

Terapia antibiotica della polmonite di comunità (CAP) di lieve e media gravità seguita sul territorio

Nicola Principi
Professore Emerito di Pediatria
Università di Milano

Criteria for Hospitalization of Children With CAP

Respiratory Distress

Age-adjusted Tachypnea

SpO₂ <90–93% in room air (if FiO₂ >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

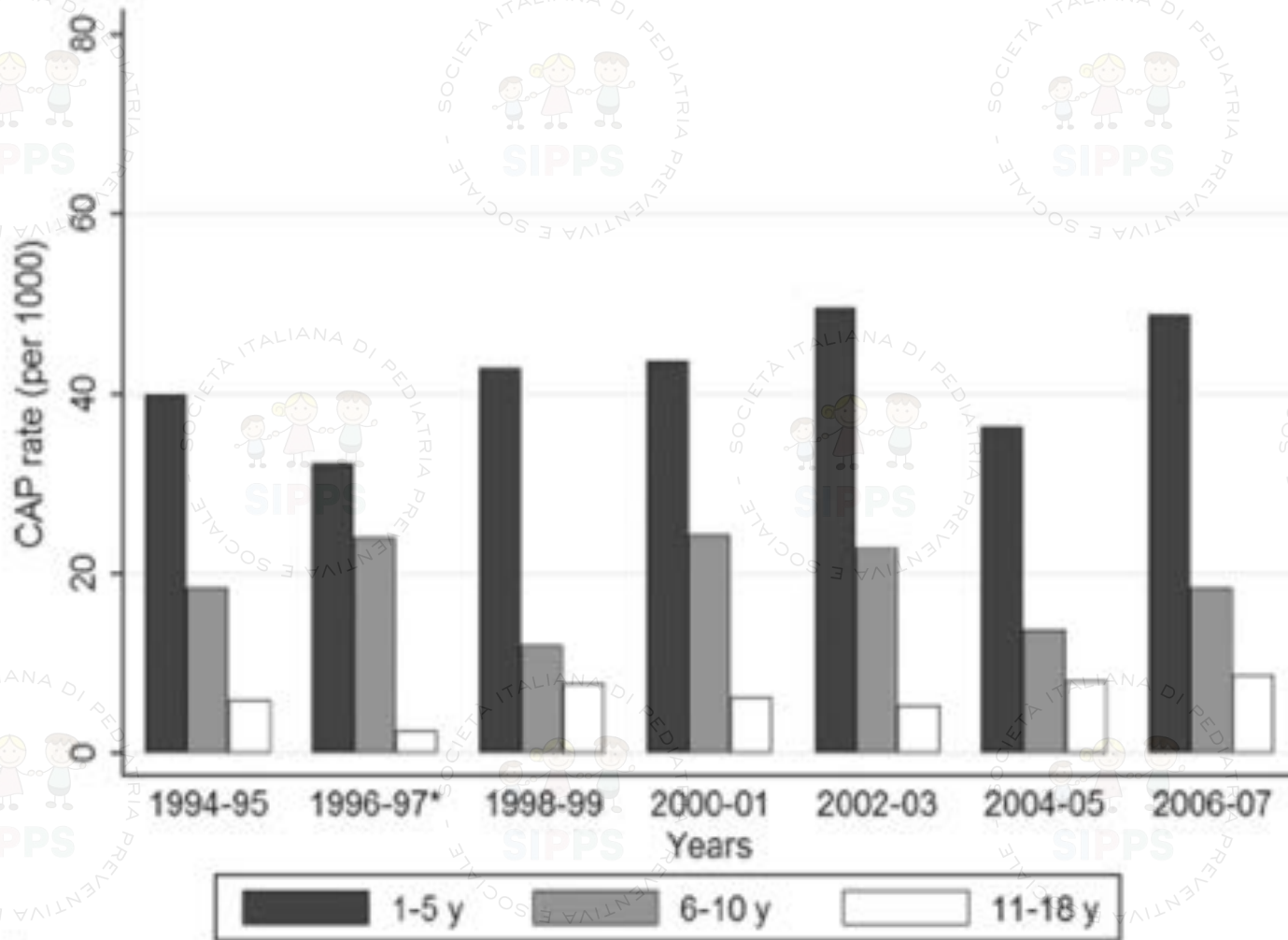
CRITERIA USED TO DEFINE SEVERITY OF CAP

(British Thoracic Society, Thorax 2011)

