British Thoracic Society Guidelines for the Management of Community

Acquired Pneumonia in Children: Update 2011

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Synopsis of Recommendations

Clinical Features

- Bacterial pneumonia should be considered in children when there is persistent or repetitive fever >38.5^{o}C together with chest recession and a raised respiratory rate. [D]

Investigations

- Chest radiography should not be considered a routine investigation in children thought to have community acquired pneumonia (CAP). [A-]
- Children with signs and symptoms of pneumonia who are not admitted to hospital should not have a chest radiograph. [A-]
- A lateral radiograph should not be performed routinely. [B-]
- Acute phase reactants are not of clinical utility in distinguishing viral from bacterial infections and should not routinely be tested. [A-]
- CRP is not useful in the management of uncomplicated pneumonia and should not be measured routinely. [A+]
- Microbiological diagnosis should be attempted in children with severe pneumonia, sufficient to require paediatric intensive care admission, or those with complications of CAP. [C]
- Microbiological investigations should not be considered routinely in those with milder disease or those treated in the community. [C]
- Microbiological methods used should include:
    - Blood culture. [C]
    - Nasopharyngeal secretions and/or nasal swabs for viral detection by PCR and/or immunofluorescence. [C]
    - Acute and convalescent serology for respiratory viruses, *Mycoplasma* and *Chlamydia*. [B+]
    - If present, pleural fluid should be sent for microscopy, culture, pneumococcal antigen detection and/or PCR. [C]
    - Urinary pneumococcal antigen detection should not be done in young children. [C]

Severity Assessment

- For a child in the community, re-consultation to the general practitioner with persistent fever, or parental concern about persistent fever, should prompt consideration of CAP. [D]
- For children with CAP, reassessment is important, whether in the community or in hospital. [D]
- Hypoxia (SaO2 <92%) in all children is an indication for hospital assessment and management. [B+]
- Auscultation revealing absent breath sounds with a dull percussion note should raise the possibility of a pneumonia complicated by effusion and should trigger a referral to hospital. [B-]
- A child in hospital should be reassessed medically if there is persistence of fever 48 hours after initiation of treatment, increased work of breathing or if the child is becoming distressed or agitated. [D]

General Management

- Families of children who are well enough to be cared for at home should be given information on managing pyrexia, preventing dehydration, and identifying any deterioration. [D]
- Patients whose oxygen saturation is 92% or less while breathing air should be treated with oxygen given by nasal cannulae, high flow delivery device, head box or face mask to maintain oxygen saturation above 92%. [B]
- Nasogastric tubes may compromise breathing and should therefore be avoided in severely ill children and especially in infants with small nasal passages. If use cannot be avoided, the smallest tube should be passed down the smallest nostril. [D]
- Plasma sodium, potassium, urea and/or creatinine should be measured at baseline and at least daily when on intravenous fluids. [C]
- Chest physiotherapy is not beneficial and should not be performed in children with pneumonia. [A-]

Antibiotic Management

- Children under 2 years, presenting with mild symptoms of lower respiratory tract infection need not be treated with antibiotics but should be reviewed if symptoms persist. A history of conjugate pneumococcal vaccination gives greater confidence to this decision. [C]
- As bacterial pneumonia cannot be clinically distinguished from viral, all other children with a clinical diagnosis of pneumonia should receive antibiotics. [C]
- Amoxicillin is first choice for oral antibiotic therapy in all children because it is effective against the majority of pathogens which cause CAP in this group, is well tolerated, and cheap. Alternatives are co-amoxiclav, cefaclor, erythromycin, azithromycin and clarithromycin. [B]
- Macrolide antibiotics may be added at any age if there is no response to first line empiric therapy. [D]
- Macrolide antibiotics should be used if either mycoplasma or chlamydia pneumonia is suspected (or in very severe disease). [D]
- Amoxicillin should be used as first line treatment at any age if *S. pneumoniae* is thought to be the likely pathogen. [B]
- If *Staph. aureus* is thought the likely pathogen, augmentin or a combination of flucloxacillin with amoxicillin, is appropriate. [D]
- In pneumonia associated with influenza, co-amoxiclav is recommended. [D]
- Antibiotics administered orally are safe and effective for children presenting with even severe CAP and are recommended. [A+]
- Intravenous antibiotics should be used in the treatment of pneumonia in children when the child is unable to tolerate oral fluids or absorb oral antibiotics (for example, because of vomiting) or presents with signs of sepsis or complicated pneumonia. [D]
- Appropriate intravenous antibiotics for severe pneumonia include amoxicillin, co-amoxiclav, cefuroxime, and cefotaxime/ceftriaxone. These can be rationalised if a microbiological diagnosis is made. [D]

- In a patient who is receiving intravenous antibiotic therapy for the treatment of CAP, oral treatment should be considered if there is clear evidence of improvement. [D]
- Children less than 2 years old, presenting with mild symptoms of lower respiratory tract infection who are unvaccinated or felt to require antibiotics, 3 days amoxicillin can be given. [B]
- All other children should have standard 5 day course amoxicillin in the absence of any short course evidence. [D]

Complications

- If a child remains pyrexial or unwell 48 hours after treatment has commenced, re-evaluation is necessary with consideration given to possible complications. [D]
- Children with severe pneumonia, empyema and lung abscesses should be followed up after discharge until they have recovered completely and their chest radiograph has returned to near normal. [D]

Follow up

- Follow-up radiography is not required in those who were previously healthy and who are recovering well, but should be considered in those with a round pneumonia, collapse or persisting symptoms. [B+]

1. Introduction and Methods

The British Thoracic Society (BTS) first published management guidelines for Community Acquired Pneumonia (CAP) in children in 2002 and covered available evidence to early 2000.

These updated guidelines represent a review of new evidence since then and consensus clinical opinion where evidence was not found. As before, these guidelines have been produced in parallel with those being produced for adults, which have also been updated.

This document incorporates material from the 2002 guidelines and supersedes the previous guideline document.

Community acquired pneumonia can be defined clinically as the presence of signs and symptoms of pneumonia in a previously healthy child due to an infection which has been acquired outside hospital. In developed countries this can be verified by the radiological finding of consolidation. In the developing world a more practical term – acute lower respiratory tract infection - is preferred, reflecting the difficulties in obtaining a radiograph.

Ideally, the definition would include the isolation of a responsible organism. However, it is apparent from many studies that a pathogen is not identified in a significant proportion of cases that otherwise meet the clinical definition (see section 3 on Aetiology). As it is assumed that CAP is caused by infection, the

presumption is that current techniques have insufficient sensitivity to detect all relevant pathogens. Treatment guidelines therefore have to assume that, where pathogens are isolated, they represent all likely pathogens. There is a clear need for better diagnostic methods.

In creating guidelines it is necessary to assess all available evidence with consideration of the quality of that evidence. This we have endeavoured to do. We have then produced a combination of evidence statements and recommendations about management based on the available evidence, supplemented by consensus clinical opinion where no relevant evidence was found.

Methods of Guideline Development

Scope of guidelines

These guidelines address the management of CAP in infants and children in the United Kingdom. They do not include neonates or infants with respiratory syncytial virus bronchiolitis, nor children with upper respiratory tract infection, mild fever and wheeze. The specific management of children with pre-existing respiratory disease or that of opportunistic pneumonias in immunosuppressed children is not addressed.

Guideline Development Group

The guideline development group was set up by the BTS Standards of Care Committee and comprised two paediatricians with a special interest in respiratory disease, a paediatrician with a special interest in paediatric infectious diseases, a general paediatrician with a special interest in ambulatory paediatrics, a specialist trainee in paediatrics, a general practitioner with an interest in childhood infection and a paediatric pharmacist. An Information Specialist developed the search strategy and ran the searches. No external funding was obtained to support the development of the guidelines.

Identification of evidence

A search strategy was developed by an Information Specialist from the Centre for Reviews and Dissemination in York (part of the National Institute for Health Research). The Search strategy and the results are located in Appendix 1.

The Cochrane Library (DARE and Cochrane Database of Systematic Reviews), MEDLINE and EMBASE were searched from 2000 onwards. There were some technical changes made to the original search strategies to reduce the chances of missing studies: a single search strategy was used, rather than separate strategies for each subject. Studies were limited to English language in view of the limitations on time and resources.

2076 studies were identified by the searches, which were rerun in July 2010. The updated search identified a further 511 titles.

Assessing the literature

Initial review of the 2076 titles and abstracts was undertaken by one reviewer, screening for relevance. This was repeated after the second search by another reviewer. The relevant titles and abstracts were grouped by subject matter with many papers being relevant for more than one subject area.

Two reviewers then assessed the studies for inclusion. Studies from countries where the populations or clinical practices were very different from the UK were excluded unless they addressed questions that could be generalised to the UK (such as clinical assessment). Any differences of opinion were settled by a third party.

The studies were appraised using the Cochrane data extraction template (Appendix 2).

Any guideline statements made were graded using the same table used by the group developing the adult guidelines (Table in Appendix 3).

2. Incidence and economic consequences

2.1 How common is CAP in children in the community and in hospital?

Two recent European papers give incidence rates for CAP in children seen in hospital (Table 2.1) which are lower than those reported previously from the 1980's in Finland (1) [1b].

A prospective population based study of 278 Norwegian children <16 years seen in hospital with pneumonia (temperature, clinical signs and chest radiograph infiltrate in previously well child) from 2003-2005 in Oslo gave population incidence rates per 10,000 of 14.7 aged 0-16 years, 32.8 aged 0-5 years and 42.1 aged 0-2 years (2) [III].

UK data for children seen at hospital with pneumonia (clinical findings and chest radiograph) 2001-2002 (n = 750) from a prospective population based study in 13 hospitals in the North of England are remarkably similar. Overall 14.4 aged 0-16 years per annum and 33.8 for those <5 years (per 10,000). Rates of those admitted to hospital were less at 12.2 (11.3-13.2) aged 0-16 years and 28.7 (26.2 – 31.4) aged 0-5 years (3) [II].

Table 2.1 Incidence per 10,000 population CI = confidence interval

Country	Disease	Definition of pneumonia	Age 0-1yr	CI	Age 0-2yrs	CI	Age 0-3yrs	CI	Age 0-5yrs	CI	Age 0-16yrs	CI

Whole Population Data												
Norway	Pneumonia	Signs & CXR			42.1	(32-52.3)			32.8	(26.8-38.8)	14.7	(12.2-17.1)
UK	Pneumonia	Signs & CXR							33.8	(31.1-36.7)	14.4	(13.4-15.4)
Germany (PRI.DE)	Pneumonia	Clinical including Comorbidity					137					
Germany (Schleswig-Holstein)	Pneumonia	Clinical by Parental Interview	181.1						150.1			
Admitted to hospital												
UK	Pneumonia	Signs & CXR							28.7	(26.2-31.4)	12.2	(11.3-13.2)
Germany (KIEL)	Pneumonia & Bronchiolitis	Signs & CXR including Comorbidity	111.3						65.8		30	
Germany (PRI.DE)	Pneumonia	Clinical including Comorbidity					107					
U.S.	All cause Pneumonia	Coding Including Co morbidity			129.6							

A population based study in Kiel, Germany from 1996-2000 of children (n = 514) with severe i.e. hospitalised pneumonia (clinical assessment plus chest radiograph in 96.1%) included children with comorbidities. (22.8%) and almost certainly what in the UK would be called bronchiolitis (4) [II]. Here the overall incidence (per 10,000) was 30 aged 0-16 years, 65.8 aged 0-5 years and 111.3 aged 0-1 year. A series of retrospective population based cohort studies from the same Schleswig-Holstein area of Germany conducted in

1999-2001 from parental interviews at school entry permitted the calculation of population based incidence of all community acquired pneumonia diagnosed by physician as: 181.1/10,000 aged 0-1 year and 150.5/10,000 aged 0-5 years (5) [III].

Further estimates of pneumonia incidence can be obtained from the PRI.DE (Paediatric Respiratory Infection in Germany) study (6) [II]. This prospective cohort study was designed to represent the German population of children <3 years and included children with lower respiratory tract infection (including pneumonia, wheeze, bronchitis, bronchiolitis and croup) presenting to primary or secondary care from 1999-2001. Some 2386 children were seen as outpatients (2870/10,000 population 95% CI 2770-2970) and 114 given a clinical diagnosis of pneumonia (137/10,000). In addition 2924 inpatients (294/10,000 population (95% CI 284-304) were included in the study with 1004 given a clinical diagnosis of pneumonia (101/10,000).

Incidence of all cause and pneumococcal pneumonia in children <2 years and pneumococcal pneumonia in children 2-4 years decreased in the US after pneumococcal (PCV) vaccination became universal (7) [III]. In the UK childhood pneumonia admission rates decreased by 19% between 2006 and 2008 to 10.79/10,000 following introduction of PCV7 to the national childhood immunisation programme (8) [III].

2.2 Are there pathogen-specific incidence rates?

As discussed in Chapter 3 determining pneumonia aetiology is critically dependent on the thoroughness of the search and the methods used. Recently there have been attempts to estimate the contribution of pneumococcal disease. Data from an enhanced surveillance system for laboratory confirmed invasive pneumococcal disease in England and Wales from 1996 - 2000 together with hospital episode statistics for codes related to pneumonia or pneumococcal disease and data from weekly Royal College of General Practitioner returns were examined (6) [II]. Age-specific incidence rates per 100,000 population were calculated for non-meningitis, confirmed invasive pneumococcal disease and range from 59.7 in infants <1 month to 0.8 in children 10-14 years (table 2.2). These rates are lower than the pre-conjugate vaccine data on hospital admissions coded for pneumonia with pneumococcal disease from the US (8) [III].

