Dott. Eugenia Bruzzese

Dipartimento di Scienze Medico Traslazionali
Università Federico II

Impiego razionale degli antibiotici nelle infezioni delle vie aeree in età evolutiva: le polmoniti

Bari 12-14 Settembre 2013

AGENDA

- Epidemiologia delle polmoniti
- Diagnosi di polmonite di comunità
- Trattamento delle polmoniti di comunità
- Possibili strategie per un uso giudizioso degli antibiotici

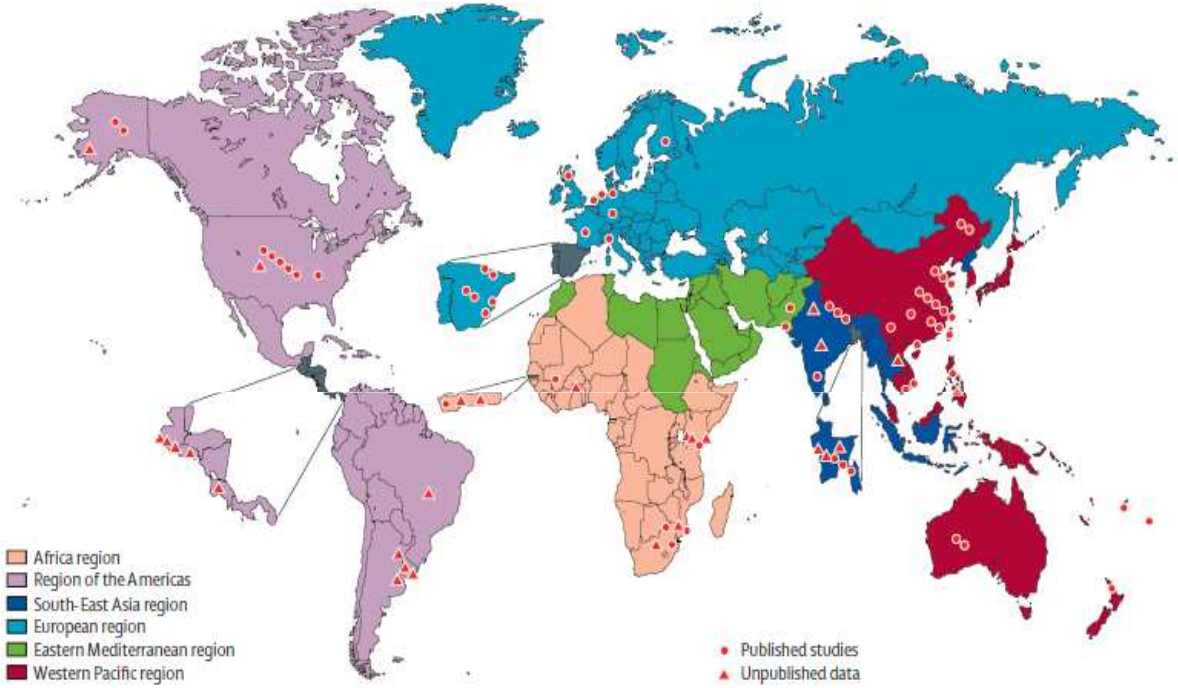
British Thoracic Society

American Academy of Pediatrics

NHS
North West & North Wales Paediatric Critical Care Network

Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis

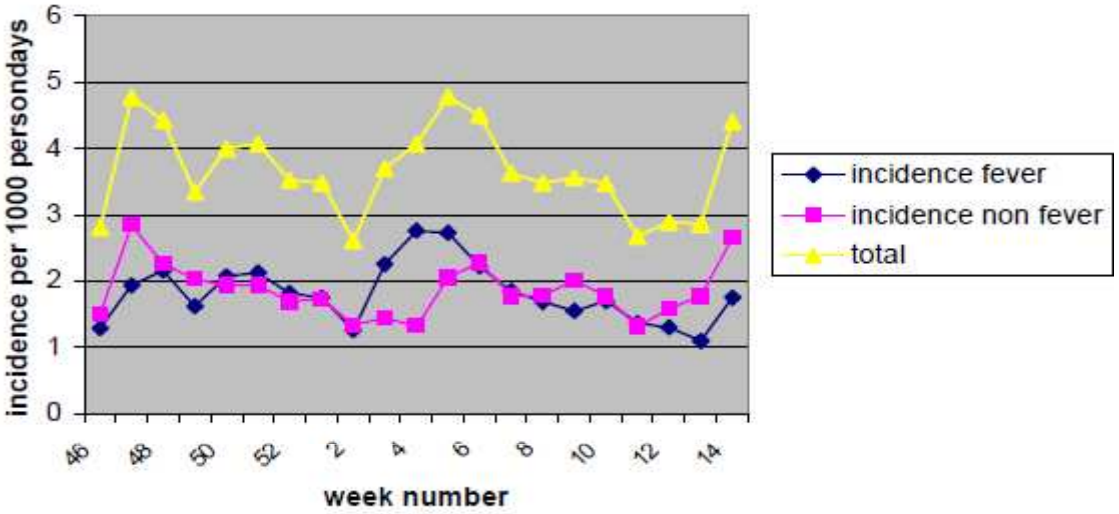
Lancet 2013



- Acute lower respiratory infections (**ALRI**), such as pneumonia and bronchiolitis, are a leading cause of **morbidity and mortality** in young children.
- In 2010, **1·4 million children died** because of such infections
- In 2010, **11·9 million** (95% CI 10·3–13·9 million) episodes of **severe** and **3·0 million** (2·1–4·2 million) episodes of **very severe** ALRI resulted in hospital admissions in young children worldwide.