Table 6 Severity assessment

	Mild to moderate	Severe
Infants	Temperature <38.5°C Respiratory rate <50 breaths/min Mild recession Taking full feeds	Temperature >38.5°C Respiratory rate >70 breaths/min Moderate to severe recession Nasal flaring Cyanosis Intermittent apnoea Grunting respiration Not feeding Tachycardia* Capillary refill time ≥ 2 s
Older children	Temperature <38.5°C Respiratory rate <50 breaths/min Mild breathlessness No vomiting	Temperature >38.5°C Respiratory rate >50 breaths/min Severe difficulty in breathing Nasal flaring Cyanosis Grunting respiration Signs of dehydration Tachycardia* Capillary refill time ≥ 2 s

*Values to define tachycardia vary with age and with temperature.⁶⁷[11]



Two-yearly community-acquired pneumonia rates by age group *Estimate for the 11- to 18-year-old age group contains fewer than 30 unadjusted records.

From Kronman M et al., Pediatrics 2011

Rispetto alla CAP grave che viene ospedalizzata, la CAP curata sul territorio è quella che pone il più elevato rischio di abuso e di cattivo uso degli antibiotici perché:

- Maggiore è il rischio di abuso perché:
 - la diagnosi è meno certa (no radiografia, pochissimo uso dell'ecografia, scarsa utilità diagnostica dei segni e sintomi di malattia)
 - la differenziazione delle forme batteriche dalle virali è estremamente difficile (poca efficacia dei test di laboratorio disponibili sul territorio)
- Maggiore è il rischio di cattivo uso perché:
 - difficile, se non impossibile, l'identificazione del batterio responsabile della malattia

Performance of Symptoms In Diagnosing Pneumonia

(from Shah SN, et al. JAMA 2017)

Finding, Source	Sample Size, No.	Sensitivity (95% CI), %	Specificity (95% CI), %	LR+ (95% CI)	LR- (95% CI)
Symptoms					
Chest pain ^{47,50,67}	3164	22 (5-62)	91 (56-99)	1.9 (1.1-3.4)	0.82 (0.66-1.0)
Poor feeding ^{47,48,50,52,63,69}	3784	58 (32-80)	60 (39-78)	1.4 (1.3-1.6)	0.71 (0.51-0.88)
Cough ^{45-47,50,53,55,57,61,63,67,68,70}	7446	88 (80-97)	25 (08-42)	1.2 (0.98-1.4) $I^2 = 89\%$	0.47 (0.24-0.70) $I^2 = 76\%$
Difficulty breathing ^{45,50,52,53,62,67b}	5723	37 (10-64)	69 (42-95)	1.2 (0.61-1.7)	0.92 (0.70-1.1)
Symptom duration >3 days (cough, fever, illness) ^{53,64}	2979	25 (18-32)	81 (72-87)	1.2 (1.1-1.4)	0.94 (0.90-0.98)
Vomiting or diarrhea ^{45,47,48,50,53,64}	11 377	27 (15-39)	76 (67-85)	0.96 (0.89-1.0)	0.96 (0.89-1.0)

Performance of Signs In Diagnosing Pneumonia (I)

(from Shah SN, et al. JAMA 2017)

