 2001; 56 (5): 398-405 with permission from the BMJ Publishing Group)

Author	Year	No. of cases	Incidence per 1000 deliveries	Maternal mortality (%)	Preterm delivery (%)
Finland & Dublin[60]	1939	164	6.3	18/74 (24)	32/74 (43)
Hopwood[61]	1965	23	8.5	2/23 (8.7)	Not reported
Benedetti et al.[62]	1982	39	0.44	0/39 (0)	3/20 (15)
Madinger et al.[63]	1989	25	0.78	1/25 (4)	9/21 (43)
Berkowitz & LaSala[64]	1990	25	2.7	0/25 (0)	1/18 (6)
Richey et al.[65]	1994	71	1.2	2/71 (3)	1/71 (1)
Yost et al.[66]	2000	133	1.5	0/133 (0)	14/107 (13)

patients (table I). In the years before 1965, the recorded incidence of pneumonia in pregnancy was 6.3 to 8.5 per 1000 deliveries,[60,61] which decreased in the 1970s and early 1980s to between 0.44 and 0.78 per 1000 deliveries, presumably because of the introduction of antibacterials and improvements in obstetric care.[62,63] More recently, a small increase in the incidence of pneumonia to 1.2–2.7 per 1000 deliveries has been noted.[64-66] As these study cohorts may not be directly comparable, it is unclear whether this reported increase in incidence in the most recent studies is a true change reflecting the higher proportion of pregnant women with chronic medical conditions and therefore susceptible to pneumonia, as has been proposed.[64]

Perhaps more importantly, the incidence of pneumonia during pregnancy reported in recent studies do not differ from the estimated incidence of CAP in young nonpregnant adults. In a Finnish population-based study, the age-specific incidence of community-acquired pneumonia per year was 6 per 1000 population for persons aged 15–59 years. The incidence was higher in men than in women.[68] Other estimates from the US and UK are similar; 5–8 per 1000 population per year for persons aged 15–59 and 5 per 1000 for persons aged 15–79 years, respectively.[26,69]

6.2 Mortality

Pneumonia has been cited as the third most frequent cause of indirect obstetric death in North America and is the most frequent cause of fatal non-obstetric infection.[70,71] However, in the UK, of 134 indirect deaths during the period 1994 to 1996 (equivalent to a rate of 6.1 per 100 000 maternities), only six were due to pneumonia. Three of the six deaths due to pneumonia were in patients with concurrent cystic fibrosis. Therefore, in absolute terms, maternal death from pneumonia remains rare in the UK. This is reflected in the reported maternal mortality of 0–4%, which is similar to the mortality from CAP in young hospitalized nonpregnant adults.[72,73]

6.3 Fetal Outcome

Pregnant patients with pneumonia are significantly more likely to deliver before 34 weeks gestation and preterm delivery has been reported to occur in up to 43% of cases.[74] Also, infants born to mothers with pneumonia weigh significantly less than controls. One study found a difference of 150g in birth weight and a difference of 8% (16 vs 8%) in the frequency of low birth weight (≤2500g) in cases compared with controls.[66] Perinatal mortality appears to be unaffected.

6.4 Risk Factors for Development of Pneumonia

Among pregnant women, maternal age and parity have not been shown to be associated with pneumonia.[66] On the other hand, gestational age appears to be important. The risk of pneumonia during pregnancy is lowest in the first trimester, with 0–16% of cases occurring during this period. Mean gestational age at admission for pneumonia ranges from 24 to 31 weeks.[63,66]

The presence of anemia as a risk factor for pneumonia was first proposed by Benedetti et al.,[62] who noted that 19 (47%) of 37 pregnant patients with pneumonia had a hemoglobin level of 10 g/dL or less. A further association between asthma and pneumonia during pregnancy was suggested by Richey et al.,[65] who noted that in their series, 17 (24%) of 71 patients had asthma. In a recent case-control study comprising 59 cases and 118 controls, both of these factors (haematocrit <30% and history of asthma) were confirmed to be independently associated with a 5-fold increased risk for the development of pneumonia.[74]

Antepartum corticosteroids given to reduce morbidity and mortality in the premature neonate have been found to be associated with a higher rate of infectious disease (65% cases compared with 17.5% controls) with serious bacterial infections occurring in 9 (24%) of 37 cases (4 of these pneumonias) compared with 0 of 74 controls.[75] More specifically, antepartum corticosteroids have also been identified as being independently associated with pneumonia during pregnancy.[74]