Table 2.2 Incidence rate per 100 000 population CI = confidence interval

Age	Groups	**Pneumococcal** Sepsis & Pneumonia	CI	**Pneumonia** Pneumococcal
		UK		U.S.
> 1 month		59.7	50.8-64.8	
1-11 months		23.4	21.7-25.2	
	0-2 yrs			26.2
1-4 yrs		9.9	9.4-10.4	
	2-4 yrs			27.2
5-9 yrs		1.8	1.6-2	
	5-17 yrs			3.5
10-14 yrs		0.8	0.7-1	

2.3 Are there any known risk factors?

In the UK study (3) [II] males had higher incidence rates at all ages. Severe disease as assessed by BTS management guidelines 2002 was significantly more likely in children <5 years (19.4 (95% CI 17.4-21.7)/10,000 per year (OR 1.5, 95% CI 1.07-2.11) and in those born at 24 – 28 weeks gestation versus those born at >37 weeks (OR 4.02, 95% CI 1.16-13.85).

When based on pattern of chest radiograph changes (defined as patchy, lobar or perihilar), patchy pneumonic changes were most common in those <5 years (18.7/10,000) compared with lobar (5.6/10,000) and perihilar (7.2/10,000), with rates of patchy, 2.7/10,000, lobar, 0.9/10,000 and perihilar, 0.5/10,000 of those aged 5-15 years. Overall lobar pneumonia accounted for only 17.6% of all cases

Use of gastric acid inhibitors is associated with increased pneumonia risk in adults. A single study has suggested this may also be true in children (9) [III].

2.3.1 Seasonality

A marked seasonal pattern with winter preponderance was seen for laboratory reported invasive pneumococcal disease and hospital admissions due to confirmed pneumococcal infection. December and January showed a peak 3-5 times higher than August (10) [III]. Senstad also reported a low incidence of hospital CAP in summer and a peak in January (2) [III]. There is marked seasonal variation in viral infections such as RSV, Influenza and Parainfluenza 1+2 (11) [III], (12) [II], (10) [III]. Parainfluenza 3, however, is found throughout the year (6) [II].

2.4 What are the economic consequences of CAP in children?

A number of recent studies have examined the economic costs of CAP. An Italian study of 99 children hospitalised with pneumonia in 1999 (11) [III] calculated the costs of hospital management. Mean cost per patient was 1,435 Euro (£1289). Cost increased in those solely treated with intravenous antibiotics - 2,553 Euro (£2294). Costs were reduced in those switched to the oral route after 24-48 hours -1,218 Euro (£1094) or those treated exclusively with oral antibiotics – 1,066 Euro (£958).

In the PRI.DE study of infants and children up to 36 months of age with lower respiratory tract infection, economic resource data was collected (12) [II]. A total of 1329 cases in primary care and 2039 hospitalised cases were analysed. For those classified as pneumonia, direct medical costs were 85 Euro (£76) per office-based case and 2,306 Euro (£2072) per hospitalised case. Parental costs amounted to a further 53 Euro (£47) per office-based case and 118 Euro (£106) per hospitalised case. Further information on indirect family costs for a child with CAP, such as days of work missed, travel costs to primary/secondary care, and so forth, amounted, in an Israeli study, to 976 Israeli shekels (£161) for hospitalised patients; 747 (£123) for those seen at emergency facilities and 448 (£73) for those seen in primary care (13) [III].

Resource use data was routinely collected in the North of England CAP study 2001-2002 (14) [IVb]. This included preadmission GP visits, antibiotics prescribed in the community and in hospital, and number of days of hospital care including any intensive care. Standard NHS list cost data were applied and inflated to 2005/6 levels. The average cost per admitted patient (n= 636)

was £2,857. Mean cost for severe pneumonia was £3,513 (mean hospital stay 5.5 days), falling to £2,325 in moderate (hospital stay 4.7 days), and £909 in mild cases (hospital stay 1.7 days). Hospitalisation (non-intensive care) costs accounted for 70% of the total with a further 25% accounted for by intensive care stays. Cost analysis has also been performed on the PIVOT trial, a randomised controlled equivalence trial that demonstrated therapeutic equivalence for oral amoxicillin and intravenous benzyl penicillin in children admitted to hospital (15) [III]. The average costs to the health service were lower at £1,410 for intravenous treatment and £937 for oral treatment, demonstrating cost savings of £473-518 per child when oral amoxicillin was used.

Overall, therefore, the potential annual direct medical costs of children aged 0-16 years admitted to hospital with pneumonia are £12-18k/10,000/year in the UK. The UK population 0-16 years is 11.509million (Office for National Statistics 2007). Therefore, around £13-20 million per annum is spent on children with CAP admitted to hospital. In addition, there are direct costs to families and indirect costs to the economy from parental time off work.

Evidence Statemements

- The European incidence of CAP, defined as fever, clinical signs and chest radiograph infiltrate in a previously well child is approximately 33/10,000 aged 0-5 years and 14.5/10,000 aged 0 -16 years. [A-]

- Males have higher incidence at all ages. Children < 5 years of age and those born between 24 and 28 weeks gestation have a higher incidence of severe disease. [B-]

3. Aetiology

Studies of the aetiology of CAP are complicated by the low yield of blood cultures, (16) [II] (17) [Ib] (18) [II] (19) [II] (20) [II], the difficulty in obtaining adequate sputum specimens, and the reluctance to perform lung aspiration and bronchoalveolar lavage in children.

All of the following also limit the ability to extrapolate the results of published studies to other populations: the season of the year in which the study was done, the age of those studied, the setting, whether or not children were admitted to hospital and the local criteria for admission, as well as whether or not the study period coincides with an epidemic of a certain pathogen. It is now further complicated by the increasing numbers of studies using specific serological or polymerase chain reaction (PCR) techniques that include relatively small sample sizes. However, over the last 10 years PCR techniques have considerably developed and been applied both to viral detection on nasopharyngeal aspirates (NPA) or secretions, thus increasing respiratory viral identification, and to blood, increasing pneumococcal detection (21) [II] (22) [Ib].

3.1 What are the causes of CAP?

Studies of specific pathogens in developed countries are summarized in Table 3.1. All of these are prospective studies in which pneumonia was community acquired and where the case definition includes clinical findings compatible

with pneumonia together with radiological changes. All constitute levels of evidence of [Ib] or [II] (indicated). In the columns, the percentage indicates the percentage of all CAP cases in which that organism was detected. Where both viral and bacterial isolates were detected, it was classified as mixed and indicated in a separate column. In some studies it was not possible to determine whether infections were single or mixed (as indicated). Bacterial isolates are not included if isolated from a sputum or upper respiratory tract specimen in the absence of other evidence of significance — for example, a rise in antibody concentrations.

The studies are updated from the previous guidelines and cover years 2000–10. Only two come from a UK population, though several are from Europe. Most studies are designed to investigate specific pathogens, either viruses or Mycoplasma/Chlamydia, with only a few studies designed to look more widely at aetiology. In these, the diagnostic yield has improved since 2000, with a pathogen identified in 65-86% (23) [II] (24) [Ib] (25) [Ib] (26) [Ib]. It is also apparent that a significant number of cases of CAP represent a mixed infection. The most comprehensive studies find a mixed viral-bacterial infection in 23-33% (17) [Ib] (24) [Ib] (26) [Ib].

Ref [level]	Age	Year and setting	Tests	Total episodes	Viral %	Bacteria % (no)	Mycoplasma % (no)	Chlamydia % (no)	Mixed % (no)	Total diagnosed % (no)
Wolf (27) [Ib]	< 5 years	ED	NPA hMPV PCR; NPIA	1296	RSV 23.1 HMPV 8.3 Adeno 3.4 Inf A 2.9 Paraflu 2.9					
Cilla (28) [Ib]	1-35 months	2004-6; Spain; IP+OP	NPIA + PCR, BC, serology, Binax pleural fluid	338	67 (18 viral co-infection) RSV 19.8 HboV 14.2 RV13.6 HMPV 11.5 Corona 6.5	Spn 2.1 (7)	1.8 (6)	*	n/a	n/a
Haman (29) [II]	0-19 years	2005-6 Japan	NPA PCR	1700	27.9 (2.1% multiple) RV14.5 RSV 9.4 HMPV 7.2 HboV 2.9	§	14.8 (251)	1.4 (24)	15.2	n/a§
Don (23) [II]	0.3-16yrs	2001-2; Italy; IP+OP	Serology (viral and bacterial)	101	42 (3 dual) RSV 17 Paraflu 12 Inf 9 HMPV 5	44 Spn18 HI 3 Mcat 1	26.7(27) <2years;1 2-5 years;8 >5 years;18 p<0.0001	7.9(8)	20	65(66)
Lin (30) [II]	3mths-18years	2001-2; Taiwan; IP	NPIA, NPVC; hMPV PCR; BC; Urine Spn ag; serology MP+CP	116	38.8 (45) RSV 28.9 Adeno 28.9 HMPV 13.3 Inf 13.3	§	37.9 (44)	4.3 (5)	n/a	n/a§
Michelow (24) [Ib]	6wks-18yrs	1999-2000; USA; IP	NPIA, NPVC; Spn BPCR; BC; Serology – viral, Spn, MP, CP	154	45(65) RSV13 Infl 22 Paraflu13 Adeno 7	60(93) Spn 44(68) GAS 1(2) SA 1(2)	14(21)	9(14)	23	79(122)
Macherel (26) [Ib]	2mths-5yrs	2003-5; Switzerland: IP	NPIA + PCR; Spn BPCR; BC; Serology-viral, Spn, MP, CP;	99	67 RV 20 Hmpv 13 RSV 13 Inf 14 Paraflu 13 Adeno 7 Coron 7	53(52) Spn 46(45) GAS 1(1)	11	7	33(33)	86(85)

Drummond (31) [II]	0-16yrs	1996-1998; UK; IP	NPIA; NPVC Serology- viral, Spn, MP, CP; urine Spn ag;	136	37(50) RSV 25 InfA 5 CMV 3 Adeno1.4	12.5 (17) GAS 7(9) Spn 4 (5)	2(3)		11(15)	51(70)
Laundy (32) [II]	0-5yrs	2001-2; UK; IP+OP	NPIA+PCR;BC Specifically viral testing	51	43(22) RSV18(9) InflA16(8) Adeno6(3) PIV6(3)	12 (6) Spn 6	4(2)	n/a	n/a	49(25)
Tsolia (25) [Ib]	5-14yrs	?year; Greece; IP	NPA PCR; serology – MP, CP, Spn, HI, Mcat;	75	65(49) RV 45(34) Adeno 12(9) PIV 8(6) Inf 7(5) RSV3(2) HMPV 1(1)	40(30) Spn 7(5)	35(26)	3(2)	28(21)	77(58)

Table 3.1 Prospective Studies of Specific Pathogens from Developed Countries

IP = inpatients; OP = outpatients; ED = emergency department; BC = blood culture; NPIA = nasopharyngeal immunoassay; NPVC = nasopharyngeal viral culture; PC = pharyngeal culture; NPA PCR = nasopharyngeal polymerase chain reaction; BPCR = blood polymerase chain reaction; RSV = respiratory syncytial virus; hMPV = human metapneumovirus; Infl = Influenza A&B virus; Paraflu = parainfluenza virus 1-3; HboV = human Bocavirus; RV = rhinovirus; Corona = coronavirus; adeno = adenovirus; Spn =Streptococcus pneumoniae; GAS = Group A streptococcus; MP = mycoplasma; CP = Chlamydia pneumoniae; HI = H.influnzae; Mcat = M.catarrhalis; ag = antigen *No serological tests for Cpn performed. †Studies designed as trials of antibiotic therapy. § All bacterial cases identified by NPA PCR therefore difficult to distinguish carriage from pathogen. ¶Assumes no mixed infections.. n/a= not available

3.2.1 Which viruses are associated with CAP?

A number of viruses appear to be associated with CAP, the predominant one being respiratory syncytial virus (RSV). RSV, parainfluenza and influenza are detected in similar proportions of children with pneumonia both in the community and in hospital (6) [II]. Influenza virus was detected relatively infrequently in paediatric pneumonia using immunofluorescence (IF) (31) [II]. However, with PCR techniques, Influenza is found in 7 to 22% (28) [Ib] (25) [Ib] (24) [Ib]. In the UK, during a six month winter 'flu season, 16% of children with pneumonia had Influenza A (32) [II]. Other viruses isolated in children with pneumonia include: adenovirus, rhinovirus, varicella zoster virus, cytomegalovirus, herpes simplex virus, and enteroviruses.

Several new viruses have been identified and are regularly associated with pneumonia. Human metapneumovirus (HMPV) has been identified in 8% to 11.9% (33) [Ib] (34) [Ib] (35) [Ib] (28) [Ib] and Human Bocavirus (HboV) recently from 4.5% in Thailand (36) [Ib] to 14.2% in Spain (28) [Ib] and 15.2% in Korea (33) [Ib]. Coronavirus is identified in 1.5% (33) [Ib] to 6.5% (28) [Ib] (26) [Ib]. Overall, viruses appear to account for 30-67% of CAP cases in childhood and are more frequently identified in children < 1 year old compared with over 2 years (77% v 59%) (28) [Ib] (24) [Ib].

3.2.2 Which bacteria are associated with CAP?

Quantifying the proportion of CAP caused by bacteria is more difficult. *Streptococcus pneumoniae* (SPn) is assumed to be the most common bacterial cause of CAP, but is infrequently found in blood cultures. Overall, blood or pleural fluid culture of SPn is positive in 4–10% of cases of CAP (16) [II] (17) [Ib] (18) [II] (19) [II] (20, 28) [II] (37) [II]. It is commonly found in routine cultures of upper respiratory tract specimens, yet is known to be a commensal in this setting. A review of lung tap studies found 39% identified SPn (38) [III]. A recent study of 34 children in Finland who had a lung aspirate, identified SPn in 90% either by culture or PCR (39) [II]. Pneumolysin-based PCR is increasingly used and validated (21) [II] (22) [Ib]. Studies incorporating this into diagnosis in children not immunized with the conjugate pneumococcal vaccine have detected Spn in around 44% (24) [Ib], often as a co-pathogen with either viruses or other bacteria. The proportion of CAP due to *S. pneumoniae* increases up to 41% where serological testing is used (26) [Ib]. Mixed pneumococcal and viral infections appear important and are found in 62% of pneumococcal pneumonias (26) [Ib].