Finding, Source	Sample Size, No.	Sensitivity (95% CI), %	Specificity (95% CI), %	LR+ (95% CI)	LR- (95% CI)
Fever					
Temperature, thresholds					
≥39°C, ^{47,59,64}	2281	40 (23-60)	68 (51-81)	1.3 (0.89-1.8)	0.90 (0.77-1.0)
>38°C or 38.5°C, ^{46,48,52,68}	1170	48 (23-73)	67 (45-90)	1.5 (0.88-2.0)	0.78 (0.57-0.99)
>37.5°C, ^{48,69}	366	80-92	47-54	1.7-1.8	0.17-0.37
Any fever during visit ^{57,63,67,70}	921	72 (53-86)	50 (37-63)	1.4 (1.2-1.7)	0.55 (0.35-0.79)
Fever, reported by parent ^{50,52,53,57,69}	5517	92 (73-98)	14 (4-38)	1.1 (1.0-1.2)	0.59 (0.39-0.87)
Respiratory rate					
Tachypnea, physician assessment ^{45,47,55,60,67,70}	3192	46 (27-64)	72 (60-83)	1.6 (1.2-2.0)	0.76 (0.59-0.93)
Respiratory rate >40 breaths/min ^{56,58,69}	859	79 (40-96)	51 (34-68)	1.5 (1.3-1.7)	0.41 (0.17-0.99)
Tachypnea, age defined ^{46,49,51,52,57,60,62,63}	4393	54 (23-82)	64 (35-86)	1.5 (0.49-4.4)	0.73 (0.25-1.7)
Oxygen saturation					
≤96% ⁵⁸	510	64 (49-78)	77 (73-81)	2.8 (2.1-3.6)	0.47 (0.32-0.67)
≤95% ⁴⁵	514	16 (11-22)	96 (93-97)	3.5 (2.0-6.4)	0.88 (0.82-0.94)
≤92% ⁴⁶	394	26 (21-32)	88 (82-93)	2.2 (1.3-3.8)	0.84 (0.76-0.92)
<90% ⁶⁴	588	37 (31-43)	75 (70-79)	1.5 (1.1-1.9)	0.84 (0.76-0.94)

$I^2 = 0\%$

$I^2 = 87\%$

Performance of Signs In Diagnosing Pneumonia (II)

(from Shah SN, et al. JAMA 2017)

Finding, Source	Sample Size, No.	Sensitivity (95% CI), %	Specificity (95% CI), %	LR+ (95% CI)	LR- (95% CI)
Auscultatory findings					
Discontinuous sounds ^{45-52,55,57,58,60-64,67,69,70c}	10 599	39 (29-48)	71 (62-81)	1.4 (0.96-1.7)	0.86 (0.74-0.98)
Rales ^{45,47,49,51,55,60,62,70}	4136	43 (32-54)	64 (47-81)	1.2 (0.53-1.8)	0.90 (0.14-2.5)
Wheeze (not rhonchi) ^{45-47,53,58,60,63,67,70}	5888	16 (10-21)	83 (75-91)	0.93 (0.64-1.2)	1.0 (0.95-1.1)
Continuous sounds (wheezes or rhonchi) ^{45-47,50,53,58,60,63,67,70}	8842	16 (7-24)	83 (76-90)	0.91 (0.54-1.3)	1.0 (0.94-1.1)
Diminished breath sounds ^{46,47,51,57,58,60,62,63}	4434	25 (13-36)	72 (48-95)	0.88 (0.04-1.7)	1.0 (0.67-1.4)
Work of breathing					
Grunting ^{47,48,55,57,58,63}	1836	13 (5-32)	95 (83-99)	2.7 (1.5-5.1) $I^2 = 62\%$	0.92 (0.80-0.97) $I^2 = 67\%$
Nasal flaring ^{45,47,49,52,55,58,61,64,68,69}	3541	36 (17-54)	84 (71-97)	2.2 (1.3-3.1) $I^2 = 85\%$	0.77 (0.64-0.90) $I^2 = 77\%$
Retractions or indrawing ^{47-50,52,57,58,60,61,63,68,69}	8080	38 (20-56)	80 (70-90)	1.9 (1.2-2.5) $I^2 = 81\%$	0.78 (0.61-0.94) $I^2 = 89\%$