INCIDENZA DELLE IRA DURANTE LA STAGIONE INFLUENZALE

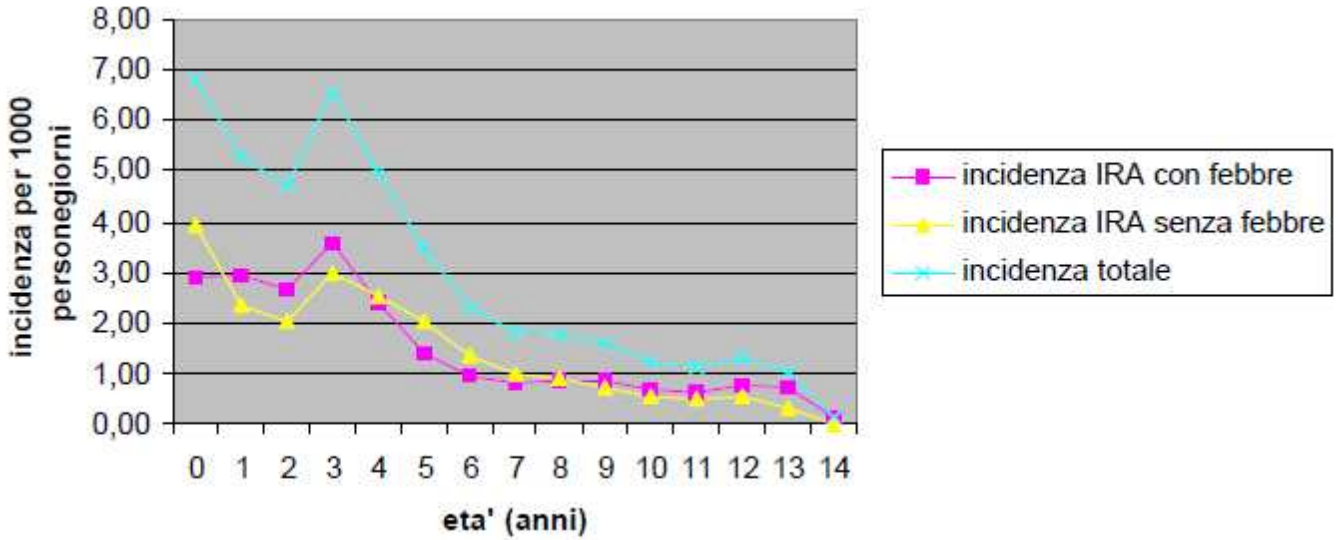
INCIDENZA DELLE INFEZIONI RESPIRATORIE ACUTE



pedianet

LE INFEZIONI RESPIRATORIE ACUTE IN ETA PEDIATRICA

INCIDENZA ED ETA'



INFEZIONI RESPIRATORIE E PRESCRIZIONE DI ANTIBIOTICI

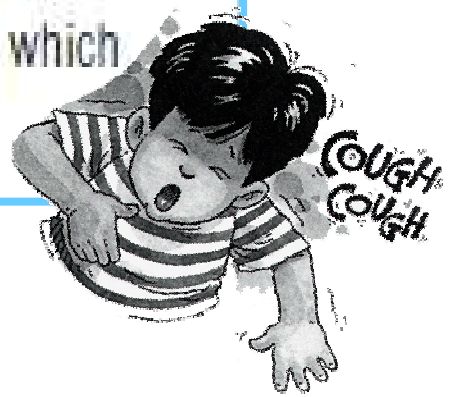
Pediatrics. 2011 Dec;128(6):1053-61. Epub 2011 Nov 7.

Antibiotic prescribing in ambulatory pediatrics in the United States.

Hersh AL, Shapiro DJ, Pavia AT, Shah SS.

Department of Pediatrics, University of Utah, Salt Lake City, UT 84108, USA. adam.hersh@hsc.utah.edu

WHAT THIS STUDY ADDS: Respiratory conditions account for >70% of antibiotic prescriptions in ambulatory pediatrics. Broad-spectrum antibiotics, especially macrolides, represent 50% of pediatric antibiotic use. Broad-spectrum antibiotics are frequently prescribed unnecessarily for conditions for which antibiotics are unlikely to provide benefit.