Pneumococcal serotypes (ST) are important with ST 14, 6B, 19F, and 23F implicated more frequently with invasive pneumococcal disease and ST 1 in empyema. The most common IPD isolates since the introduction of conjugate pneumococcal vaccine (PCV7) in Europe, including the UK, were serotypes 1, 19A, 3, 6A, and 7F (40) [Ib]. There are no UK data on the most frequent serotypes found in pneumonia, though ST 1 has been predominantly responsible for empyema (41) [Ib]. Recent, post PCV7 data on serotypes identified in bacteraemic pneumonia in children from Italy, found ST1 and 19A

to be the most common (22) [Ib]. Both these serotypes are included in PCV13, introduced into the UK immunisation schedule in 2010.

With the introduction of conjugate pneumococcal vaccines, indirect evidence of vaccine efficacy for the prevention of pneumonia can be used to assess the contribution of SPn to CAP. In children under 2 years, all trials have consistently shown a decrease in radiologically confirmed pneumonia from 23% in the Phillipines using PCV 11 (42) [Ib] to 37% in the Gambia with PCV 9 (43) [Ib] and 23.4% in California with PCV 7 (44) [Ib]. The effect is most striking in the first year with a 32.2% reduction, and a 23.4% reduction in the first 2 years (44) [Ib]. A recent PCV11 study found that although 34% of radiologically confirmed pneumonias were prevented in children under 1 year, there was only a 2.7% decrease in those 12 to 23 months old (42) [Ib]. In children over 2 years there was only a 9.1% reduction (44) [Ib]. A Cochrane systematic review found a pooled vaccine efficacy for PCV 11 for reduction of radiograph-confirmed pneumonia in children under 2 years was 27% and clinical pneumonia 6% (45) [Ia].

The introduction of PCV7 has dramatically decreased invasive pneumococcal disease (IPD) due to vaccine serotypes in those countries where it has been universally introduced, but a steady increase in vaccine serotype replacement has been evident in the UK to 2010, so that the total IPD rate due to all serotypes was climbing back to similar rates before the introduction of PCV7 (http://www.hpa.org.uk/HPA/Topics/InfectiousDiseases/InfectionsAZ/1203008863939/). This trend is expected to reverse with the introduction of PCV13 (http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1245581527892).

Other bacterial pathogens appear to be less frequent causes of CAP. Group A streptococcal infection (GAS) is important in terms of severity as, when present, is more likely to progress to PICU admission or empyema (46) [III] (31) [II]. When looked for, it may be found in 1% (24) [Ib] (26) [Ib] to 7% (31) [II]. It is increasingly associated with pneumonia complicated by empyema, as is *S. aureus* (7) [Ib].

S. aureus has also long been associated with increased mortality in influenza. Recent reports indicate a 5-fold increase in influenza and *S. aureus* mortality in children in the USA from 2004-7 (47) [Ib].

Claesson *et al* (48) [II] assessed the antibody responses to noncapsulated *Haemophilus influenzae* and isolated it as the only pathogen from the nasopharynx of 43 of 336 children. A significant increase in IgG or IgM was shown in 16 (5% of all CAP). In the same study, 3% also had a significant increase in antibodies to *Moraxella catarrhalis*, suggesting that it, too, is an uncommon cause of CAP in children (49) [II]. This was supported by another study by Korppi *et al* (50) [II] in which seroconversion to *M. catarrhalis* was documented in only 1.5% of cases of CAP.

3.2.3 What is the contribution of atypical organisms?

In aetiology studies, *Mycoplasma pneumoniae* (MPn) previously accounted for 4–39% of isolates (51). Since 2000, those studies published where Mpn is

specifically sought in children admitted to hospital show remarkable consistency, with rates of detection from 27-36% (see Table 3.2). Where *Chlamydia pneumoniae* is sought, it appears to be responsible for 5-14% of cases, however a single US study detected it in 27% (52) [II]. Biases which need to be considered in these reports include whether children with mycoplasmal (or chlamydial) pneumonia are over represented in hospital based studies because of failure of penicillin related antibiotic treatment in the community, or are over represented in community studies because they are less sick and therefore less likely to be referred to hospital.

New bacteria are also being described. *Simkania negevensis*, a Chlamydia-like organism, is detected frequently by PCR in respiratory samples, though antibody studies suggest it may be rarely implicated in pneumonia (53) [III] (54) [III].

Table 3.2 Aetiology Studies Looking for Atypical Organisms

Ref [level]	Age	Year and Setting	Tests	Total Episodes	Mycoplasma % (no)	Chlamydia % (no)	Mixed % (no)
Kurz (55) [II]	2mths-18yrs	2006-2007; Austria; IP	NPA culture PCR serology	112		6.7 (4 of 60 tested)	
Principi (56) [Ib]	2-14yrs;	1998-1999; Italy; IP	Serology NPA PCR	418	35.8 (150)	11(46)	6(26)

Baer(57) [II]	1-18yrs	1999-2000; Switzerland IP	Serology NPA PCR	50	32 (16) 1-3; 22% >3-7;35% >7;40%	8(4)	6(3)
Somer (58) [II]	2mths-15yrs	1996-1998; Turkey; IP	Serology	140	27 (38)	5(7)	?0
Korppi (59) [II]	<15yrs	1981-2; Finland; IP+OP	Serology (updated from previous study)	201	30 (61) 0-4yrs:9% 5-9yrs:40% 10-14yrs:67%	14(29) 6% 13% 35%	5(10)

3.3 Does the aetiology differ by age?

Several generalisations are possible with respect to age. With improved diagnostic tests, including serology and PCR, evidence of specific aetiology tends to be more commonly found in younger children (23) [II] (24) [Ib] (28) [Ib]. Michelow (24) [Ib] detected a pathogen in 92% of children under 6 months but in only 75% of those over 5 years. Although viral infections (especially RSV) are more commonly found in younger children (1) [II] (16) [II] (17) [II] (19) [II] (60) [II] (28) [II], bacteria are also isolated in up to 50% of children under 2 years, together with a virus in up to half of these (24) [Ib]. However bacteria are more frequently identified with increasing age, (24) [Ib]. Hence, mixed infections become less frequent with age (61) [II] (23) [II]. Vaccine probe studies indicate a third of young children with radiological changes have pneumococcal pneumonia (45) [Ia], with serological studies

indicating at least 20% have a pneumococcal aetiology across all ages (23) [II]. This has implications for the way in which we consider antibiotic choices.

Chlamydia and Mycoplasma species have been more commonly found in older children (16) [II] (19) [II] (60) [II] (62) [II] (63) [II] (23) [II] (57) [II] (64) [II] (55) [II]. However, Block *et al* (52) [II] found the incidence of *M. pneumoniae* and *C. pneumoniae* infections to be comparable in all age groups between 3 and 12 years of age. In particular, the finding of a 23% incidence of *M. pneumoniae* infection and 23% of *C. pneumoniae* infection in children aged 3–4 years is high. Studies recently have supported this, with Baer also noting a 22% Mpn incidence in children 1-3 years (57) [II]. This raises questions about appropriate treatment in this age group, although young children may have milder Mpn infection (65) [IVb] and many recover without specific antibiotic treatment (66) [II].

Evidence Statements

- *Streptococcus pneumoniae* is the most common bacterial cause of pneumonia in childhood. [A-]
- *Streptococcus pneumoniae* causes about 1/3rd of radiologically confirmed pneumonia in children under 2 years. [A+]
- The introduction of PCV7 has dramatically decreased invasive pneumococcal disease (IPD) due to vaccine serotypes in the UK, but a steady increase in vaccine serotype replacement is evident in the UK. [B+]

- Pneumonia caused by GAS and *S.aureus* are more likely than pneumococcal to progress to PICU or empyema. [B-]
- Overall, viruses account for 30-67% of CAP cases in childhood, and are more frequently identified in children < 1 year old compared with over 2 years. [B+]
- A third of cases of CAP (8–40%) represent a mixed infection. [B+]
- Mycoplasma is not unusual in children between 1-5 years. [B+]
- Age is a good predictor of the likely pathogens:
    - Viruses alone are found as a cause in younger children in up to 50%.
    - In older children, when a bacterial cause is found, it is most commonly *S. pneumoniae* followed by mycoplasma and chlamydial pneumonia [B+].

4. Clinical Features

4.1 How do children with Community Acquired Pneumonia (CAP) present?

Children with CAP may present with fever, tachypnoea, breathlessness or difficulty in breathing, cough, wheeze or chest pain. They may also present with abdominal pain and/or vomiting and may have headache. Children with upper respiratory tract infection and generalised wheeze with low grade fever do not have pneumonia.

The clinical features of CAP vary with the age of the child (see Table 6.1 in Section 6, 'Severity Assessment'). Criteria for diagnosis based on signs and symptoms tend not be very specific. Early work on diagnostic features was mainly undertaken in developing countries to assist non-healthcare workers in identifying need for antibiotics or referral for hospital assessment in areas without access to radiology. Studies on pneumonia are often difficult to collate as the clinical settings and criteria for diagnosis can vary widely.

Clark *et al* (20) [II] recently studied 711 children presenting to hospitals in the North East of England with a history or signs of lower respiratory tract infection. Only children seen by a hospital paediatrician with radiograph-confirmed pneumonia were studied.

This study confirms the importance of respiratory rate as a valuable sign, as there was a significant correlation between respiratory rate and oxygen

saturation (r=-28, p<0.001). This supports previous findings. In infants under a year, a rate of 70 breaths per minute had a sensitivity of 63% and specificity of 89% for hypoxaemia (67) [II].

Previously, Palafox *et al* (68) [II], found that, in children under 5 years, the WHO definitions for tachypneoa (respiratory rate >60/min for infants <2 months, >50/min in children aged 2-12 months and >40/min in children >12 months) had the highest sensitivity (74%) and specificity (67%) for radiographically-defined pneumonia. Of note was that respiratory rate was less sensitive and less specific in the first 3 days of illness.

Respiratory rate was also significantly higher in patients with breathlessness or difficulty breathing (p<0.001). Significantly lower oxygen saturation was seen in children of all ages with increased work of breathing.

Respiratory rate is of some value, but work of breathing is more indicative of the likelihood of pneumonia.

It is worth noting that prolonged fever associated with influenza should raise the possibility of pneumonia due to secondary bacterial infection (69) [II].

4.2 Are there clinical features that are associated with radiological changes of pneumonia?

In previous studies in infants, chest indrawing and/or respiratory rate of >50/min gave a positive predictive value of 45% of radiological consolidation and a negative predictive value of 83% (70) [II]. In children older than 3 years, tachypnoea and chest recession or indrawing were not sensitive signs. Children can have pneumonia with respiratory rates <40/min (71) [II]. Crackles and bronchial breathing have been reported to have a sensitivity of 75% and specificity of 57% (67) [II].

An emergency room prospective study of 510 children between 2 and 59 months identified similar clinical findings significantly associated with chest radiograph infiltrates as follows:

- Age older than 12 months (Adjusted Odds Ratio (AOR) 1.4, 95% CI 1.1-1.9),
- respiratory rate 50 or greater (AOR 3.5, CI 1.6-7.5),
- oxygen saturation 96% or less (AOR 4.6, CI 2.3-9.2) and,
- in infants 12 months old or younger, nasal flaring (AOR 2.2, CI 1.2-4.0) (72) [Ib].

It must be noted that these features are also likely to be associated with children with viral induced wheeze where radiographic changes do not represent pneumonia.

4.3 Can clinical features distinguish between viral, bacterial and atypical pneumonias?

Many studies have sought clinical features which might help direct treatment options. These have largely been retrospective reviews and one small prospective study that have confirmed previous evidence that there is no way of reliably distinguishing clinically (nor radiologically) between aetiological agents (73) [II] (74) [II] (75) [IVb] (76) [III]. This is complicated by mixed infections, the reported incidence of which varies from 8.2% to 23% (24) [Ib].

4.4 Are there specific clinical features associated with individual causative agents?

4.4.1 Pneumococcal pneumonia

Pneumococcal pneumonia starts with fever and tachypneoa. Cough is not a feature initially as alveoli have few cough receptors. It is not until lysis occurs and debris irritates cough receptors in the airways that cough begins.

Many studies therefore emphasise the importance of the history of fever and breathlessness and the signs of tachypnoea, indrawing and ‘toxic’ or ‘unwell’ appearance.

4.4.2. Mycoplasma pneumonia

Mycoplasma pneumonia can present with cough, chest pain and be accompanied by wheezing. Classically the symptoms are worse than the

signs would suggest. Non-respiratory symptoms, such as arthralgia and headache, might also suggest mycoplasma infection (77) [IVb].

Michelow's study (24) [Ib] of 154 children found, as has been proposed more recently, that pre-school children are just as likely as school age to have atypical pneumonia. There are likely to be geographical variations in these findings.

4.4.3. Staphylococcal pneumonia

This is indistinguishable from pneumococcal pneumonia at the beginning of the illness. It remains rare in developed countries where it is usually a disease of infants. It can complicate influenza in infants and older children. The incidence is increasing.

Evidence Statements

- Children with CAP may present with fever, tachypnoea, breathlessness or difficulty in breathing, cough, wheeze or chest pain. These clinical features of CAP vary with the age of the child and tend not be very specific for diagnosis. [D]
- In children older than 3 years, a history of difficulty breathing is an additional valuable symptom. [B+]
- A raised respiratory rate is associated with hypoxaemia. [B+]

Recommendations

- Bacterial pneumonia should be considered in children when there is persistent or repetitive fever >38.5^{o}C together with chest recession and a raised respiratory rate. [D]

5. Radiological, general and microbiological investigations

5.1 When should a chest radiograph be performed?

The National Institute for Clinical Excellence has recently produced a guideline (78) for the assessment of febrile illness in children. There is comprehensive advice on when radiographs should and should not be done in febrile children.

The recommendation of the guideline development group relevant to pneumonia is:

- Children with symptoms and signs suggesting pneumonia who are not admitted to hospital should not routinely have a chest radiograph.

There are also several other studies that have examined the relationship between radiographic findings and clinical pneumonia.