MARCATORI CAPACI DI DIFFERENZIARE CAP VIRALI E BATTERICHE

(from Principi N, Esposito S. Int J Mol Sci 2017)

Leucocitosi e neutrofilia
Velocità di eritrosedimentazione
Proteina C Reattiva (PCR)
Procalcitonina (PCT)

Soluble triggering receptor espresso dalle cellule mieloidi
(sTREM)
Mid regional pro-adrenomedullin (MR-proADM)
Peptide natriuretico pro-atriale (NAP)
Numero e volume delle piastrine

White blood cell count (WBC) and absolute neutrophil count (ANC), C-reactive protein (CRP) concentration and erythrocyte sedimentation rate (ESR) in relation to the aetiology of infections in the 69 children with pneumonia and serologically indicated pneumococcal or viral aetiology
(from Korppi M, et al. Eur Resp J 1997)

Parameters	Aetiological group of infection				
	Pneumococcal (n=29)	p-value	Mixed# (n=17)	p-value	Viral‡ (n=23)
WBC $\times 10^9$ cells·L ⁻¹	16.2±8.1 (13.4–19.0)	NS	12.8±6.0 (10.0–15.6)	NS	12.3±8.1 (9.5–15.1)
ANC $\times 10^9$ cells·L ⁻¹	13.4±7.3* (8.7–13.7)	<0.05	6.4±3.6 (4.7–8.1)	NS	7.0±5.9 (4.4–9.6)
CRP mg·L ⁻¹	89.9±102.0* (53.9–126.0)	NS	51.2±61.8 (21.4–81.0)	NS	40.9±48.8 (21.5–60.3)
ESR mm·h ⁻¹	42.8±34.8* (32.0–54.8)	NS	34.3±21.9 (24.4–44.2)	NS	29.4±15.3 (23.4–35.4)