Rapporto ARNO 2011: PRESCRIZIONE DI ANTIBIOTICI

CINECA

Gli antibiotici più prescritti nei bambini: dettaglio per ATC III livello

Rank	ATC	Descrizione	Trattati	% Trattati (N=549.401)[1]	% spesa	Spesa media per trattato	% pezzi	N. medio pezzi per trattato
1	J01C	Penicilline ad ampio spettro	374.405	68,1	36,9	15,41	52,4	2,2
2	J01F	Macrolidi e lincosamidi	201.472	36,7	25,5	19,73	21,3	1,7
3	J01D	Cefalosporine	169.913	30,9	30,7	28,2	24,3	2,3
4	J01X	Altri antibatterici	8.392	1,5	0,8	14,24	0,6	1,2
5	J01E	Sulfonamidi e trimetoprim	5.188	0,9	0,2	5,99	0,5	1,4
6	J01M	Chinolonici	1.790	0,3	0,3	27,08	0,2	1,8
7	J01G	Aminoglicosidici	1.647	0,3	5,6	527,29	0,6	5,6
8	J01A	Tetracicline	636	0,1	0,1	18,5	0,1	2,4
Totale			**549.401**	**-**	**100**	**28,42**	**100**	**2,9**

Quali sono i principali problemi nella gestione della polmonite di comunità in pediatria?

- **Difficoltà nella diagnosi**
- **Difficoltà nell'isolamento dell'agente eziologico**
- **Dati limitati su farmacocinetica/farmacodinamica degli antibiotici in età pediatrica**
- **Comparsa di resistenze**

British Thoracic Society

American Academy of Pediatrics

NHS
North West & North Wales
Paediatric Critical Care Network

Definizione di polmonite di comunità in età pediatrica

Definition of CAP	
World Health Organization	Cough or difficulty breathing Fast breathing: 2-12 mo ≥ 50 breaths/min 12-60 mo: ≥40 breaths /min
British Thoracic Society	Persistent or repetitive fever > 38.5° C together with chest recession and an increased respiratory rate
Infectious Diseases Society of America	Presence of signs and symptoms of pneumonia in a previously healthy child caused by an infection that has been acquired outside the hospital

Pediat Clin N Am 2013

Quali sono gli agenti eziologici più frequenti di polmonite?

TABLE 1. Principal Bacteria Causing Childhood Pneumonia (Community-Acquired Apart From the Age Group Birth-1 Month), by Age

Bacteria	Age group			
	Birth to 1 month	1 to 3 months	3 months to 5 years	5 to 18 years
Streptococcus pneumoniae	+	+++	++++	+++
*Haemophilus influenzae**	+	+	+	±
Streptococcus pyogenes		+	+	+
Staphylococcus aureus	++	++	+	+
Streptococcus agalactiae	+++	+		
Escherichia coli	++	+		
Mycoplasma pneumoniae		+	++	++++
Chlamydiophyla pneumoniae		+	+	++
Chlamydia trachomatis	+	++		
Bordetella pertussis	±	++	+	+

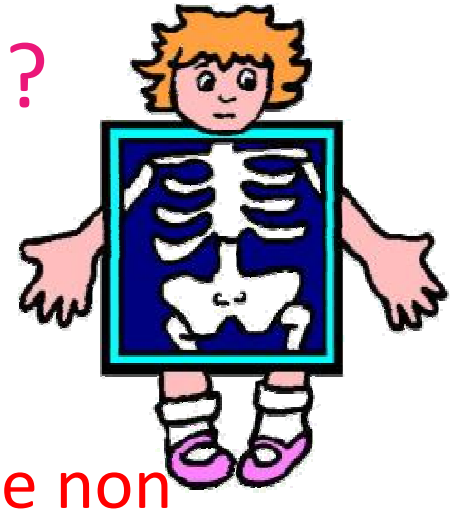
Adapted from Principi and Esposito.[2,5]

*Mainly untypeable because of wide use of Hib vaccine across Europe.

++++ indicates very common; +++, common; ++, relatively uncommon; +, rare; ±, very rare; –, absent.

Esposito et al, PIDJ 2012

Quando fare la radiografia del torace?