Tocolytics, administered to halt labor, have been associated with the development of pneumonia and, through the promotion of pulmonary edema, also increase the risk of subsequent respiratory insufficiency.[74,76] They are therefore not recommended for use in pregnant patients with pneumonia.[77]

No other risk factors have been definitely identified from studies of pregnant patients with pneumonia. However, large studies in nonpregnant adults have found smoking to be strongly associated with the development of pneumonia and also invasive pneumococcal disease.[78,79] Such an association would be expected to hold true for pregnant women as well and represents an important risk factor that is potentially modifiable. This is especially relevant, since up to a third of pregnant women smoke.[80]

6.5 Diagnosis

The diagnosis of pneumonia in a pregnant patient is not always easy. In Madinger and colleagues'[63] series of 25 patients, 5 (20%) were initially misdiagnosed, 1 was initially treated for suspected pyelonephritis, 2 had surgery for suspected appendicitis and 2 were thought to have preterm labor with no predisposing cause identified. Similarly, Yost et al.[66] found that 14 (10.5%) of 133 patients were initially misdiagnosed.

One of the main challenges in diagnosing pneumonia during pregnancy is differentiating between respiratory symptoms related to physiological changes and those related to disease. Dyspnea, in particular, is common during pregnancy. It is experienced by 50% of women at 19 weeks gestation and up to 76% at 31 weeks.[81] Physiologic dyspnea characteristically begins early in pregnancy and improves or plateaus as term approaches. It does not usually interfere with daily activities and rarely occurs at rest. Clinical experience and a high index of suspicion are therefore crucial in identifying patients with disproportionate dyspnea in whom pneumonia must be considered. Associated cough should arouse clinical suspicion of an underlying cause. Clinical examination may reveal abnormal chest signs. However, a firm diagnosis of pneumonia can be made only with the aid of a chest radiograph. Therefore, given the appropriate clinical scenario, the risk of misdiagnosing pneumonia is greater than the small risk from radiation exposure.[82] The differential diagnosis of alveolar shadowing on a chest x-ray in the context of pregnancy includes noncardiogenic pulmonary edema in preeclampsia and eclampsia, pulmonary edema secondary to tocolytic agents, aspiration pneumonitis and, rarely, choriocarcinoma with pulmonary metastases.[83] Such conditions are rare in the first trimester and an argument could be made for not performing chest x-rays at this stage in a pregnant woman who presents with the clinical features of mild pneumonia and improves satisfactorily with empiric antibacterials.

6.6 Pathogens

There are no detailed studies of the microbial agents involved in pneumonia during pregnancy. The available data are derived mainly from observational, and often retrospective, studies where only routine microbiological investigations have been used. Sputum and blood cultures were the main methods of diagnosis. Based on four recent studies, the range of pathogens identified is similar to that described for hospitalized nonpregnant adults with CAP (table II).

S. pneumoniae was the most common organism identified, followed by *H. influenzae*. There were few cases of infection by atypical pathogens, such as *M. pneumoniae*, or viruses. This may be partly explained by the inconsistent use of serological tests. Infection with *Legionella* spp. has been documented but is rare. There is no good evidence to suggest an increased risk of Legionnaire's disease during pregnancy or any increase in severity of illness.

Coxiella burnetii (Q fever) is occasionally implicated in pneumonia during pregnancy. In the largest reported series of 1383 infections identified over a 13-year period, 15 patients had Q fever during pregnancy.[84] These patients reported significantly more

Table II. Pathogens implicated in community-acquired pneumonia during pregnancy (n = 161)[62-65]

	No. patients (%)
Bacterial pathogens	
Streptococcus pneumoniae	28 (17)
Haemophilus influenzae	9 (6)
Staphylococcus aureus	2 (1.2)
Gram-negative enteric bacilli	2 (1.2)
Group A β-hemolytic streptococci	1 (0.6)
Atypical pathogens	
Legionella spp.	2 (1.2)
Mycoplasma spp.	5 (3)
Viruses	
Influenza A or B virus	3 (2)
Measles	1 (0.6)
Varicella	5 (3)
Others	
Mycobacterium tuberculosis	2 (1.2)
Mycobacterium avium complex	1 (0.6)
Pneumocystis carinii	1 (0.6)
Unknown	99 (61)

contact with farm or newborn animals than other patients with acute Q fever. Fetal outcome was poor. The fetus was aborted in ten patients and born prematurely in three. Most human infection with *C. burnetii* is due to inhalation of the organism from aerosols generated by pregnant farm animals.[85] *C. burnetii* has been isolated from the placentas of asymptomatic women, and human-to-human transmission during delivery of the fetus and placenta has been reported.[86] Hence, although Q fever during pregnancy is rare, it is important to make the diagnosis in view of the impact on fetal outcome and the wider public health issues. In addition, pregnant women are advised to avoid being involved with lambing or calving.