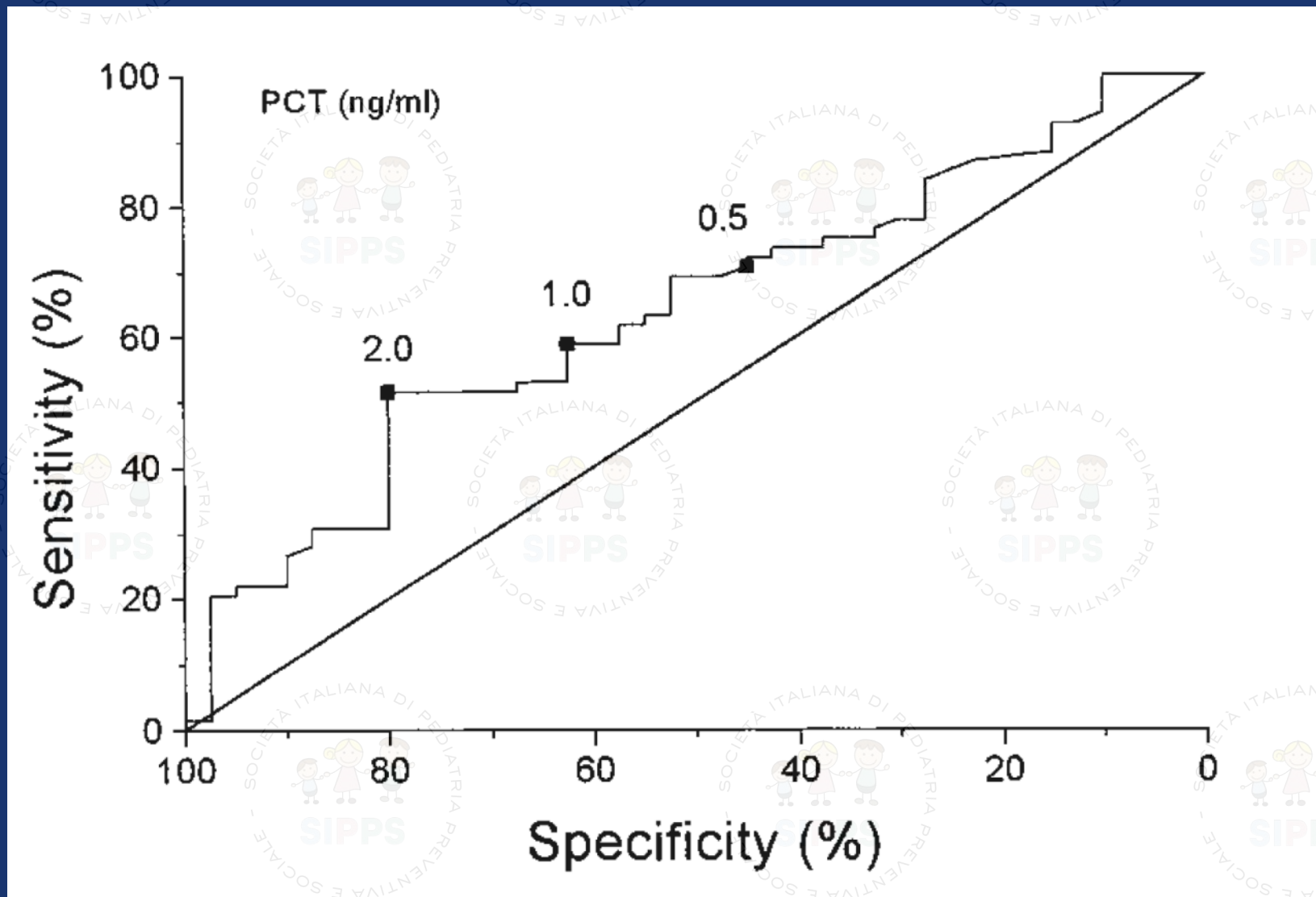
Values are presented as mean±SD, and 95% confidence intervals in parentheses. *: p<0.05 vs patients with viral infection alone. #: the viruses were RSV in 14 cases, parainfluenza in one, and adenovirus in three cases, including one dual virus infection; ‡: the viruses were RSV in 28 cases, parainfluenza in two, and adenovirus in two cases, including no dual virus infections. NS: nonsignificant; RSV: respiratory syncytial virus.

Combined evaluation of laboratory tests for bacterial CAP identification

- The highest likelihood ratio (1.74) was achieved with the combination CRP > 80 mg/L or WBC > $17.0 \times 10^9/L$ or PCT > $0.84 \mu\text{g/L}$ or ESR > 63 mm/h For this combination, the sensitivity was 61% and the specificity 65%.
- There was no combination of these markers which was sufficiently sensitive and specific to be used in clinical pediatric practice.

Procalcitonin for bacterial CAP diagnosis

(from Toikka P, et al. Pediatr Infect Dis J 2000)



Test microbiologici rapidi

- *Streptococcus pneumoniae* sulle urine: non utile per l'elevata dimensione dei portatori sani
- Test influenza e SARS-CoV2: buona attendibilità anche se variabile in funzione epidemiologia
- Test RSV antigenico: scarsa attendibilità

Le difficoltà di fare diagnosi di CAP e quelle di individuare l'esatta eziologia o, almeno, di diagnosticare le forme virali creano due inevitabili fenomeni:

- 1) complicano pesantemente l'esecuzione di studi clinici controllati capaci di valutare la necessità e l'efficacia di una qualsiasi terapia antibiotica.
- 2) rendono impossibile lo stabilire raccomandazioni terapeutiche assolute e totalmente indiscutibili

Quindi, a fronte di una CAP di lieve o media entità il medico ha due possibili scelte. Trattare tutte o cercare di selezionare i casi sfruttando al massimo le sue conoscenze cliniche, i possibili dati laboratoristici e la situazione epidemiologica locale. In ogni caso la scelta deve essere tale da limitare al massimo il cattivo uso di antibiotici

Community acquired pneumonia pathogens in children by age group

(from Jain S, et al. NEJM 2015)