NO DI ROUTINE IN BAMBINI CON SOSPETTA CAP (A-)

- Bambini con segni o sintomi di polmonite che non richiedono spedalizzazione non devono effettuare RX torace

o La Rx del torace non è predittiva di eziologica batterica, da atipici o virale (II)

o Follow-up radiografico deve essere richiesto solo in soggetti con persistenza di sintomi o in presenza di o sospetta complicanza (B+)

British Thoracic Society

Application of the World Health Organization Criteria to Predict Radiographic Pneumonia in a US-based Pediatric Emergency Department

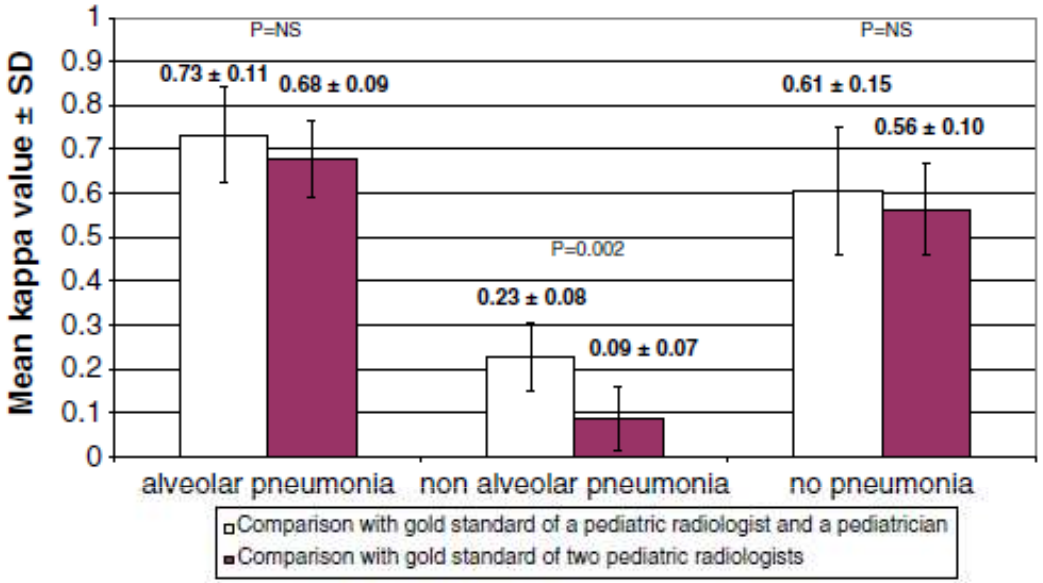
TABLE 1. Test Characteristics of WHO Classification of Pneumonia for the Diagnosis of Radiographic Pneumonia

Patient Population (n)	n (%)			Test Characteristics of WHO Pneumonia Classification for the Diagnosis of Radiographic Pneumonia				
	Meets WHO Criteria for Pneumonia	Radiographic PNA	Radiographic PNA Among Patients Who Meet WHO Classification for PNA	Sensitivity(%)	Specificity(%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Likelihood Ratio (+)
All Patients (n = 2008)	554 (27.6)	324 (16.1)	111 (20.0)	34.3	73.7	20.0	85.4	1.30
Subgroups								
Without wheezing (n = 1452)	312 (21.5)	247 (17.0)	76 (24.4)	30.8	80.4	24.4	85.0	1.57
History of fever (n = 1538)	406 (26.4)	279 (18.1)	95 (23.4)	34.1	75.3	23.4	83.8	1.38
Fever [triage T ≥ 38.0°C] (n = 787)	222 (28.2)	156 (19.8)	54 (24.3)	34.6	73.4	24.3	82.0	1.30
Hypoxia [O2 sat < 95%]* (n = 227)	134 (59.0)	64 (28.2)	43 (32.1)	67.2	44.2	32.1	77.4	1.20
Fever and hypoxia (n = 81)	50 (61.7)	32 (39.5)	21 (42.0)	65.6	40.8	42.0	64.5	1.11
Age subgroups								
<2 mo (n = 102)	15 (14.7)	9 (8.82)	2 (13.3)	22.2	86.0	13.3	92.0	1.59
2–12 mo (n = 583)	142 (24.4)	60 (10.3)	15 (10.6)	25.0	75.7	10.6	89.8	1.03
1–5 yr (n =1323)	397 (30.0)	255 (19.2)	94 (23.7)	36.9	71.6	23.7	82.6	1.30

Conclusions: The WHO criteria demonstrated poor sensitivity for the diagnosis of radiographic pneumonia in a US-based pediatric emergency department. Compared with respiratory rate, oxygen saturation offered slightly improved test characteristics. Although applied to a different target

Wingherter Pediatr Infect Dis J 2012

Evaluation of the World Health Organization criteria for chest radiographs for pneumonia diagnosis in children



Conclusions The WHO guidelines for interpretation of chest radiographs result in high level of agreement between readers for the definition of alveolar pneumonia and no pneumonia but poor agreement for non-alveolar pneumonia. The disagreement with regard to the latter was associated with overdiagnosis by pediatricians, which may lead to overtreatment. We believe that radiographic non-alveolar pneumonia should not be an endpoint for clinical trials and research, nor should it be implemented in clinical setting.

Shimol et al, Eur J Pediatr 2012

Quando fare altre indagini?