A prospective cohort study (72) [Ib] of 510 patients in the United States sought to elucidate clinical variables that could be used to identify children likely to have radiographic pneumonia, in an effort to spare unnecessary radiography in children without pneumonia. Radiographic pneumonia was defined as confluent opacification without volume loss, peripheral rather than central opacification, and pleural effusion. Hyerinflation, increased peribronchial markings or subsegmental (band-like) atelectasis were not considered evidence of pneumonia. 44/510 (8.6%) of cases had radiographic evidence of pneumonia. The clinical features thought to be more significantly associated

with radiographic evidence of pneumonia have been previously discussed (see Section 4.2).

Evidence from 1848 radiographs taken as part of a double blind prospective randomized controlled trial (79) [Ib] based at 6 centres in Pakistan, in which children were diagnosed with non-severe pneumonia (and treated with antibiotics) based on the WHO criteria of tachypnoea without 'danger symptoms', showed that a radiological diagnosis of pneumonia was present in 14% (263/1848) with 26 (~1%) of these constituting lobar pneumonia. 223 were classified as having 'interstitial parenchymal changes'. 82% of radiographs were classified as normal and 4% were classified as 'bronchiolitis'. Of those with radiographic evidence of pneumonia, 96% had fever, 99% had cough and 89% had difficulty breathing. Of those without radiographic evidence of pneumonia, 94% had fever, 99% had cough and 91% had difficulty breathing. From this study, it would appear that there is poor agreement between clinical signs and chest radiography.

Other studies (80) [II] have drawn similar conclusions. In an ambulatory setting chest radiology did not improve outcome (81).

5.1.1 Should a lateral radiograph be performed?

In a retrospective study of 1268 cases (7608 radiograph interpretations) (82) III], frontal and lateral chest radiographs of patients referred from an emergency department in the United States were reviewed by 3 radiologists

independently. The sensitivity and specificity of the frontal radiograph alone for lobar consolidation was 100%. For non-lobar infiltrates, the sensitivity was 85% and the specificity 98%, suggesting that these types of radiographic changes may be underdiagnosed in 15% of cases. The authors admit that some of the loss of sensitivity may be due to the wide variability in what is considered radiographic pneumonia. The clinical implications of these radiographically underdiagnosed pneumonias are not evident from the study.

Lateral radiographs are not routinely performed in paediatric community-acquired pneumonia and the recommendation is that they are not necessary (83) [II] and would mean exposing the child to further radiation.

5.1.2 How good is agreement on interpretation of radiographs?

There is great intra- and inter-observer variation in radiographic features used for diagnosing CAP. The WHO (84) produced a method for standardizing the interpretation of chest radiographs in children for epidemiologic purposes, but even using this scheme, the concordance rate between two trained reviewers was only 48% (250/521).

5.1.3 Can chest radiography be used to distinguish aetiology?

It is common in clinical practice that alveolar infiltration is thought to be secondary to a bacterial cause and bilateral diffuse interstitial infiltrates to atypical bacterial or viral infections. Adequate sensitivity is lacking for either of

these assignations. Chest radiography is generally unhelpful for deciding upon a potential causative agent.

Toikka (85) [II] studied 126 patients, all of whom had radiographs. Bacterial aetiology was established in 54% and viral in 32%. 14% had unknown aetiology. Radiographs were divided into 2 groups by 3 radiologists unaware of the clinical diagnoses and characteristics. Group 1 (n=61), mild or moderate changes: interstitial infiltrations not covering a whole lung, minor alveolar infiltrations, hyperaeration, perihilar pneumonia; group 2 (n=61), marked changes: interstitial changes covering a whole lung, major alveolar infiltrations, lobar alveolar infiltrations, pleural fluid, abscess formation, atelectasis. Of those in group 1, 39% had bacterial pneumonia and 45% viral pneumonia. Of those in group 2, 69% had bacterial pneumonia and 18% viral pneumonia. Clearly, some bacterial infections are only mild, producing less marked changes on the chest radiographs and conversely, some viral infections are severe, producing marked changes on the radiograph. Aetiology is difficult to assign on the basis of the radiograph.

Virkki (86) [II] studied 254 children with radiographically diagnosed CAP, assigning aetiology in 215/255 patients. Radiographic findings were classified as alveolar and/or interstitial pneumonia, hyperaeration, hilar enlargement, atelectasis, pleural fluid, and location in one or both lungs. Of 137 children (64%) with alveolar infiltrates, 71% had evidence of bacterial infection. 72% of 134 cases with bacterial pneumonia had alveolar infiltrates. 49% with viral pneumonia had alveolar infiltrates. Half of those with interstitial infiltrates had

bacterial infection. Sensitivity for bacterial infection in those with alveolar infiltrates was 0.72 and specificity was 0.51. For viral pneumonia with interstitial infiltrates, sensitivity was 0.49 and specificity 0.72.

Drummond (31) [II] demonstrated in a prospective study of 136 children that there was no significant difference in aetiology amongst the 5 radiographic groups into which their cases were divided (lobar consolidation, patchy consolidation, increased perihilar and peribronchial markings, pneumonitis, and effusion).

Korppi (76) [II], in a study of 101 Italian children with radiographically defined pneumonia found no association between radiographic appearances and aetiology. They found that in 62% (n=44) of children, alveolar infiltrates were present. In those more than 5 years old, these were present in 68%, although blood cultures were negative in all cases. Alveolar infiltrates were present in 46% of those with viral aetiology, 67% with pneumococcal aetiology and 70% in each of those with atypical bacterial and unknown aetiologies.

5.1.4 Are follow-up radiographs necessary?

Two recent studies have examined the utility of follow-up radiographs in previously healthy children with CAP.

Virkki (87) [II] published the results of a 3 year prospective study of 196 children with CAP. They also followed the children up at 8-10 years post

diagnosis. Of 196 follow-up radiographs, there were abnormalities in 30% (infiltrates 67%, atelectasis 47%, lymph nodes 28%). 20% were new abnormalities. No change in management was instituted on the basis of these radiographic findings. 8-10 year follow-up of 194 patients showed no new illnesses associated with the previous pneumonia. In those with an uneventful recovery, radiographs are unnecessary.

Suren (88) [III] published the results of a retrospective study of 245 children recovering from CAP. Of these, 133 had follow-up radiographs, 106 of which were normal and 27 of which were abnormal. Of the 106 patients with normal follow-up radiographs, 2 went on to develop further clinical problems (both recurrent pneumonias with no established underlying cause). Of the 27 patients with abnormal radiographs, 3 developed further clinical problems that could be related to the previous pneumonia. Of 112 who did not have follow-up radiographs, 10 developed subsequent clinical problems. Most of these occurred within the first 4 weeks after discharge, before the regular scheduling of the follow-up radiograph. The authors established that a follow-up radiograph might have been helpful in 5/245 cases. These modest benefits should be balanced against the exposure of children to radiation.

Evidence Statements

- Chest radiography is too insensitive to establish whether CAP is of viral or bacterial aetiology. [B+]

Recommendations

- Chest radiography should not be considered a routine investigation in children thought to have CAP. [A-]
- Children with signs and symptoms of pneumonia who are not admitted to hospital should not have a chest radiograph. [A-]
- A lateral radiograph should not be performed routinely. [B-]
- Follow-up radiography is not required in those who were previously healthy and who are recovering well, but should be considered in those with a round pneumonia, collapse or persisting symptoms. [B+]

5.2 What general investigations should be done in a child with suspected CAP in the community?

There is no indication for any tests in a child with suspected pneumonia in the community. Again, the recent guidance published by the National Institute for Health and Clinical Excellence regarding the management of feverish illness in children provides a useful framework for assessing these patients (see section 5.1).

5.3 What general investigations should be done in a child with CAP who comes to hospital?

5.3.1 Pulse oximetry

Oxygen saturation measurements provide a non-invasive estimate of arterial oxygenation. The oximeter is easy to use and requires no calibration. It does require a pulsatile signal from the patient and is susceptible to motion artifacts. The emitting and receiving diodes need to be carefully opposed. To obtain a reliable reading:

- the child should be still and quiet
- a good pulse signal should be obtained
- once a signal is obtained, the saturation reading should be watched over at least 30 seconds and a value recorded once an adequate, stable trace is obtained.

In a prospective study from Zambia, the risk of death from pneumonia was significantly increased when hypoxaemia was present (67) [II].

5.3.2 Acute Phase Reactants

Several studies (85) [II] (89) [II] (90) [II] (91) [II] (92) [II] (64) [II] have looked at using various acute phase reactants as means of differentiating the aetiology and/or severity of CAP. The utility of procalcitonin (PCT), cytokines, C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR) and White Blood Cell (WBC) count individually and in combination has been assessed.

Korppi (64) [II] examined WBC, CRP, ESR and PCT levels and chest radiograph findings in 132 cases in an effort to find combinations of markers

that would differentiate pneumococcal from viral aetiology. They found for a combination of CRP >80mg/l, WBC >17 x 10^9/l, PCT >0.8mcg/l and ESR >63mm/h, the likelihood ratio of the pneumonia being pneumococcal was 1.74 with a sensitivity of 61% and specificity of 65%. If alveolar infiltrates on the radiograph were included, the likelihood ratio was 1.89, specificity 82% and sensitivity 34%. None of these combinations of parameters was sensitive or specific enough to differentiate bacterial, specifically pneumococcal, from viral pneumonia.

Michelow (92) [II] investigated a panel of 15 cytokines in 55 patients who had CAP. 43 children had an aetiological diagnosis. 21 children had *S. pneumoniae*, 17 had *M. pneumoniae*, 11 had Influenza A, 3 had *C. pneumoniae*, and 1 had *Staph. aureus* and 8 had viruses identified. 11 had mixed viral and bacterial infections. Of the cytokines, IL-6 was the only one significantly associated with a rise in white cell band forms, procalcitonin levels and unequivocal consolidation on the radiograph. However, there was no correlation with aetiology. There remains little evidence that cytokine profiles have any clinical utility.

Don (90) [II] evaluated the usefulness of PCT for assessing both the severity and aetiology of CAP in a study of 100 patients. The cases were assigned into 4 aetiological groups: pneumococcal (n=18), atypical bacterial (n=25), viral (n=23) and unknown (n=34). There was no significant association between procalcitonin levels and aetiological group. PCT levels were found to be significantly associated with severity of CAP, as defined by admission to

hospital and the presence of alveolar infiltrates on chest radiograph. Median PCT values (25^{th} – 75^{th} centiles) for inpatients and outpatients, respectively, were 17.81 and 0.72.

Korppi (89) [II] published a prospective, population-based study of 190 children in an ambulatory primary care setting with radiologically diagnosed pneumonia and aetiological diagnoses for 5 bacteria and 7 viruses. They discovered that there was no association between severity of CAP (as defined by inpatient vs outpatient management) and no association between aetiology of CAP and PCT. The median values for each of the 4 aetiological groups (pneumococcal, mycoplasma/chlamydia, viral and unknown) were not significantly different (p value = 0.083). For inpatient versus outpatient management, PCT was 0.42 and 0.45mcg/l, respectively, p = 0.77.

According to these two studies, there may be some alignment between PCT levels and severity, as defined by admission to hospital, but the evidence is still lacking for the ability of PCT to discriminate between viral and bacterial causes of CAP.

Toikka (85) [II] studied 126 children with CAP, measuring PCT, CRP and IL-6 levels. Aetiology was established for 6 bacteria and 11 viruses. 54% had bacterial infection, 32% viral and 14% unknown. Median procalcitonin and CRP values were found to be significantly different, but there was marked overlapping of values. There were no significant differences for IL-6 levels. The sensitivity and specificity of CRP and PCT levels were low. If PCT, CRP

and IL-6 levels are very high, then bacterial pneumonia is more likely, but generally, they have little value in differentiating viral from bacterial CAP.

Flood (93) [Ia] produced a meta-analysis of 8 studies, including several revealed in our recent search (94) [II] (95) [II] (86) [II], that examined the use of CRP in establishing aetiology in CAP. The pooled study population was 1230. 41% had bacterial CAP. A CRP range of 35-60mg/l was significantly associated with bacterial pneumonia, producing an Odds Ratio for bacterial vs non-bacterial CAP of 2.58 (95% CI, 1.2 – 5.55). Given the prevalence of bacterial pneumonia of 41%, the positive predictive value for CRP values of 40-60mg/l was 64%. The conclusion of the meta-analysis was that CRP was only weakly predictive for bacterial pneumonia.

CRP on its own it is not reliably predictive of bacterial pneumonia.

Recommendations

- Acute phase reactants are not of clinical utility in distinguishing viral from bacterial infections and should not routinely be tested. [A-]
- CRP is not useful in the management of uncomplicated pneumonia. [A+]

5.4 What microbiological investigations should be performed?

Determining the causative agent in acute lower respiratory tract infection can be frustrating and difficult. The gold standard would be a sample directly from

the infected region of lung (lung puncture). In the developed world, less invasive sampling methods are usually used to achieve a diagnosis.

5.4.1 Are there any microbiological investigations that should be performed in the community?

There is no indication for microbiological investigations to be done in the community. Some workers have investigated the feasibility of performing PCR analysis for viruses in nasopharyngeal secretions in the context of pandemic respiratory virus infections (96) [II], but this is not currently practical in the United Kingdom.

5.4.2 Which microbiological investigations should be performed on a child admitted to hospital?

It is important to attempt microbiological diagnosis in patients admitted to hospital with pneumonia severe enough to require paediatric intensive care admission or with complications of CAP. They should not be considered routinely in those with milder disease.

Microbiological methods that may be used are several and include: blood culture, nasopharyngeal secretions and nasal swabs for viral detection (by PCR or immunofluorescence), acute and convalescent serology for respiratory viruses, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* and, if present,

pleural fluid for microscopy, culture, pneumococcal antigen detection and/or PCR.

Cevey-Macherel and co-workers (26) [Ib] identified a causative agent in 86% of 99 patients using a variety of microbiological, serological and biochemical means. 19% were of bacterial aetiology alone, 33% of viral aetiology alone, and 33% of mixed viral and bacterial aetiology.

5.4.3 Which investigations are helpful in identifying a bacterial cause?

Blood culture

Positivity is often quoted as <10% in CAP (26) [Ib]. Pneumococcal pneumonia is seldom a bacteraemic illness. *S.pneumoniae* is cultured in the blood in <5% of pneumococcal CAP cases (97) [Review].