Pathogen	Younger than 2 years	2 to 4 years	5 to 9 years	10 to 17 years
Viral				
Adenovirus	18%	9%	4%	2%
Coronaviruses	6%	6%	3%	4%
Human metapneumovirus	14%	17%	10%	4%
Human rhinovirus	29%	25%	30%	19%
Influenza A/B	6%	5%	9%	11%
Parainfluenza virus 1 to 3	7%	8%	6%	4%
Respiratory syncytial virus	42%	29%	8%	7%
Bacterial				
<i>Mycoplasma pneumoniae</i>	2%	5%	16%	23%
<i>Staphylococcus aureus</i>	1%	1%	1%	1%
<i>Streptococcus pneumoniae</i>	3%	4%	4%	3%
<i>Streptococcus pyogenes</i>	1%	1%	<1%	<1%

Trattamento antibiotico della CAP lieve o moderata

- **Bambini 3 mesi - 5 anni:**
Amoxicillina 90 mg/kg/die in 3 somministrazioni
- La grande maggioranza delle pubblicazioni dimostrano che l'efficacia delle aminopenicilline non è inferiore a quello di antibiotici a spettro allargato
- L'eventuale presenza di *S. pneumoniae* aminopenicillino-resistente non modifica sostanzialmente l'efficacia
- Può essere discusso il dosaggio e il frazionamento
- Nei bambini con allergia non IgE mediata alle penicilline è consigliata la terapia con cefalosporine di II e III generazione.
- **Nei bambini con allergia IgE mediata è consigliata la terapia con macrolidi o fluorochinoloni a seconda della prevalenza locale di resistenze dello pneumococco alla specifica classe di farmaci.**

Sp penicillin resistance and CAP outcome

(Cardoso MRA et al. Arch Dis Child 2008)