- Acute phase reactants are not of clinical utility in distinguishing viral from bacterial pneumoniae and should not be routinely tested (A-)

  CRP is not useful in management of not complicated pneumonia

- Microbiological diagnosis should be attempted in severe pneumonia or in presence of complications
- Microbiological methods should include : blood culture , nasopharingeal secretions or nasal swab for viral detection by PCR or immunofluorescence, pleural fluids , serology for viruses , Mycoplasma and Chlamydia

British Thoracic Society

Health Technology Assessment 2012; Vol. 16: No. 15
ISSN 1366-5278

Parametri di laboratorio per definire una CAP severa?

Systematic review and validation of prediction rules for identifying children with serious infections in emergency departments and urgent-access primary care

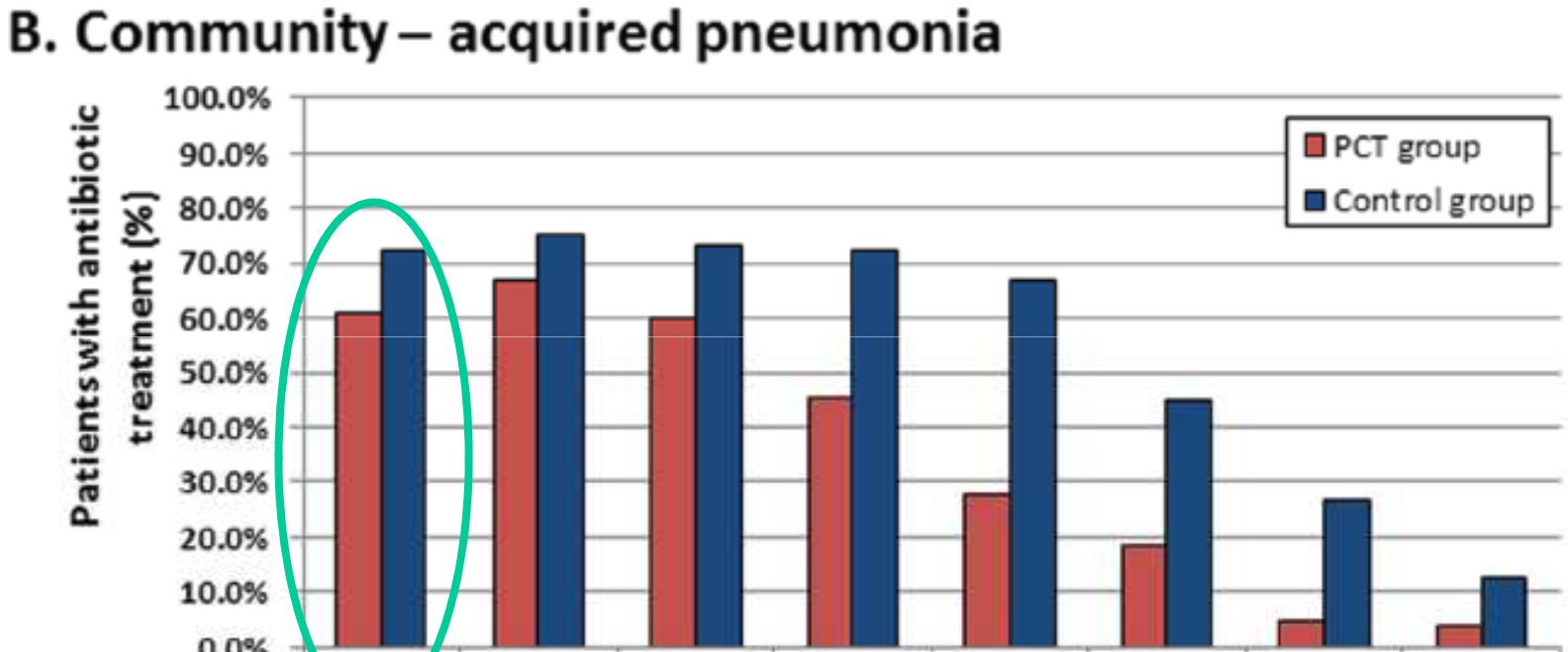
Our findings indicate that both CRP and PCT provide comparable diagnostic accuracy.

to 0.35. The optimal cut-off point to use for CRP and PCT depends on whether the clinical goal is to rule in or rule out serious infection. Based on our results, cut-off levels of 2 ng/ml for PCT and 80 mg/l for CRP provide good diagnostic value (a LR+ of ≥ 4) to rule-in serious infection. To rule out effectively, cut-off levels of 0.5 ng/ml for PCT or 20 mg/l for CRP may be a better choice (providing a LR– of ≤ 0.2).

White blood cell indicators (total WBC, absolute neutrophil count, band count or left shift) provided substantially lower diagnostic value than CRP or PCT for ruling in serious infection, and no value for ruling out. This also confirms the findings of a previous review which showed

M Thompson et, al 2012

E’ utile la procalcitonina nel decidere se iniziare la terapia antibiotica in un bambino con polmonite?