Nasopharyngeal bacterial culture

This is uninformative. Presence of bacteria in the nasopharynx is not indicative of lower respiratory tract infection. Normal bacterial flora as well as bacteria known to cause CAP are often identified (26) [Ib].

Pleural fluid

Pleural fluid cultures often show no growth, with just 9% of 47 cultures positive in a UK study (41) [Ib]. Most children will have received antibiotics for some time before aspiration of pleural fluid, which may explain why culture is so often uninformative. In this study, 32/47 were positive for pneumococcal DNA by PCR, whereas pneumococcal latex agglutination antigen testing was positive in 12/47, all of which were accounted for by PCR. Other studies have confirmed some utility for pneumococcal antigen detection in pleural fluid, identifying 27/29 empyemas in one study (98) [II] and with an apparently useful sensitivity of 90% and specificity of 95%, when compared with culture and/or PCR, in another study (99) [Ib].

Biochemical and Immunological Methods

Serum

A review of pneumococcal serology in childhood respiratory infections (97) [Review] concluded that pneumococcal antibody and immune complex assays, whilst sensitive and specific enough for the detection of pneumococcal infections in children, were too complex for routine clinical use. Several other serological techniques exist and have been used in combinations with other culture and non-culture techniques to increase diagnostic yield. Paired serology seems to have the best yield (31) [II] (26) [Ib].

Urine

Rapid detection of the capsular polysaccharide (CPS) antigen of *S. pneumoniae* has shown promise for excluding pneumococcal infection. A study undertaken in France (100) [Ib] identified both a sensitivity and negative predictive value of 100% for an immunochromatographic test for CPS. However, specificity was too low to be clinically useful.

Rajalakshmi et al (101) [Ib] studied the efficacy of antigen detection assays of pneumolysin versus capsular polysaccharide antigen in urine. The rationale behind this study is that there is cross reactivity between antigens of *Viridans streptococci* and capsular polysaccharide antigen (CPS), whereas pneumolysin is a protein produced only by *S. pneumoniae*. The cases in this study were diagnosed by clinical and radiological evidence, with blood culture positivity in 29.5%. The sensitivities of CPS and pneumolysin in urine when compared with blood culture were identical (52.3%) whereas specificity for pneumolysin was 61.2% and for CPS, 67.3%. In 37.1 – 42.9% of cases, pneumolysin was detected in urine compared with 2.1% in controls. CPS was detected in 38.6% of cases and not detected in any controls. The negative predictive value of pneumolysin was 77.2% and CPS was 76.7%.

Polymerase Chain Reaction

Pneumolysin-based PCR is increasingly used to detect pneumococcus in blood, pleural fluid and secretions. Some studies have found good sensitivity (100%) and specificity (95%) in children with pneumonia (21) [Ib] (102) [II], but others have been concerned about its specificity, especially in young children

(103) [II]. The laboratory techniques in this area are rapidly evolving and improving and show promise in helping to make microbiological diagnoses.

5.4.4 Which investigations are helpful for identifying atypical bacteria?

Paired serology (rising titres in antibody complement fixation tests) remains the mainstay for diagnosing *M. pneumoniae* and *C. pneumoniae* infections. However, there are at least 2 studies that have investigated the use of PCR in identifying atypical bacterial infections.

Michelow (102) [II] used PCR to diagnose *M. pneumoniae* from naso- and oropharyngeal swabs. They compared 21 children with serologically proven *M. pneumoniae* infections with 42 controls. 12/21 (57%) were PCR positive, 9/12 each positive on naso- and oropharyngeal samples, 6 on both. The greatest diagnostic yield was therefore when samples from both sites were combined and analyzed. 1 of the controls was PCR positive. The odds ratio for detecting *M. pneumoniae* by PCR in serologically proven cases was 54.7 (range 5.9 – 1279.3). When compared with ELISA, PCR had a sensitivity of 57.1%, specificity of 97.6%, PPV of 97.3% and NPV of 82.0%. The authors argue that PCR positivity for *M. pneumoniae* in the upper respiratory tract is suggestive of LRTI. Of interest, in their study, PCR positive cases had a significantly longer duration of oxygen therapy (1.7 vs 0.78 days, p=0.045).

Maltezou *et al* (104) [II] used PCR to diagnose *Legionella* and mycoplasma LRTI's by collecting serum and sputum or throat swabs. Of 65 children,

serology (IgM EIA) was positive in 18 (27.5%) for *M. pneumoniae* and 1 (1.5%) for *Legionella*. 11/18 were diagnosed in the acute phase. 9/18 (50%) serologically diagnosed were positive for *M. pneumoniae* by PCR of sputum. Taken together, 15/18 were diagnosed by PCR and IgM serology. 3/18 were diagnosed by convalescent serology. The sensitivity of PCR vs IgM EIA in this study was 50%. This is consistent with recent observations that PCR can detect persistent MP infection up to 7 months after disease onset (105) [II].

5.4.5 Which investigations are useful in identifying viral pneumonia?

Viruses are significant causes of paediatric CAP, either on their own or in mixed infections. Several studies have looked at the various techniques available for identifying viruses. These include viral culture, antigen detection, serology and PCR.

In the previously mentioned study undertaken by Cevey-Macherel and colleagues (26) [Ib], they found viral PCR of nasopharyngeal aspirates to be very sensitive. In their study, 66/99 children had evidence of acute viral infection (33/99 as co-infection with bacteria). In those with a negative PCR, viral infection could not be detected by any other method. As well as viral culture and PCR, they used viral antigen detection and serum complement fixation tests.

Shetty et al (106) [Ib] subjected 1069 nasopharyngeal swabs to viral culture and direct fluorescent antibody (DFA) staining. 190/1069 were DFA and viral

culture positive (true positive) and 837/1069 were DFA and culture negative (true negative). The sensitivity for DFA in this study was 84%, specificity 99%, PPV 96% and NPV 96%. 120/140 hospitalised patients (86%) had viral cultures that reported positive only after the children had been discharged. The authors make the point that the viral cultures were not of any utility in making clinical management decisions.

Lambert (96) [II] collected nose-throat swabs (NTS's) and nasopharyngeal aspirates (NPA's) in 295 patients (303 illnesses) and subjected them to PCR analysis for 8 common respiratory viruses. NTS's are thought to be 'less invasive' samples, more easily collected by parents and hence, of possible benefit in rapid diagnosis in the context of a respiratory virus pandemic. In 186/303 (61%) of paired NTS/NPA samples, at least 1 virus was detected. For NTS, sensitivity for RSV was 91.9% and for Influenza A, 93.1%. For adenovirus, NTS sensitivity was 65.9% (95% CI, 50.1 – 79.5%) whilst NPA sensitivity was 93.2% (81.3% - 98.6%). Concordance between NPA and NTS samples was 89.1%. The authors argue that the combination of PCR and the less-invasive NTS sample provides adequate sensitivity for the detection of respiratory viruses.

Evidence Statements

- Blood culture positivity is uncommon. [A-]

- Urinary antigen detection may be helpful as negative predictors of pneumococcal infection in older children. Positive tests are too non-specific and may represent carriage. [A-]
- Molecular methods have shown promise, but are currently most useful in identifying viral pathogens. [A-]

Recommendations

- Microbiological diagnosis should be attempted in children with severe pneumonia, sufficient to require paediatric intensive care admission, or those with complications of CAP. [C]
- Microbiological investigations should not be considered routinely in those with milder disease or those treated in the community. [C]
- Microbiological methods used should include:
    - Blood culture. [C]
    - Nasopharyngeal secretions and/or nasal swabs for viral detection by PCR and/or immunofluorescence. [C]
    - Acute and convalescent serology for respiratory viruses, *Mycoplasma* and *Chlamydia*. [B+]
    - If present, pleural fluid should be sent for microscopy, culture, pneumococcal antigen detection and/or PCR. [C]
- Urinary antigen detection should not be done in young children. [C]

6. Severity Assessment

6.1 Why is severity assessment important?

Children with CAP may present with a range of symptoms and signs: fever, tachypnoea, breathlessness, difficulty in breathing, cough, wheeze, headache, abdominal pain and chest pain (see chapter 4, 'Clinical Features'). The spectrum of severity of CAP can be mild to severe (see table 6.1). Infants and children with mild to moderate respiratory symptoms can be managed safely in the community. [D]

Table 6.1 Severity Assessment

	Mild to Moderate	Severe
Infants	Temperature <38.5°C	Temperature >38.5°C
	RR <50 breaths/min	RR >70 breaths/min
	Mild recession	Moderate to severe recession
	Taking full feeds	Nasal flaring
		Cyanosis
		Intermittent apnoea
		Grunting respiration
		Not feeding
		Tachycardia*
		Capillary refill time $\geq$ 2 sec
Older Children	Temperature <38.5°C	Temperature >38.5°C

	RR <50 breaths/min	RR >50 breaths/min
	Mild breathlessness	Severe difficulty in breathing
	No vomiting	Nasal flaring
		Cyanosis
		Grunting respiration
		Signs of dehydration
		Tachycardia*
		Capillary refill time $\geq$ 2 secs

The most important decision in the management of CAP is whether to treat the child in the community or refer and admit for hospital based care. This decision is best informed by an accurate assessment of severity of illness at presentation and an assessment of likely prognosis. In previously well children there is a low risk of complications and treatment in the community is preferable. This has the potential to reduce inappropriate hospital admissions and the associated morbidity and costs. .

Management in these environments is dependent on an assessment of severity. Severity assessment will influence microbiological investigations, initial antimicrobial therapy, route of administration, duration of treatment and level of nursing and medical care.

6.2 What are the indications for referral and admission to hospital?

A referral to hospital will usually take place when a general practitioner assesses a child and feels the clinical severity requires admission. In addition to assessing severity the decision as to whether to refer to hospital or not should take account of any underlying risk factors the child may have together with the ability of the parents/carers to manage the illness in the community. This decision may be influenced by the level of parental anxiety.

Children with CAP may also access hospital services when the parents/carers bring the child directly to a hospital emergency department. In these circumstances hospital doctors may come across children with mild disease that can be managed in the community. Some with severe disease will require hospital admission for treatment. One key indication for admission to hospital is hypoxaemia. In a study carried out in the developing world, children with low oxygen saturations were shown to be at greater risk of death than adequately oxygenated children (67) [II]. The same study showed that a respiratory rate of 70 breaths per minute or more in infants aged <1 year was a significant predictor of hypoxaemia.

There is no single validated severity scoring system to guide the decision on when to refer for hospital care. An emergency care based study assessed vital signs as a tool for identifying children at risk from a severe infection. Features including a temperature > 39˚C, saturations < 94%, tachycardia and capillary refill time > 2 seconds were more likely to occur in severe infections (107) [II]. Auscultation revealing absent breath sounds with a dull percussion note should raise the possibility of a pneumonia complication by effusion and

should trigger a referral to hospital (108) [III] (109) [III]. There is some evidence that an additional useful assessment is the quality of a child's cry and response to their parent's stimulation (110) [II]; if these are felt to be abnormal and present with other worrying features they may also strengthen the case for referral for admission to hospital.

A global assessment of clinical severity and risk factors is crucial in identifying the child likely to require hospital admission.

Features of severe disease in an infant include:

- SaO2 <92%, cyanosis;
- respiratory rate >70 breaths/min
- significant tachycardia for level of fever (age dependent)*
- prolonged central capillary refill time >2 seconds
- difficulty in breathing
- intermittent apnoea, grunting
- not feeding
- chronic conditions (e.g. congenital heart disease, chronic lung disease of prematurity, chronic respiratory conditions leading to infection – CF, bronchiectasis, immune deficiency)

Features of severe disease in an older child include:

- SaO2 <92%, cyanosis
- respiratory rate >50 breaths/min
- significant tachycardia for level of fever (age dependent)*

- prolonged central capillary refill time >2 seconds
- difficulty in breathing
- grunting
- signs of dehydration
- chronic conditions (e.g. congenital heart disease, chronic lung disease of prematurity, chronic respiratory conditions leading to infection – CF, bronchiectasis, immune deficiency)

(*Tachycardia: values to define tachycardia vary with age and with temperature (111) [II].)

6.3 What are the indications for transfer to intensive care?

There are two main scenarios when a child is likely to need admission to an intensive care unit. First when the pneumonia is so severe the child is developing severe respiratory failure requiring assisted ventilation. Second a pneumonia complicated by septicaemia. Key features that suggest a child requires transfer include:

- failure to maintain an SaO2 of >92% in FiO2 of >0.6 [D]
- shock [D]
- rising respiratory and pulse rate with clinical evidence of severe respiratory distress and exhaustion, with or without a raised arterial carbon dioxide tension (PaCO2) [D]
- recurrent apnoea or slow irregular breathing [D]

6.4 When should the child be reassessed?

For children with CAP, reassessment is important, whether in the community or in hospital.

In the community after a treatment for CAP has been initiated (e.g. oral antibiotics plus advice on antipyretics and hydration) parents/carers should be advised on what symptoms and signs to look for when reassessing their child. Looking for the features in the following three areas may be useful in identifying cases where the infection is not being adequately treated and reassessment by a doctor is required:

- Fever – a high swinging or persistent fever (the temperature should start to settle 48 hours after treatment starts). [D]
- Effort of breathing – the child seems to be working harder to breath with a fast breathing rate and chest recession. [D]
- Effect of breathing – the child is not comfortable and relaxed but is agitated and distressed. [D]

In hospital all the above should be assessed in addition to vital signs outlined in Table 4. Medical assessment should always look for signs of overwhelming infection and septicaemia, for pleural collections that may develop into empyema thoracis, (109) [III] and for signs of dehydration. A prolonged fever is a useful pointer to empyema developing (112) [III] and this may require

drainage for successful treatment (113). Less common complications should be also considered (see Chapter 9).