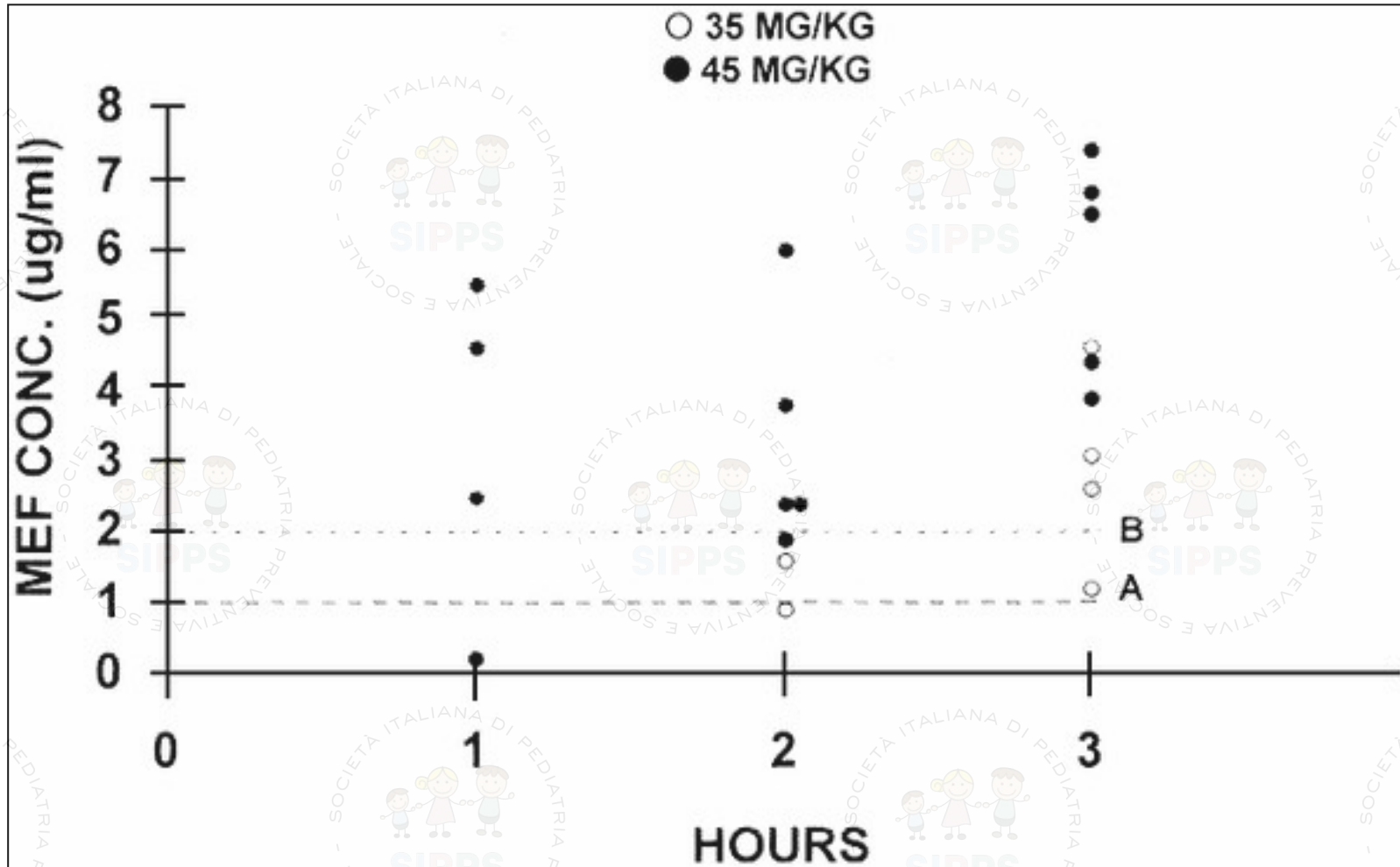
Treatment outcome	Susceptible	Intermediate	Resistant	Total	P
All children (n = 240)					0.75*
Success	94 (78)	49 (77)	46 (82)	189 (79)	
Failure	26 (22)	15 (23)	10 (18)	51 (21)	
Children without pleural effusion on admission (n = 111)					0.87*
Success	48 (86)	29 (91)	20 (87)	97 (87)	
Failure	8 (14)	3 (9)	3 (13)	14 (13)	
Children with pleural effusion on admission (n = 129)					0.37*
Success	46 (72)	20 (63)	26 (79)	92 (71)	
Failure	18 (28)	12 (37)	7 (21)	37 (29)	

*Fisher's exact test.