	D 1	D 3	D 5	D 7	D 9	D 11	D 13	> D 15
PCT group	61.1%	66.7%	60.2%	45.4%	27.8%	18.5%	4.6%	3.7%
Control group	72.4%	75.2%	73.3%	72.4%	66.7%	44.8%	26.7%	12.4%

Baer et al, PLOS One 2013

E’ utile la procalcitonina nel decidere se sospendere la terapia antibiotica in un bambino con polmonite?

Compared with clinical guidelines, PCT guidance did not reduce the antibiotic prescribing rate in children and adolescents with LRTI. However, antibiotic treatment duration was reduced.

PCT guidance in children with LRTI did not reduce the rate and duration of hospitalization. This is most likely due to the fact that determinants for admission were hypoxemia, failure to take oral fluids, or the need for intravenous antibiotic treatment. These factors are independent of PCT levels.

PCT group

Control group

Baer et al, PLOS One 2013

Quali sono gli indicatori di severità in corso di CAP?

Severe disease in infants

- Sat O2 < 92%, cyanosis
- RR >70b/m
- Significant tachycardia
- Capillary refill time> 2''
- Difficulty in breathing
- Intermittent apnoea, grunting
- Not feeding

Severe disease in older child

- Sat O2 < 92%, cyanosis
- RR >50b/m
- Significant tachycardia
- Capillary refill time> 2''
- Difficulty in breathing
- Grunting
- Signs of dehydration

- Underlying chronic condition
- Inability of parents to manage the illness

British Thoracic Society

Thorax, 2011

Criteri per il ricovero in ospedale del bambino con CAP

TABLE 3. Criteria for Hospitalization of Children With CAP

Respiratory Distress	Age-adjusted Tachypnea
	SpO2 <90–93% in room air (if FiO_2 >0.50, ICU or continuous cardiorespiratory monitoring are required to maintain saturation >92%)
	Cyanosis
	Retractions
	Grunting
	Nasal flaring
Capillary refill time >2 min	
Dehydration	
Vomiting/not feeding	
Comorbidities (eg, congenital heart disease, chronic lung disease of prematurity, chronic respiratory conditions leading to infection such as cystic fibrosis, bronchiectasis, immunodeficiency)	
Etiological agent (eg, MRSA, bacterial/viral coinfections)	
Unreliable family environment	

Esposito et al, PIDJ 2012

TERAPIA EMPIRICA DELLE POLMONITI ACQUISITE IN COMUNITA'

Recommendations

- Amoxicillin is recommended as 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 empirical therapy. [D]
- Macrolide antibiotics should be used if either mycoplasma or chlamydia pneumonia is suspected or in very severe disease. [D]
- In pneumonia associated with influenza, co-amoxiclav is recommended. [D]

British Thoracic Society

Thorax, 2011

Cause dell'uso inappropriato di antibiotici

1. Incertezza dell'eziologia di infezioni respiratorie e/o febbre
2. Prevenzione di complicanze
3. Pressione ambientale e socioculturale
4. Motivi "legali"
5. Aspettative dei genitori
6. Formazione del medico
7. Cultura dei genitori

Consensus conference

Impiego giudizioso della terapia antibiotica nelle infezioni delle vie aeree in età pediatrica

5. TRATTAMENTO DELLA POLMONITE ACQUISITA IN COMUNITÀ (31-41)

5.a. Quali sono le indicazioni all'uso di antibiotici nel trattamento ambulatoriale della polmonite acquisita in comunità?