Evidence Statements

- Children with CAP present with a range of symptoms and signs. A global assessment of clinical severity and risk factors is crucial in identifying the child likely to require hospital admission. [D]

Recommendations

- For a child in the community, re-consultation to the general practitioner with persistent fever, or parental concern about fever, should prompt consideration of CAP. [D]
- For children with CAP, reassessment is important, whether in the community or in hospital. [D]
- Hypoxia (SaO2 <92%) in all children is an indication for hospital assessment and management. [B+]
- Auscultation revealing absent breath sounds with a dull percussion note should raise the possibility of a pneumonia complication by effusion and should trigger a referral to hospital. [B-]
- A child in hospital should be reassessed medically if there is persistence of fever 48 hours after initiation of treatment, increased work of breathing or if the child is becoming distressed or agitated. [D]

7. General management in the community and in hospital

7.1 What general management strategy should be provided for a child treated in the community?

The general management of a child who does not require hospital referral comprises advising parents and carers about:

- management of fever
    - use of antipyretics
    - avoidance of sponging
- preventing dehydration
- identifying signs of deterioration
- identifying signs of other serious illness
- how to access further healthcare (providing a 'Safety Net').

The safety net should be one or more of the following:

- Provide the parent or carer with verbal and/or written information on warning symptoms and how further healthcare can be accessed.
- Arrange a follow-up appointment at a certain time and place.
- Liaise with other healthcare professionals, including out-of-hours providers, to ensure the parent/carer has direct access to a further assessment for their child.

Recommendations

- Families of children who are well enough to be cared for at home should be given information on managing pyrexia, preventing dehydration, and identifying any deterioration. [D]

7.1.2 Over the counter remedies

No over the counter cough medicines have been found to be effective in pneumonia (114) [Ia].

7.2 What is the general management for children cared for in hospital?

7.2.1 Oxygen therapy

Hypoxic infants and children may not appear cyanosed. Agitation may be an indicator of hypoxia.

Patients whose oxygen saturation is less than 92% while breathing air should be treated with oxygen given by nasal cannulae, head box or face mask to maintain oxygen saturation above 92% (67) [II].

There is no strong evidence to indicate that any one of these methods of oxygen delivery is more effective than any other. A study comparing the different methods in children under 5 years of age concluded that the head

box and nasal cannulae are equally effective (115) [II], but the numbers studied were small and definitive recommendations cannot be drawn from this study. It is easier to feed with nasal cannulae. Alternative methods of delivering high flow, humidified nasal oxygen are available and increasingly used. Higher concentrations of humidified oxygen can also be delivered via face mask or head box if necessary.

Where the child's nose is blocked with secretions, gentle suctioning of the nostrils may help. No studies assessing the effectiveness of nasopharyngeal suction were identified.

No new published studies about oxygen therapy were identified in the update searches.

Evidence Statement

- Agitation may be an indicator that a child is hypoxic. [D]

Recommendations

- Patients whose oxygen saturation is 92% or less while breathing air should be treated with oxygen given by nasal cannulae, high flow delivery device, head box or face mask to maintain oxygen saturation above 92%. [B]

7.2.2 Fluid therapy

Children who are unable to maintain their fluid intake due to breathlessness or fatigue need fluid therapy. Studies on pre-term infants or infants weighing <2000g have shown that the presence of a nasogastric tube compromises respiratory status (116) [II] (117) [IVb]. Older children may be similarly affected, although potentially to a lesser extent because of their larger nasal passages, so although tube feeds offer nutritional benefits over intra-venous fluids, they should be avoided in severely ill children. Where nasogastric tube feeds are used, the smallest tube should be passed down the smaller nostril (117) [IVb]. There is no evidence that nasogastric feeds given continuously are any better tolerated than bolus feeds (no studies were identified); however, in theory, smaller more frequent feeds are less likely to cause stress to the respiratory system.

Patients who are vomiting or who are severely ill may require intravenous fluids and electrolyte monitoring. Attention is drawn to the 2007 National Patient Safety Agency alert 'Reducing the risk of hyponatraemia when administering intravenous fluids to children' (118). Serum sodium can be low in children with pneumonia and there is debate as to whether this is related to inappropriate antidiuretic hormone secretion or overall sodium depletion. Good quality evidence is lacking.

Recommendations

- Nasogastric tubes may compromise breathing and should therefore be avoided in severely ill children and especially in infants with small nasal passages. If use cannot be avoided, the smallest tube should be passed down the smallest nostril. [D]

- Plasma sodium, potassium, urea and/or creatinine should be measured at baseline and at least daily when on intravenous fluids. [C]

7.2.3 Physiotherapy

Two randomised controlled trials (119) [Ib], (120) [II] and an observational study (121) [Ib] conducted on adults and children showed that physiotherapy did not have any effect on the length of hospital stay, pyrexia, or chest radiograph findings in patients with pneumonia. There is no evidence to support the use of physiotherapy, including postural drainage, percussion of the chest, or deep breathing exercises (120) [II] (119) [Ib] (122) [IVb]. There is a suggestion that physiotherapy is counterproductive, with patients who receive physiotherapy being at risk of having a longer duration of fever than the control group (119) [Ib]. In addition, there is no evidence to show that physiotherapy is beneficial in the resolving stage of pneumonia.

A supported sitting position may help to expand lungs and improve respiratory symptoms in children with respiratory distress.

There were no new studies identified.

A summary article (121) [Ib] summarised the studies discussed above.

Recommendation

- Chest physiotherapy is not beneficial and should not be performed in children with pneumonia. [A-]

8. Antibiotic management

8.1 Introduction

The management of a child with CAP involves a number of decisions regarding treatment with antibiotics:

- whether to treat with antibiotics;
- which antibiotic and by which route;
- when to change to oral treatment if intravenous treatment initiated;
- duration of treatment.

The British Thoracic Society guidelines of 2002 (51) found scanty evidence with which to address these questions. Trials comparing various different antibiotic combinations found little differences in efficacy, one trial indicating equivalence of intramuscular penicillin and oral amoxicillin in children with pneumonia treated in the Emergency Department (123) [Ib], and no evidence to inform parenteral to oral switch or duration of antibiotics. Since then a number of large studies from many different countries, have attempted to address some of these issues. There are, however, some difficulties in assessing their relevance to the UK as children have been enrolled from developing and developed countries, with different criteria used as definitions for pneumonia and with different immunization backgrounds, circulating bacteria and resistance patterns.

8.2 Which children should be treated with antibiotics?

One of the major problems in deciding whether to treat a child with CAP with antibiotics is the difficulty in distinguishing bacterial pneumonia (which would benefit from antibiotics) from non-bacterial pneumonia (which would not). This difficulty has been described in Section 3 on Aetiology. Resistance to antibiotics among bacterial pathogens is increasing and is of concern; an important factor in this increase is the overuse of antibiotics.

Two studies were identified in which children with diagnosed respiratory infections treated with antibiotics were compared with a group not treated with antibiotics (124) [II] (125) [II] (126) [II]. However, both enrolled many children who, in the UK, would have bronchiolitis not pneumonia. One was a randomised controlled trial of 136 young Danish children aged 1 month to 6 years, either with pneumonia or bronchiolitis, with 84% RSV positive. Severe disease was excluded. There were no differences in the course of the illness between the two groups (ampicillin or penicillin treated or placebo) though 15 of the 64 in the placebo group did eventually receive antibiotics (124) [II]. The other in India enrolled children aged 2-59 months with cough, rapid breathing or difficulty breathing, audible or auscultatory wheeze, non-response to bronchodilator without chest radiograph changes. There was a non-significant difference in failure rate of 24% with placebo and 19.9% with amoxicillin for 3 days (126) [II].

Unfortunately as most children in these studies appeared to have bronchiolitis, not pneumonia, it is impossible to draw conclusions from them regarding whether young children with pneumonia benefit from antibiotics.

The other way of approaching this is relating knowledge of aetiology in specific ages to the likelihood that these will be effective. Both viruses and bacteria are found in young children, with vaccine probe studies suggesting a third of children less than 2 years old with radiological signs have pneumococcal pneumonia (44) [Ib] (45) [Ia]. However in those with a clinical pneumonia diagnosis this drops to 6%. (45) [Ia]. With the introduction into the UK primary immunization schedule in 2006 of PCV7 and latterly PCV13 in April 2010, the likelihood of bacterial pneumonia in a fully vaccinated young child is therefore very small.

Recommendation

- Children less than 2 years old, presenting with mild symptoms of lower respiratory tract infection need not be treated with antibiotics but should be reviewed if symptoms persist. A history of conjugate pneumococcal vaccination gives greater confidence to this decision. [C]
- As bacterial pneumonia cannot be clinically distinguished from viral, all other children with a clinical diagnosis of pneumonia should receive antibiotics. [C]

8.3 How much of a problem is antibiotic resistance?

Antibiotic resistance has the potential to impact on therapeutic choices and there is worldwide concern about increasing antibiotic resistance among pneumococci and its potential impact on therapy of pneumonia and invasive pneumococcal disease.

8.3.1 *S. pneumoniae* resistance

Despite the rapid reduction in PCV7 serotypes following introduction of conjugate vaccine in 2000, penicillin resistance increased steadily in Cleveland, USA, until 2003-4. At this time 51% of isolates were penicillin non-susceptible (127) [Ib].

Pneumococcal conjugate vaccines (PCVs) have reduced drug-resistant *Streptococcus pneumoniae* (DRSP), but, because of increased intermediate resistance among non-PCV7 serotypes, reductions in intermediately penicillin-resistant strains have not followed. Serotype 19A, which is both antibiotic resistant and a common cause of disease, is not covered by PCV7, and is now increasing worldwide, including in countries without PCV7 (128) [Ia] (129) [Ia] (130) [Ia]. However, it is included within PCV 13, the introduction of which would potentially prevent a further 50% of continuing invasive pneumococcal disease in children.

S. pneumoniae macrolide resistance is also increasing, and different mechanisms of resistance drive different levels of resistance. High level

resistance also involves clindamycin resistance, whereas low level only involves macrolides. Resistance mechanisms vary geographically with mostly low-level resistance in the USA, but high level in Europe (131) [Ia]. US surveillance data between 2000-4 of respiratory isolates indicate a stable 30% are macrolide resistant, though an increasing proportion has high level macrolide resistance (132) [Ib].

A study from Portugal significantly associated macrolide use with the increase of penicillin and erythromycin non-susceptible isolates from adults ($p < 0.01$) and erythromycin non-susceptible isolates among children ($p = 0.006$) (133) [Ib].

In the UK, however, penicillin resistance is far less prevalent. Pneumococcal penicillin non-susceptibility in pneumococci causing bacteraemia rose in the 1990s to 6.7% in 2000, and has since declined to around 4% in 2007. Geographical variation ranges from 1.5% in the East Midlands to 8.0% in London. This is in contrast to much of mainland Europe where rates are between 25-50% France and Spain (134) [Ib]. Erythromycin resistance is higher at 9.3% in 2007, but has decreased since 2004, and also varies across the country between 5.2% in the North East of England to 14.7% in London. It is much higher in mainland Europe with 25-50% macrolide resistance in France and Italy (134) [Ib]. In 2006-7 erythromycin resistance was found in 12% of invasive isolates from children, with serotype 19A still very uncommon (135) [Ib].

8.3.2 Group A Streptococcus.

There is also varying prevalence of macrolide resistance in *Streptococcus pyogenes* (GAS) worldwide, in some areas up to 40% (136) [Ib], and beta-lactamase production in *Haemophilus influenzae* is widespread. In the UK, overall, the reported resistance rates for GAS to clindamycin, erythromycin and tetracycline were 5.1%, 5.6% and 14.0% respectively in 2007, with 4.4% resistant to all three. Penicillin resistance has not been seen to date and penicillin remains the therapeutic drug of choice (134) [Ib].

8.3.3 *S. aureus*

MRSA is of increasing concern within the USA and has been implicated in the increase in pleural empyemas seen in the USA (137) [III]. Although MRSA contributes to 31% of *S. aureus* bacteraemia within the UK (134) [Ib], it has not yet been a significant factor in either empyema or pneumonia in the UK (31) [II] (138) [II] (41) [II].

8.3.4 What is the clinical impact of antibiotic resistance?

Management of pneumococcal infections has been challenged by the development of resistance and, more recently, the unexpected spread of resistant clones of serotypes, such as 19A, following the introduction of a conjugate pneumococcal vaccine for use in children in 2000.

Despite the increasingly wide literature on antibiotic resistance, the impact this has on clinical outcomes for children has less evidence. However series of children with pneumonia from USA (139) [III] and South Africa (140) [II] found no difference in outcome between penicillin resistant or sensitive pneumococcal pneumonias. Nor were differences noted in children with pleural empyema and sensitive or resistant pneumococcal disease in terms of duration of fever and tachypnea, need of surgical treatment, bacteremia incidence, mean duration of therapy, or length of hospital stay (141) [III].

Outcomes in pneumococcal meningitis have not been shown to differ significantly between susceptible and resistant isolates (142) [III].

In the face of no widespread failure of antibiotic therapy, high-dose penicillin G, other beta lactams and many other agents continue to be efficacious parenterally for pneumonia and bacteraemia (130) [III].

Increased macrolide use is associated with pneumococcal and GAS resistance (133) [Ib] and bacteria may acquire macrolide resistance very fast if used indiscriminately (143) [Ib]. However, the clinical impact of macrolide resistance is unclear with case reports describing clinical failure in adults with bacteraemic infection (144) [III] but not with pneumonia (145) [II] (146) [II]. No association with resistance and treatment failure has been demonstrated as yet in children.

8.4 Which antibiotic should be used?

It is clear that there is variation in medical prescribing that largely reflects custom, local practice and availability. We have reviewed the relevant scientific evidence and provide recommendations based, where possible, on that evidence, but more frequently recommendations are based on judgements about what constitutes safe and effective treatment. In pneumonia in children, the nature of the infecting organism is almost never known at the initiation of treatment and the choice of antibiotic is therefore determined by the reported prevalence of different pathogens at different ages, knowledge of resistance patterns of expected pathogens circulating within the community and the immunization status of the child.