Anaerobic organisms are not usually implicated in CAP unless there is evidence of aspiration. In the pregnant patient, anaerobic infection may need to be considered in pneumonia occurring during the peripartum period.

6.7 Treatment

6.7.1 Severity Assessment

The most important decision in the management of CAP is where to treat the patient. This is perhaps even more important for pregnant patients. Numerous severity assessment tools to help guide this decision have been evaluated and specific recommendations are detailed in the guidelines on management of CAP issued by national bodies.[33,87-89] It is outside the scope of this paper to discuss the relative merits of the different severity assessment tools recommended. Common to all is the fact that these tools were developed mainly in hospitalized nonpregnant adults and there are no data specifically relating to pregnant patients. Yost et al.[66] retrospectively applied the 1993 American Thoracic Society (ATS) guidelines to 119 pregnant women with pneumonia admitted to hospital. Twenty-two (96%) of the 23 women who had a complicated course were correctly identified, based on the presence of any of the following: coexisting illness (including asthma, diabetes, COPD, heart failure, chronic renal failure, chronic liver disease or a postsplenectomy state); altered mental status; respiratory rate >30/min; temperature >38.3°C; white cell count <4000 or >30 000 cells/mm^3; arterial oxygen tension (PaO_2) <60mm Hg or arterial carbon dioxide tension >50mm Hg; creatinine >1.2 mg/dL or chest radiographic evidence of multilobar involvement or pleural effusion. The ATS guidelines have since been updated and we recommend that where possible, national guidelines are consulted. We favor the use of the severity assessment tool detailed in the 2001 British Thoracic Society CAP management guidelines in view of its simplicity and hence ready applicability (figure 2). Ultimately, clinical judgement exercised at the individual level remains essential.