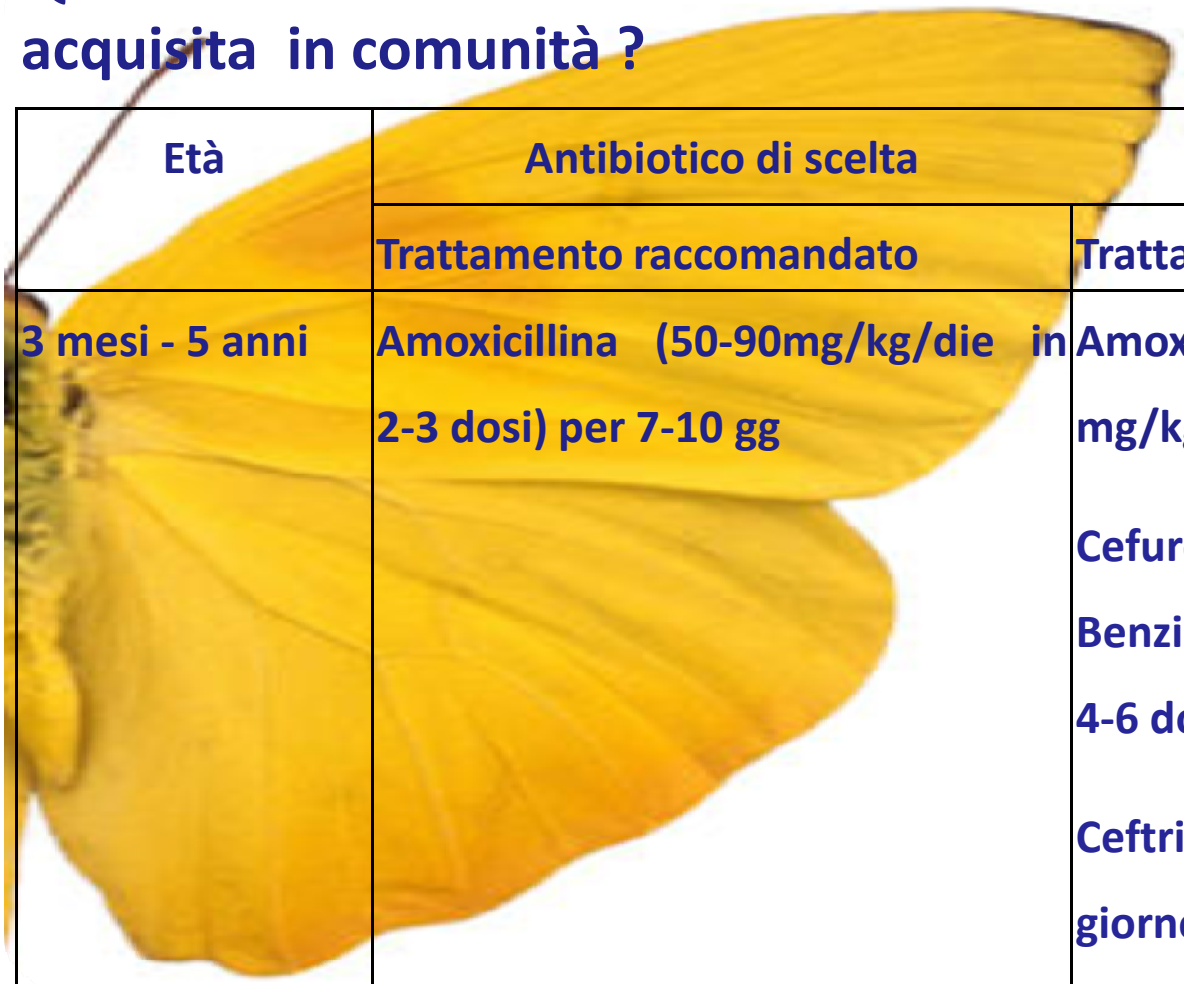
Sebbene il trattamento ospedaliero delle polmoniti gravi sia ben codificato, al contrario, l'approccio razionale al trattamento ambulatoriale delle polmoniti lievi o moderate è spesso basato su pareri di esperti e l'evidenza disponibile è scarsa. Ciò può portare ad una sovradiagnosi dei casi di polmonite, e a un incremento dell'uso non necessario di antibiotici. C'è quindi un urgente bisogno di ulteriori studi per meglio definire la gestione della polmonite lieve-moderata soprattutto nel bambino di età pre-scolare. Basandosi sui pochi dati disponibili si suggerisce il seguente approccio: i bambini (soprattutto quelli in età pre-scolare che hanno fatto la vaccinazione con lo pneumococco coniugato) con una forma lieve che possono essere seguiti da vicino e per i quali tutti i dati disponibili sulla epidemiologia, clinica, laboratorio e dati radiologici suggeriscano chiaramente una infezione virale, dovrebbero ricevere solamente una terapia di supporto. Tuttavia si dovrebbe garantire anche un *follow-up* a breve ed una rivalutazione a seconda dell'andamento della patologia.

Quali antibiotici utilizzare nel trattamento della polmonite acquisita in comunità ?

Età	Antibiotico di scelta	
	Trattamento raccomandato	Trattamento alternativo
1-3 mesi^	Amoxicillina (50-90 mg/kg/die in 2-3 dosi) per 7-10 gg *Claritromicina os (15mg/kg/die orale in 2 dosi) per 10-14 gg *Azitromicina os (10mg/kg/die in 1 dose per 3 gg)	Amoxicillina+acidoclavulanico (50-90 mg/kg/die in 2 dosi) per 7-10 gg Benzilpenicillina ev 200,000 U/kg/die in 4-6 dosi per 7 gg Ceftriaxone ev (50 mg/kg 1 volta al giorno) per 7 gg Cefotaxime ev (100-150 mg/kg/die in 3 dosi)

* In caso di sospetta polmonite da Mycoplasma o Clamidia pneumoniae

Quali antibiotici utilizzare nel trattamento della polmonite acquisita in comunità ?