Randomised controlled trials comparing different antibiotics have shown similar or equivalent efficacy variously for: macrolides, amoxicillin, co-amoxiclav, cefaclor, erythromycin, cefixime, cefpodoxime, cefuroxime. Ceftriaxone (147) [II] (148) [II] (149) [II] (63) [II] (19) [II] (150) [II] (151) [II] (152) [II]. Additionally, newer antibiotics such as levofloxacin (153) [II] in similar studies from the USA show efficacy. Despite pharmacological differences in oral cephalosporins, (cefaclor has an association with skin reactions but, compared to cefalexin, good activity against *S pyogenes* and *S pneumoniae*; cefixime is poorly active against *S aureus* and cefuroxime axetil has poor oral absorption), no differences in clinical efficacy have been identified. There also appears to be little difference between different macrolides (154) [II] (52) [II]

(155) [II], although clarithromycin may be better tolerated than erythromycin (156) [II].

A Cochrane review of antibiotics in childhood pneumonia in 2006 (157) [Ia] was updated in 2010 (158) [Ia]. 27 studies were reviewed, encompassing 11,928 children, comparing multiple antibiotics. However, most of these were enrolled on the basis of WHO defined clinical criteria for pneumonia and were from developing countries. It is recognized that 82% of children identified clinically fulfilling the WHO criteria for pneumonia have normal chest radiographs (159) [Ib]. Five studies were from high income developed countries and less than a quarter enrolled using chest radiograph definitions. Findings included equivalence for amoxicillin and macrolides (azithromycin and clarithromycin), procaine penicillin and cefuroxime. On the basis of single studies co-amoxiclav was comparable to azithromycin and cefpodoxime but superior to amoxicillin.

High dose amoxicillin twice daily is a pharmacokinetically satisfactory dosing regime and may aid compliance (160) [Ib], though in Pakistan, outcomes for infants aged 2-59 months with non-severe outpatient treated clinical pneumonia were the same with standard and double dose amoxicillin (161) [Ib].

In adults macrolide antibiotics have been shown to reduce the length and severity of pneumonia caused by *Mycoplasma pneumoniae* compared with penicillin or no antibiotic treatment (162) [abstract only]. In an experimental

mouse model of respiratory *M. pneumoniae* infection, clarithromycin significantly decreased *M. pneumoniae* levels and cytokines compared with placebo (163) [II]. There is little evidence for specific antibiotics in children.

Improved short and long term outcomes have been described in children with respiratory tract infections (a mixture of upper and lower by clinical diagnosis), treated with macrolides compared to those not treated (66) [II]. Of those children with LRTI due to *M. pneumoniae* and/or *C. pneumoniae* assessed as "clinical failures", 83% had not been treated with macrolides (56) [II]. Children with *M. pneumoniae* pneumonia in Taiwan had significantly shorter fever durations if receiving macrolides (164) [II]. However, Cochrane review of specific mycoplasma treatment in children with lower respiratory tract infections did not find enough evidence to indicate whether antibiotics improved outcomes in children with *M. pneumoniae* LRTI, though they suggested that the Esposito study indicated that some children may benefit (165) [IVa].

A recent report of a closed audit loop showed that prescribing can be rationalised to simple narrow spectrum antibiotics with the introduction of a local management protocol. This has the potential to reduce the likelihood of antibiotic resistance developing (138) [II].

Information on the antibiotics recommended for treatment of CAP is available in the British National Formulary for Children.

Evidence statement

- Although there appears to be no difference in response to conventional antibiotic treatment in children with penicillin resistant *S. pneumoniae*, the data are limited and the majority of children in these studies were not treated with oral beta-lactam agents alone. [B-]

Recommendations

- Amoxicillin is first choice for oral antibiotic therapy in all children because it is effective against the majority of pathogens which cause CAP in this group, is well tolerated, and cheap. Alternatives are co-amoxiclav, cefaclor, erythromycin, azithromycin and clarithromycin. [B]
- Macrolide antibiotics may be added at any age if there is no response to first line empiric therapy. [D]
- Macrolide antibiotics should be used if either mycoplasma or chlamydia pneumonia is suspected (or in very severe disease). [D]
- Amoxicillin should be used as first line treatment at any age if *S. pneumoniae* is thought to be the likely pathogen. [B]
- If *Staph. aureus* is thought the likely pathogen, augmentin or a combination of flucloxacillin with amoxicillin, is appropriate. [D]
- In pneumonia associated with influenza, augmentin is recommended. [D]

8.5 How should antibiotics be given?

One large, adequately powered trial (123) [Ib] compared the efficacy of treatment with intramuscular penicillin (one dose) and oral amoxicillin given for 24–36 hours to children with pneumonia treated in the Emergency Department. Evaluation at 24–36 hours did not show any differences in outcome between the groups.

Oral amoxicillin has been shown to be as effective as parenteral penicillin, even in severe pneumonia, in the UK, Africa/Asia and Pakistan (166) [Ib] (167) [Ib] (159) [Ib]. The PIVOT trial (167) [Ib] randomized UK children over the age of 6 months admitted to hospital with pneumonia to either oral amoxicillin or intravenous penicillin. Only the most severe were excluded (oxygen saturation < 85%, shock, pleural effusion requiring drainage). The antibiotics produced equivalent outcomes.

A large multicentre, randomised, open-label equivalency study in eight developing countries in Africa, Asia, and South America enrolled 1702 infants aged 3-59 months with severe, clinically defined pneumonia, and randomized them either to oral amoxicillin or parenteral penicillin. Identical outcomes were obtained in each group, with 19% treatment failure (166) [Ib].

In a randomized control trial, a group in Pakistan also studied severe pneumonia and compared home treatment using twice daily oral high dose amoxicillin with parenteral ampicillin, with equivalent results in both groups (159) [Ib].

Two of these were reviewed in a Cochrane review (168) [Ia], which concluded oral therapy was a safe and effective alternative to parenteral treatment, even in severe disease in hospitalized children.

Parenteral administration of antibiotics in children (which, in the UK, is generally intravenous) is traumatic as it requires the insertion of a cannula, drug costs are much greater than with oral regimens, and admission to hospital is generally required. However, in the severely ill child, parenteral administration ensures that high concentrations are achieved rapidly in the lung. The parenteral route should also be used if there are concerns about oral absorption.

Recommendations

- Antibiotics administered orally are safe and effective for children presenting with even severe CAP. [A+]
- Intravenous antibiotics should be used in the treatment of pneumonia in children when the child is unable to tolerate oral fluids or absorb oral antibiotics (for example, because of vomiting) or presents with signs of sepsis or complicated pneumonia. [D]
- Appropriate intravenous antibiotics for severe pneumonia include amoxicillin, co-amoxiclav, cefuroxime, and cefotaxime/ceftriaxone. These can be rationalised if a microbiological diagnosis is made. [D]

8.6 When should antibiotics be switched from parenteral to oral?

No randomised controlled trials were identified that addressed the issue of when it is safe and effective to transfer from intravenous to oral antibiotic therapy. There can thus be no rigid statement about the timing of transfer to oral treatment and this is an area for further investigation.

Recommendation

- In a patient who is receiving intravenous antibiotic therapy for the treatment of CAP, oral treatment should be considered if there is clear evidence of improvement. [D]

8.7 What is the optimal duration of antibiotic treatment?

Since 2000, there have been a few trials and a Cochrane review comparing duration of antibiotic treatments (169) [II]. All are from developing countries, except for a trial from Finland, which randomized children with pneumonia (a high proportion of which had a bacterial cause) to either 4 or 7 days of parenteral penicillin or cefuroxime, with no difference in outcome (150) [Ib].

Three randomised trials of short course oral antibiotics, only 2 of which are published (170) [II] (125) [II], were reviewed in the Cochrane review by Haider (169) [II]. These studies enrolled infants in developing countries with WHO defined clinical criteria of non severe pneumonia to either 3 or 5 days oral amoxicillin. No difference was seen in acute cure or relapse rates between

the groups. There are some difficulties translating this data as these cohorts of infants include many who would be defined as having bronchiolitis with wheeze (13%) and 23% RSV positive in the Agarwal group; 23% wheeze, 18% RSV positive in the Qazi group. Some had simple upper respiratory tract infections as, although 99% had a cough, only 38% had difficulty breathing and 80% had < 10 breaths excess respiratory rate. Only 14% had chest radiograph changes (170) [II]. Most of these children may not have needed antibiotics at all, and indeed fall into the group that, if vaccinated, it is suggested do not require antibiotic treatment in the UK. It is therefore still not known whether a 3 day antibiotic course is sufficient to treat a child with a bacterial pneumonia.

Recommendations

- In children less than 2 years old, presenting with mild symptoms of lower respiratory tract infection, who are unvaccinated or felt to require antibiotics, 3 days amoxicillin can be given. [B]
- All other children should have standard 5 day course amoxicillin in the absence of any short course evidence. [D]

9. Complications and failure to improve

9.1 What factors should be considered in children who fail to improve?

If a child remains pyrexial or unwell 48 hours after treatment has commenced, re-evaluation is necessary. Answers to the following questions should be sought:

- Is the patient having appropriate drug treatment at an adequate dosage?
- Is there a lung complication of pneumonia such as a collection of pleural fluid with the development of an empyema or evidence of a lung abscess?
- Is the patient not responding because of a complication in the host such as immunosuppression or coexistent disease such as cystic fibrosis?

There has been concern that the increased incidence of penicillin resistant *S pneumoniae* would lead to failure of treatment. However, one study (171) [III] has shown that there is no difference in the percentage of children in hospital treated successfully with penicillin or ampicillin when the organism was penicillin susceptible or penicillin resistant. The authors noted that the serum concentration of penicillin or ampicillin achieved with standard intravenous dosages was much greater than the MIC for most penicillin resistant strains.

9.2 What are the common complications of CAP?

9.2.1 Pleural effusions and empyema

Parapneumonic effusions are thought to develop in 1% of community acquired pneumonias (172) [III] but in those admitted to hospital effusions may be found in as many as 40% of cases (173) [III]. It has been reported recently that empyema thoracis may be increasing in incidence (174) [III] (175) [III]. A persisting pyrexia despite adequate antibiotic treatment should always lead the clinician to be suspicious of the development of empyema (175) [III]. Fluid in the pleural space is revealed on the chest radiograph and the amount of fluid is best estimated by ultrasound examination. A clinician should consider empyema when a child has a persistent fever beyond 7 days in total (175) [III] or a fever not settling after 48 hours of antibiotics. Where an effusion is present and the patient is persistently pyrexial, the pleural space should be drained, ideally in a specialist centre.

There is debate as to the best method of draining effusions. For more details on diagnosis and management of empyema refer to the BTS Guidelines on Pleural Disease in Children (113).

9.2.2 Necrotising pneumonias

Lung abscess, although a rare complication of CAP in children, is believed to be an increasing and important complication to be aware of (176) [III] (177) [III]. There is some data suggesting some children are predisposed to this more severe form of lung infection. The predisposing factors include: congenital cysts, sequestrations, bronchiectasis, neurological disorders, and

immunodeficiency (178) [III]. There is also emerging data that certain serotypes of pneumococcal disease are more likely to lead to necrotising pneumonia and abscess formation than others (176) [III] and that *S. aureus* with Panton-Valentine Leukocidin (PVL) toxin can lead to severe lung necrosis with a high risk of mortality (179) [III]. Suspicion of abscess/necrosis is often raised on the chest radiograph and diagnosis can be confirmed by CT scanning (180) [IVb]. Prolonged intravenous antibiotic courses may be required until the fever settles. Lung abscess with an associated empyema may be drained at decortication if the abscess is close to the parietal pleura and is large. Ultrasound or CT guided percutaneous drainage can be used (181) [III].

9.2.3 Septicaemia and metastatic infection

Children can present with symptoms and signs of pneumonia but also have features of systemic infection. Children with septicaemia and pneumonia are likely to require high dependency or intensive care management. Metastatic infection can rarely occur as a result of the septicaemia associated with pneumonia. Osteomyelitis or septic arthritis should be considered, particularly with *S. aureus* infections.

9.2.4 Haemolytic Uraemic Syndrome

Strep. pneumoniae is a rare cause of haemolytic uraemic syndrome (HUS). A recent case series found that out of 43 cases of pneumococcal HUS, 35

presented with pneumonia and 23 presented with empyema (182) [II]. Although a rare complication, in cases with pallor, profound anaemia and anuria, this should be considered.

9.2.5 Long term sequelae

Severe pneumonia, empyema and lung abscess can lead to long term respiratory symptoms secondary to areas of fibrosis or bronchiectasis. Children with empyema and lung abscess should be followed up after discharge until they have recovered completely and their chest radiograph has returned to near normal. There is also prospective data to suggest children who have had an episode of CAP are more likely to suffer from prolonged cough (19% vs 8%), chest wall shape abnormality (9% vs 2%) and also doctor diagnosed asthma (23% versus 11%) (41) [Ib]. In this study those children with a pre-existing diagnosis of asthma were far more likely to suffer persistent cough symptoms. The reasons for this are as yet unclear but it is advised to counsel parents and carers at discharge to consult their doctor if these symptoms occur.

9.3 Complications of specific infections

S. aureus pneumonia

Pneumatoceles occasionally leading to pneumothorax are more commonly seen with *S. aureus* pneumonia. The long-term outlook is good with normal

lung function (183) [III] (184) [III]. There has been an increase in methicillin resistant *staphylococcus aureus* (MRSA) and some severe cases reported requiring extra-corporeal membrane oxygenation (ECMO) (185) [III]. The Panton-Valentine Leukocidin (PVL) toxin-producing *S. aureus* can lead to severe lung necrosis with a high risk of mortality (179) [III]. In the UK and other developed countries, *S. aureus* pneumonia is sufficiently unusual to warrant investigation of the child's immune system.

Mycoplasma pneumonia

Complications in almost every body system have been reported in association with *M. pneumoniae*. Rashes are common; the Stevens-Johnson syndrome occurs rarely; haemolytic anaemia, polyarthritis, pancreatitis, hepatitis, pericarditis, myocarditis and neurological complications including encephalitis, aseptic meningitis, transverse myelitis and acute psychosis have all been reported.

S. pneumoniae

Pneumococcus is the most common bacteria to cause CAP and the major complication of empyema thoracis. It is increasingly being found to cause necrotic pneumonia and abscess formation that is believed to be associated with certain serotypes (176) [III]. Vaccination programmes against pneumoccocus do not protect against all serotypes and surveillance studies monitoring for shift in serotype prevalence are ongoing. The rare complication

of haemolytic uraemic syndrome (HUS) is described with pneumococcal pneumonia.