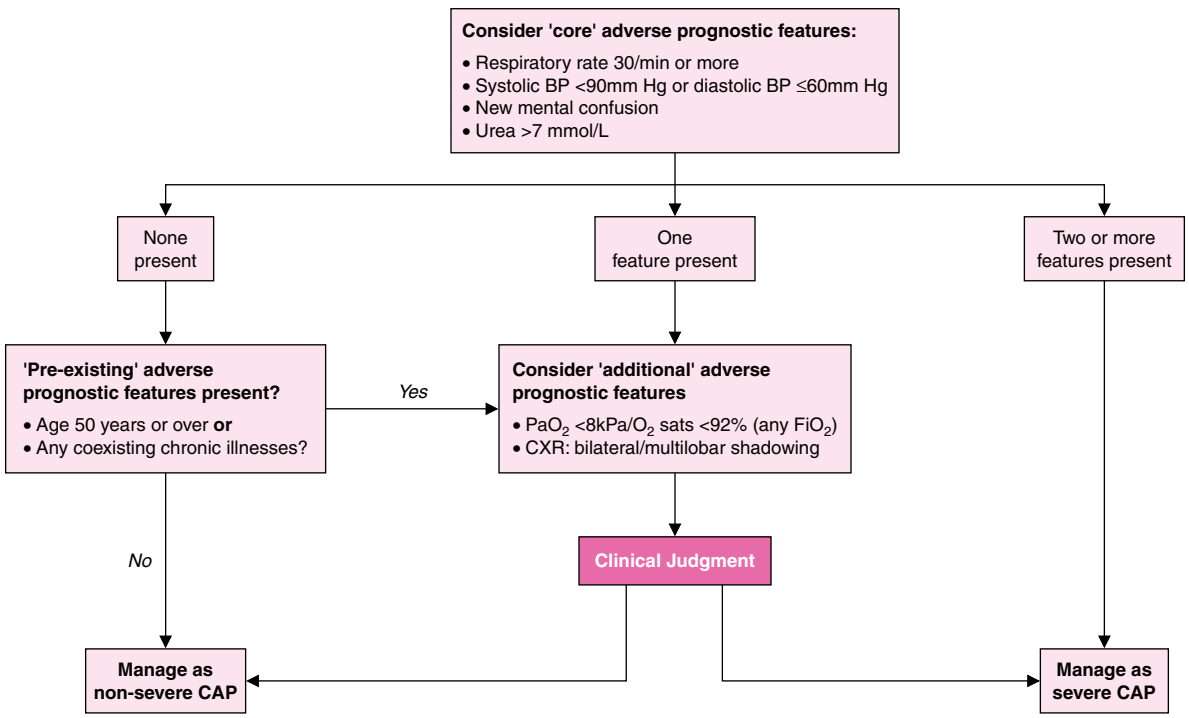

Fig. 2. Severity assessment in the management of CAP (reproduced from the British Thoracic Society,[89] Thorax 2001; 56 Suppl. 4: IV1-64, with permission from the BMJ Publishing Group). **CAP** = community-acquired pneumonia; **CXR** = chest x-ray; **FiO_2** = inspired oxygen fraction; **PaO_2** = oxygen partial pressure.

6.7.2 Appropriate Antimicrobial Agents

In the absence of severe maternal toxicity there is no evidence to suggest that penicillins are associated with an increased risk of malformations or other forms of fetal toxicity in human pregnancy. If the mother is allergic to penicillin, any fetal toxicity is likely to be secondary to maternal toxicity.[90] In a paired analysis of cases with congenital abnormalities and matched controls, treatment of pregnant patients with seven studied cephalosporins did not seem to present a detectable teratogenic risk to the fetus.[91]

Erythromycin is not associated with an increased risk of malformations or other forms of fetal toxicity in human pregnancy.[90]

In a prospective, controlled, multicenter study, 122 of 157 women were exposed to clarithromycin during the first trimester.[92] There were no significant differences between exposed and unexposed groups in the rates of major and minor malformations. The higher rate of reported spontaneous abortions in the exposed group warrants further study. In a retrospective surveillance study of 143 mothers and their 149 infants, five infants were identified with major malformations, three with minor malformations, and four with undescended testicles likely to resolve with time.[93] The observed rate of 3.4% (95% CI 0.5–6.3) for major malformations was not statistically significantly different from an expected rate of 2.8% based on earlier national data. There was no consistency across types of major malformations.

No congenital anomalies were observed among the infants of ten mothers who were treated with azithromycin during the first trimester of pregnancy in one series[52]. No adverse effects were observed in the infants of two women who were treated with azithromycin during the second trimester of pregnancy.[52]

The newer macrolides, clarithromycin and azithromycin, are reported to have fewer gastrointestinal adverse effects than erythromycin.[94] This is an important consideration in pregnant patients.

Exposure to tetracyclines prior to 12 weeks has not been associated with an increased risk of fetal toxicity. However, administration of tetracyclines in the second or third trimesters of pregnancy can cause yellow-brown staining and banding of the teeth of the child and reversible growth retardation of the long bones.[95] There may be up to a 40% depression of bone growth, especially of the fibula in preterm pregnancies. Although there are a number of case reports of congenital anomalies in human pregnancies following tetracycline use by the mother, the Collaborative Perinatal Project was not able to establish a causal relationship with tetracyclines among the children of 341 women treated with tetracycline during the first 4 lunar months of pregnancy.[90] Similarly, the frequency of congenital anomalies was not increased among the children of 1336 women treated with tetracycline at any time during pregnancy. A possible association with minor defects was suggested, but there was only a small number of cases, mostly inguinal hernia; therefore no causal relationship could be established.

Although no specific data are available, it is assumed that doxycycline, like other tetracyclines, can also cause fetal staining of the teeth and depression of bone growth. A report from a Hungarian surveillance project identified 56 malformed infants whose mothers had used doxycycline in pregnancy. However, there was no convincing pattern of abnormalities and no relationship between drug use and the critical period of development of any of the malformations. The authors believed that the significant association between doxycycline use and total malformations could be attributed to recall bias and that the risk of doxycycline was very low.[52,96]

In summary, tetracyclines should generally be avoided in pregnancy

There are limited data available on the use of quinolones during human pregnancy. Quinolones have a high affinity for bone tissue, with arthralgia and tendonitis reported in adolescents and adults. Furthermore, young animals given ciprofloxacin developed arthropathy with cartilage erosion. No reports of this type of problem have been reported following *in utero* exposure in human pregnancy. The clinical significance of these findings for the fetus is not known. A review of 350 pregnancies with exposure to ciprofloxacin found no increased risk of either spontaneous abortion or congenital malformations. No specific syndrome of defects has been reported.[90]

Nevertheless, the use of quinolones in persons under 18 years old and in pregnant women is not routinely recommended.