Età	Antibiotico di scelta	
	Trattamento raccomandato	Trattamento alternativo
3 mesi - 5 anni	Amoxicillina (50-90mg/kg/die in 2-3 dosi) per 7-10 gg	Amoxicillina+acido clavulanico (50-90 mg/kg/die in 2 dosi) per 7-10 gg Cefuroxime axetil (30 mg/kg/die in 2 dosi) Benzilpenicillina ev (200,000 U/kg/die in 4-6 dosi) Ceftriaxone ev (50 mg/kg 1 volta al giorno) o cefotaxime ev (100-150 mg/kg/die in 3 dosi) Claritromicina orale (15mg/kg/die orale in 2 dosi) per 10-14 gg o azitromicina (10 mg/kg/die 1 volta per 3 gg)

Quali antibiotici utilizzare nel trattamento della polmonite acquisita in comunità ?

Età	Antibiotico di scelta	
	Trattamento raccomandato	Trattamento alternativo
5-18 anni	Amoxicillina (50-90 mg/kg/die in 2-3 dosi) per 7-10 gg *Claritromicina (15mg/kg/die in 2 dosi) per 10-14 gg *Azitromicina (10mg/kg/die in 1 dose per 3 gg)	Benzilpenicillina ev 200,000 U/kg/die in 4-6 dosi Ceftriaxone ev (50 mg/kg 1 volta/die) Cefotaxime ev (100-150 mg/kg/die in 3 dosi) Cefalexine orale o ev, cefazoline

* In caso di sospetta polmonite da Mycoplasma o Clamidia pneumoniae

Una terapia combinata con β-lattamico e macrolide può essere presa in considerazione per i casi gravi

Durata dell'antibioticoterapia in caso di CAP

… Few studies have looked at the appropriate duration of antimicrobial therapy for CAP in children .

Treatment course of 10 days for beta-lactams and 5 days for azithromycin have been best studied, although shorter courses have been studied showing no difference in acute cure or relapses between groups.

Shorter courses are acknowleged to be just as effective , particularly for milder cases…

Pediat Clin N Am 2013

Short Course Antibiotic Treatment for Community-Acquired Alveolar Pneumonia in Ambulatory Children: A Double Blind, Randomized, Placebo Controlled Trial.

A double-blind, randomized, placebo-controlled trial was conducted in 2 stages:

1) 3 days vs.10 days;
2) 2) 5 days vs.10 days.

Amoxicillin (80 mg/kg/day) divided into 3 daily doses was used for all arms.

40% of failure in the 3-day arm

No failures occurred in the 5-day and 10-day .

In 6-59 month outpatients with CAAP, a 5-day course with high-dose oral amoxicillin was not inferior to a 10-day course.

The 3-day regimen may be associated with an unacceptable failure rate.

Greenberg et al, PIDJ 2013

Valutazione clinica e prescrizione di antibiotici

Pediatr Infect Dis J. 2012 Mar 29. [Epub ahead of print]

Antibiotic Therapy for Pediatric Community-Acquired Pneumonia: Do We Know When, What and For How Long to Treat?

Esposito S, Cohen R, Domingo JD, Pecurariu OF, Greenberg D, Heininger U, Knuf M, Lutsar I, Principi N, Rodrigues F, Sharland M, Spoulou V, Syrogiannopoulos GA, Usonis V, Vergison A, Schaad UB.

- **I segni clinici** sono il **principale criterio** per decidere quando iniziare gli antibiotici

Segni/sintomi di infezione batterica e virale possono essere sorprendentemente simili
*Caratteristiche radiologiche **non possono** essere utilizzate per discernere l'eziologia*
*Indagini di laboratorio non microbiologiche spesso **non sono utili** nel processo decisionale sul singolo individuo*

- **La prescrizione routinaria** di antibiotici **non è sempre la terapia ottimale**.

- I bambini in età prescolare che hanno ricevuto vaccino pneumococcico coniugato, con una **forma lieve** e per i **quali tutti i dati** epidemiologici, clinici, laboratoristici e radiologici disponibili chiaramente **suggeriscono un'infezione virale,** dovrebbero ricevere soltanto una **terapia sintomatica** e essere monitorati strettamente.

Indicazioni alla terapia antibiotica

InnovAiT, Vol. 3, No. 1, pp. 5–12, 2010 doi:10.1093/innovait/in

Antibiotics in respiratory tract infections — communicating the NICE guidance

Offer immediate antibiotics or further investigation/management for patients who:

- are systemically very unwell
- have symptoms and signs suggestive of serious illness and/or complications
- are at high risk of serious complications because of pre-existing comorbidity. This includes:
  - patients with significant heart, lung, renal, liver or neuromuscular disease
  - immunosuppressed patients
  - patients with cystic fibrosis
  - young children who were born prematurely
- are older than 65 years with acute cough and two or more of the following, or older than 80 years with acute cough and one or more of the following:
  - hospitalisation in previous year
  - type 1 or type 2 diabetes
  - history of congestive heart failure
  - current use of oral glucocorticoids

Depending on clinical assessment of severity, consider offering immediate antibiotics for:

- children younger than 2 years with bilateral acute otitis media
- children with otorrhoea who have acute otitis media
- patients with acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria are present.