Recommendation

- If a child remains pyrexial or unwell 48 hours after hospital admission with pneumonia, re-evaluation is necessary with consideration given to possible complications. [D]
- Children with severe pneumonia, empyema and lung should be followed up after discharge until they have recovered completely and their chest radiograph has returned to near normal. [D]

10. Prevention and vaccination

General improvements in public health over the last century have contributed greatly to the prevention of CAP. However, there is still more to be done in improving housing, reducing crowding, reducing smoking, and improving the uptake of routine vaccines.

10.1 Would smoking cessation help?

A recent US paper estimated the annual excess health care service use and expenditure for respiratory conditions in children linked to exposure to smoking in the home (186) [III]. They linked data from the nationally representative Medical Expenditure Panel survey with the National Health Interview survey that has self-reported data on smoking inside the home. Data was obtained on 2759 children aged 0-4 years and respiratory health assessed in 3 groups: smoking inside the home on 1 or more days a week; smoking outside the home and no smoking, using multivariant analysis. Children exposed to smoking in the home had an increased likelihood of hospital admission (4.3% vs 1.1% at least 1 hospital stay per year) and an increased likelihood of an emergency unit visit for respiratory illness (8.5% vs 3.6%). Data was not specific for pneumonia. Indoor smoking was associated with $117 additional healthcare expenditure for respiratory conditions per child. Smoking cessation would decrease respiratory illness in children but there is no specific data for pneumonia.

10.2 What is the influence of vaccination?

Vaccination has made a real impact on pneumonia and child survival worldwide (187) [III].

10.2.1 *Haemophilus influenza*

The impact of Hib conjugate vaccine on pneumonia in the UK is not known, but a number of clinical trials and case control studies from the developing world have established that the introduction of this vaccine reduced radiologically confirmed pneumonia by 20% (188) [Ib] to 30% (189) [II].

10.2.2 *Bordetella pertussis*

Whooping cough continues to be seen in the UK and infants < 6 months of age have the highest morbidity and mortality (190) [III]. In the US from 1997-2000, 29,134 cases of pertussis were reported of whom 7203 were younger than 6 months; 5.2% overall and 11.8% of those < 6 months had pneumonia. There were 62 deaths, 56 (90%) of whom were < 6 months (191) [III]. Improved uptake of primary pertussis vaccination would help to prevent cases, but another important factor may be an increasing pool of susceptible older children and adults, which is why some countries have elected to have a booster vaccination programme in adolescence (190) [III].

10.2.3 *Streptococcus pneumoniae*

The introduction of conjugate pneumococcal vaccines has been the biggest recent change in pneumonia prevention. They have been hugely successful in decreasing invasive pneumococcal disease in children and there have been several studies of the effectiveness in decreasing respiratory morbidity. In the developed world follow up from the controlled 7 valent vaccine trial of 37,868 children in the US using the WHO standardisation for radiographic definition of pneumonia showed efficacy against first episode of radiograph confirmed pneumonia adjusting for age, gender and year of vaccination of 30.3% (95% CI = 10.7-45.7%, p = 0.0043) for per protocol vaccination (192) [Ib]. Evidence that efficacy is sustained outwith a clinical trial comes from a time series US analysis showing that 4 years after the universal vaccination programme started all cause pneumonia admission rates in children < 2 years had declined by 39% (95% CI 2-52) (193) [III]. Similarly, 3 population based pneumonia surveillance studies from US health maintenance organisations demonstrated fewer outpatient and emergency visits for pneumonia in children <2 years (a decrease of 19-33 per 1000 children per year) (194) [III]; a decrease of 6 (95% CI 5.4-6.7)per 1000 hospitalisations for all cause pneumonia and 40.8 (95% CI 38.8-42.7) per 1000 fewer ambulatory visits in children <2 years (195) [III] and in the third study, a significant 26% reduction in confirmed outpatient events for pneumonia in children < 1year old (196) [III]. A single blind observational follow up study of 7 valent vaccine in Italy also confirmed that radiologically confirmed community acquired pneumonia was significantly less in the vaccinated group (RR 0.35; 95% CI 0.22-0.53) (197) [II].

Introduction of the 7 valent conjugate vaccine in England and Wales in 2006 has almost abolished invasive disease caused by these pneumococcal serotypes in children < 2 years and has substantially reduced the number in older children. However there has been an increase in reports of invasive disease caused by non vaccine serotypes (198) [IVb]. A national time-trends study, 1997-2008 has recently published results on the impact of the seven-valent pneumococcal conjugate vaccination (PCV7) programme on childhood hospital admissions for bacterial pneumonia in the UK showing a 19% decrease (RR 0.81; 95% CI 0.79-0.83) from 2006 to 2008 (8) [III].

10.2.4 *Influenza*

The UK influenza vaccine programme for children is continually evolving following the H1N1 pandemic in 2009. There is no data of effectiveness in relation to childhood pneumonia in the UK. In Japan analysis of all age pneumonia mortality data suggested universal childhood vaccination offered population protection with prevention of 1 death for every 420 children vaccinated (199) [III]. In Ontario, Canada the effects of introduction of a universal influenza immunisation programme was compared with targeted immunisation in other provinces (200) [II]. After introduction all age mortality decreased more in Ontario than other provinces as did hospitalisations, emergency department visits and doctors office visits in the paediatric age groups (the <5 years and 5-19 years).

Evidence Statements

- Vaccination has had major impact on pneumonia and child mortality worldwide. [B+]
- Conjugate pneumococcal vaccines decrease radiographically confirmed pneumonia episodes in young children by around 30%. [A-]

Appendix 1: Search Strategy

Sources to be searched:

MEDLINE and MEDLINE In process
EMBASE
Cochrane Database of Systematic Reviews (CDSR)
Database of Abstracts of Reviews of Effects (DARE)

2000 onwards
All study types
English language only
Human only
Single search strategy used to cover all guideline sections

Searches for guidelines (in search order)

MEDLINE and MEDLINE In Process

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present>
Searched via Ovid interface 03/02/09

1 exp Pneumonia/ (59061)
2 exp Pneumonia, Bacterial/ (12548)
3 pneumoni$.ti,ab. (93895)
4 bronchopneumoni$.ti,ab. (2480)
5 pleuropneumoni$.ti,ab. (1942)
6 exp Respiratory Tract Infections/ (233912)
7 (lower respiratory adj3 infection$).ti,ab. (3958)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (289474)
9 exp Ambulatory Care/ (38374)
10 outpatient$.ti,ab. (75586)
11 ambulatory.ti,ab. (46196)
12 Community-Acquired Infections/ (6335)
13 (commun$ adj3 acquir$).ti,ab. (8442)
14 exp Family Practice/ (53901)
15 "emergency room".ti,ab. (7730)
16 9 or 10 or 11 or 12 or 13 or 14 or 15 (201181)
17 8 and 16 (11422)
18 exp Pediatrics/ (33505)
19 (pediatric$ or paediatric$).ti,ab. (142562)
20 exp Child/ (1252259)
21 exp Infant/ (774375)
22 exp Child, Preschool/ (609315)
23 exp Adolescent/ (1256580)
24 (child$ or infant$ or boy$ or girl$ or toddler$ or adolescen$ or pre-school$ or preschool$ or teenage$ or youth$).ti,ab. (1045471)
25 18 or 19 or 20 or 21 or 22 or 23 or 24 (2504020)
26 25 and 17 (4000)
27 limit 26 to yr="2000 - 2009" (2155)

28 limit 27 to english language (1788)

EMBASE
Database: EMBASE <1980 to 2009 Week 5>
Searched via Ovid interface 03/02/09

1 exp Pneumonia/ (83858)
2 exp Bacterial Pneumonia/ (4709)
3 pneumoni$.ti,ab. (73858)
4 bronchopneumoni$.ti,ab. (1507)
5 pleuropneumoni$.ti,ab. (916)
6 exp Lower Respiratory Tract Infection/ (60037)
7 (lower respiratory adj3 infection$).ti,ab. (3828)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (152142)
9 exp Ambulatory Care/ (12331)
10 outpatient$.ti,ab. (65380)
11 ambulatory.ti,ab. (35969)
12 (commun$ adj3 acquir$).ti,ab. (8151)
13 exp General Practice/ (22748)
14 "emergency room".ti,ab. (6257)
15 9 or 10 or 11 or 12 or 13 or 14 (136787)
16 8 and 15 (7939)
17 exp Pediatrics/ (28273)
18 (pediatric$ or paediatric$).ti,ab. (118140)
19 exp Child/ (628521)
20 exp Infant/ (173469)
21 exp Child, Preschool/ (104929)
22 exp Adolescent/ (437373)
23 (child$ or infant$ or boy$ or girl$ or toddler$ or adolescen$ or pre-school$ or preschool$ or teenage$ or youth$).ti,ab. (699906)
24 17 or 18 or 19 or 20 or 21 or 22 or 23 (1123738)
25 24 and 16 (1891)
26 limit 25 to yr="2000 - 2009" (1237)
27 limit 26 to english language (1054)

Cochrane Database of Systematic Reviews (CDSR)
Database of Abstracts of Reviews of Effects (DARE)
Both searched via Cochrane Library 03/02/09
http://www.mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html

#1 MeSH descriptor Pneumonia explode all trees 2084
#2 MeSH descriptor Pneumonia, Bacterial explode all trees 576
#3 pneumoni*:ti,ab 3944
#4 bronchopneumoni*:ti,ab 89
#5 pleuropneumoni*:ti,ab 1
#6 MeSH descriptor Respiratory Tract Infections explode all trees 7876
#7 ((lower respiratory) NEAR infection*):ti,ab 944
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) 10498
#9 MeSH descriptor Ambulatory Care explode all trees 3288
#10 outpatient*:ti,ab 12363

#11 ambulatory:ti,ab 5572
#12 MeSH descriptor Community-Acquired Infections, this term only 428
#13 (commun* NEAR acquir*):ti,ab 723
#14 MeSH descriptor Family Practice explode all trees 2017
#15 emergency room:ti,ab 620
#16 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15) 21703
#17 (#8 AND #16) 1161
#18 MeSH descriptor Pediatrics explode all trees 409
#19 (pediatric* or paediatric*):ti,ab 7412
#20 MeSH descriptor Child explode all trees 0
#21 MeSH descriptor Infant explode all trees 10246
#22 MeSH descriptor Child, Preschool explode all trees 0
#23 MeSH descriptor Adolescent explode all trees 60024
#24 (child* or infant* or boy* or girl* or toddler* or adolescen* or pre-school* or preschool* or teenage* or youth*):ti,ab 51439
#25 (#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24) 104464
#26 (#17 AND #25) 411
#27 <nothing>, from 2000 to 2009 260235
#28 (#26 AND #27) 189

Of the 189 total results for the entire Cochrane Library 12 were from CDSR and 1 from DARE.

Total Results

Source	Records	After de-duplication	Custom 4 field
MEDLINE and MEDLINE In Process	1788	1779	MEDLINE 03/02/09
EMBASE	1054	291	EMBASE 03/02/09
CDSR	12	5	CDSR 03/02/09
DARE	1	1	DARE 03/02/09
Total	**2855**	**2076**	

2076 results saved to a compressed Endnote X1 library (bts cap children search.enlx). Custom 4 field of each record marked as in above table to show source.

Appendix 2: Template data collection form for extracting study characteristics and study design items for risk of bias assessment

This form should be adapted for the collection of study characteristics in line with the methods outlined in the protocol of the review.

Part 1: **Administrative details**

Extractor name:

Date:

Study ID:

Citation(s):

Part 2: Study methods, participants, interventions and outcomes

(intended to be entered in section 'Characteristics of included studies')

Methods

STUDY DESIGN (parallel, crossover):

LOCATION, NUMBER OF CENTRES:

DURATION OF STUDY:

Participants

N SCREENED:

N RANDOMISED:

N COMPLETED:

M=

F=

AGE:

BASELINE DETAILS:

INCLUSION CRITERIA:

EXCLUSION CRITERIA:

Interventions

INTERVENTION:

CONTROL:

RUN-IN PERIOD:

TREATMENT PERIOD:

FOLLOW-UP PERIOD:

CO-INTERVENTIONS:

Outcomes:

Coding for subgroup analysis (e.g. adults/children; mild/moderate/severe etc):

Coding for sensitivity analysis (e.g. blinding; etc):

Part 3: Risk of bias items, notes for other extractors and correspondence

Risk of bias assessment (amend as per stated risk of bias items in protocol):

Item	Question	Judgement (delete as appropriate)	Description (provide summary or paste from trial

			report/correspondence)
Adequate allocation generation?	Was the allocation sequence adequately generated?	Yes/No/Unclear	
Allocation concealment?	Was allocation adequately concealed?	Yes/No/Unclear	
Blinding?	Was knowledge of the allocated interventions adequately prevented during the study? (the importance of this may depend on the outcome(s) being measured)	Yes/No/Unclear	
Incomplete data addressed?	Were incomplete data adequately addressed?	Yes/No/Unclear	
Free of selective reporting?	Are reports of the study free of suggestion of selective reporting bias?	Yes/No/Unclear	
Free of other bias?	(Use additional rows if further risk of bias items are required)	Yes/No/Unclear	
(Add items as appropriate)		Yes/No/Unclear	

Notes:

Requirement for further correspondence (see sheets with extracted data to see whether numerical outcome data are also required):

Yes/No

What information regarding the design of the study is needed from investigators/study sponsors?

What information regarding the results of the study is required from investigators/study sponsors?

Appendix 3: Brief description of the generic levels of evidence and guideline statement grades used

Evidence Level	Definition	Guideline statement grade
Ia	A good recent systematic review of studies designed to answer the question of interest	A+
Ib	One or more rigorous studies designed to answer the question, but not formally combined	A-
II	One or more prospective clinical studies which illuminate, but do not rigorously answer, the question	B+
III	One or more retrospective clinical studies which illuminate, but do not rigorously answer, the question	B-
IVa	Formal combination of expert views	C
IVb	Other information	D

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