Only a small number of reports involving human pregnancies have suggested that metronidazole may cause fetal toxicity.[97] Although the incidence of total malformations was apparently increased in neonates exposed to metronidazole during the first trimester, no pattern of defects was evident. One case report described two children exposed to metronidazole during the fifth to seventh gestational weeks who were born with midline facial defects.[97] The concordance between the defects noted in these two cases has been proposed as a significant indicator of a teratogenic effect that had been previously overlooked. In contrast to these observations, the accumulated data on more than 1300 births involving prenatal exposure to metronidazole suggest no increase in congenital anomalies.[98-101] In addition, a retrospective cohort study involving nearly 1400 exposed pregnancies did not detect an increase in congenital abnormality or low-birth-weight infants.[98]

No congenital anomalies in infants born to women who took vancomycin during pregnancy have been reported, in epidemiological studies. No evidence of auditory or renal damage was

found among ten infants whose mothers had been treated with vancomycin during the second or third trimester of pregnancy.[102]

No increase in abnormal outcomes was noted among the infants of 104 women treated with clindamycin in the second or third trimester of pregnancy, as part of a controlled trial of therapy to prevent low birth weight.[103] In a surveillance study of Michigan Medicaid recipients involving 229 101 pregnancies conducted between 1985 and 1992, 647 neonates had been exposed to clindamycin in the first trimester.[104] A total of 31 (4.8%) major birth defects were observed of which 28 were expected.

6.7.3 Suggested Treatments According to Disease Severity

Antibacterial therapy is usually empirical and the choice of antibiotics in the pregnant patient with CAP is influenced by disease severity and therefore site of treatment, likely pathogens involved based on local epidemiology, and drug safety. Suggested antibiotics for use in different patient groups stratified according to site of care and disease severity are given in table III. These are drawn from recently published guidelines by national bodies in the UK and US with some modification.

Apart from antibiotics, the appropriate administration of supplemental oxygen and intravenous fluids, where indicated, must not be ignored.

6.7.4 Vaccination

The pneumococcal vaccine is recommended for use in patients at high risk of developing severe pneumococcal infection.[105] These recommendations apply to some women of child-bearing age (e.g. patients with asplenia or sickle-cell anemia). As the safety profile of the pneumococcal vaccine in pregnancy is untested, women at high risk of pneumococcal disease should ideally be vaccinated before pregnancy.

7. HIV Infection and Pneumonia

The prevalence of human immunodeficiency virus (HIV) infection in mothers living in London has risen from 0.032% in 1988 to 0.19% in 1996.[106] The majority (58%) are mothers infected through heterosexual contact. This trend is also evident in the US, where over 80% of women with AIDS are of reproductive age.[107] Bacterial infections are the most common respiratory complications in patients with HIV infection.[108] The reported incidence of bacterial pneumonia ranges from 5.5 to 12.5 per 100 person-years.[109-111] A Swiss cohort found that recurrent bacterial pneumonia was the only AIDS-defining event which was significantly more common in HIV-infected pregnant women compared with nonpregnant women (RR 8.0, 95% CI 1.7–37).[112] Otherwise, no robust evidence exists to indicate that community-acquired LRTI should behave any differently in HIV-infected pregnant women.

Although *Pneumocystis carinii* pneumonia (PCP) has not been shown to be more common in HIV-infected pregnant women than nonpregnant women, it is still the most common cause of AIDS-related death in pregnant women in the US.[113] A recent review of the literature identified 22 reported cases of PCP in pregnant women.[114] All had previously undiagnosed HIV infection. Clinical presentation of disease was not altered as reported previously.[115] However, maternal and fetal outcomes were dismal. Thirteen (59%) patients developed respiratory failure requiring mechanical ventilation and 11 (50%) patients died. There were five stillbirths and four other babies died shortly after delivery. Patients presenting in the third trimester appeared to have a better prognosis. These figures compare poorly with those for nonpregnant patients with HIV disease and PCP. Unfortunately, there is a lack of studies directly comparing HIV-infected pregnant women with nonpregnant women, and the more severe disease depicted in these case reports may reflect publication bias.

Table III. Suggested empirical treatments for pregnant patients with community-acquired pneumonia

Antibiotic	Comments
Home treated Amoxicillin 500mg–1.0g 8-hourly PO or new generation macrolide (e.g. clarithromycin 500mg 12-hourly PO)	The choice of monotherapy with an aminopenicillin or a macrolide depends on the local epidemiology. Reference to locally and nationally issued guidelines is recommended. Where penicillin-resistant *Streptococcus pneumoniae* infection is likely, higher-dose amoxicillin (1g 8-hourly) is recommended ± macrolide.
Hospital treated (non-severe) Amoxicillin 500mg–1.0g 8-hourly PO and new generation macrolide (e.g. clarithromycin 500mg 12-hourly PO)	The use of antipneumococcal fluoroquinolones as an alternative agent is not recommended in view of limited data regarding their safety during pregnancy.
Hospital treated (severe) Cefuroxime 1.5g 8-hourly IV and new generation macrolide (e.g. clarithromycin 500mg 12-hourly IV)	Alternatives to cefuroxime include cefotaxime and ceftriaxone

IV = intravenous; **PO** = oral.

Table IV. Summary of the safety of selected antimicrobials in pregnancy[a]

Antimicrobial	Safety in pregnancy	
	authors' classification	US FDA classification
Amantadine	▲	C
Rimantadine	×	C
Zanamivir	▲	C
Oseltamivir	×	C
Penicillins	✓	B
Cefalosporins	✓	B
Erythromycin	✓	B
Clarithromycin	▲	C
Azithromycin	▲	B
Tetracyclines	×	D
Quinolones	×	C
Metronidazole	✓	B
Vancomycin	▲	B
Clindamycin	✓	B
Trimethoprim/ sulfamethoxazole (cotrimoxazole)	▲	C
Pentamidine	×	C

a The drugs have been classified in the light of currently available evidence, and where information is scarce the drugs have been classified as requiring monitoring.

Key to authors' classification: ✓ = adverse effects may have been shown in preclinical animal studies but published human studies do not show any adverse effects; ▲ = animal studies have revealed adverse effects in the fetus and there are no controlled studies to determine risk; × = positive evidence of fetal risk but the benefits from use in pregnancy may be acceptable despite the risk; **B** = animal studies do not indicate a risk to the fetus and there are no controlled human studies, or animal studies do show an adverse effect on the fetus but well controlled studies in pregnant women have failed to demonstrate a risk to the fetus; **C** = studies have shown that the drug exerts animal teratogenic or embryocidal effects, but there are no controlled studies in women, or no studies are available in either animals or women; **D** = positive evidence of human fetal risk exists, but benefits in certain situations (e.g. life-threatening situations or serious diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks.

7.1 Treatment and Prevention

There is one case-control study of 6228 infants with congenital anomalies that reported a statistical association with maternal use of trimethoprim/sulfamethoxazole (cotrimoxazole) during pregnancy.[116] However, no characteristic pattern was observed among exposed infants who had multiple congenital anomalies. The author concluded that the association was unlikely to have resulted from a teratogenic effect of the drugs. There is also a theoretical risk of neural tube defects with trimethoprim/sulfamethoxazole due to its folate antagonist activity. Nevertheless, trimethoprim/sulfamethoxazole is the treatment of choice for all patients with PCP, regardless of disease severity and the risks from adverse drug effects. As with nonpregnant patients, adjunctive corticosteroids are indicated for patients with PCP pneumonia presenting with hypoxemia (PaO_2 <8.3 kPa). There is little experience with the use in pregnant patients of alternative agents active against *P. carinii*.

Chemoprophylaxis for PCP in HIV-infected pregnant women is recommended using trimethoprim/sulfamethoxazole. If there are concerns regarding the theoretical risks of teratogenicity, aerosolized pentamidine, which has minimal systemic absorption, may be used as an alternative agent during the first trimester.

8. Summary

Few studies have been performed examining the issue of community-acquired LRTI during pregnancy. Pneumonia is the best studied. Currently, there are few data to indicate that community-acquired LRTI present differently or are more severe during pregnancy. However, pregnancy poses special concerns regarding the risks from adverse drug effects. In general, management strategies developed for nonpregnant patients apply equally well to pregnant patients. Antibiotic options are more limited and in all instances, the benefits of antibiotic use must be weighed carefully against their risks and adverse effects. A summary of the safety of selected antimicrobials in pregnancy is provided in table IV.

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