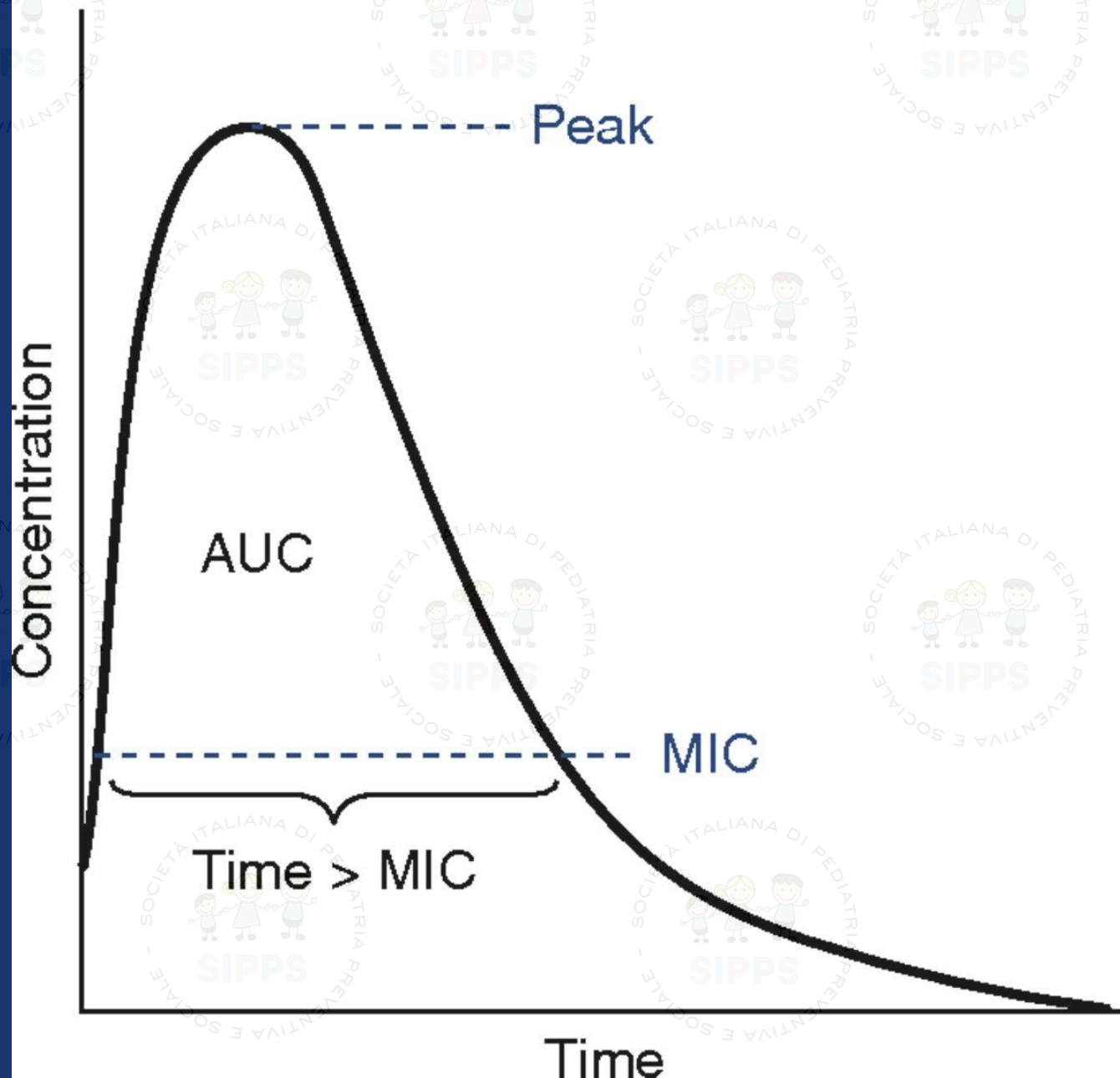
MIDDLE EAR FLUID CONCENTRATIONS OF AMOXICILLIN AFTER LARGE DOSAGES IN CHILDREN WITH ACUTE OTITIS MEDIA.

Seikel, Kathleen; Shelton, Sharon; McCracken, George *Pediatric Infectious Disease Journal*. 16(7):710-711, July 1997.

Dashed lines represent the National Committee for Clinical Laboratory Standards breakpoints for intermediate (A) and resistant (B) strains of *S. pneumoniae* for amoxicillin.



Pharmacodynamic parameters on a concentration-time curve



Cross-reactivity between penicillins and cephalosporins based on side chain similarity

(from Pichichero M., Diag Microbiol Infect Dis 2007)

7-Position side chain						
Similar side chain/ cross-reactivity possible within group ^{a,b}	Similar side chain/ cross-reactivity possible with group	Similar side chain/ cross-reactivity possible with group	Completely dissimilar side chains/unlikely cross-reactivity with each other ^{b,c}			
Cephaloridine (1st)	Cefaclor (2nd)	Cefepime (4th)	Cefoperazone (3rd)	Cefixime (3rd)		
Cephalothin (1st)	Cephadrine (1st)	Ceftizoxime (3rd)	Cefotetan (2nd)	Cefprozil (2nd)		
Penicillin G	Cephalexin (1st)	Cefpirome (4th)	Cefazolin (1st)	Cefmetazole (2nd)		
	Cefadroxil (1st)	Cefotaxime (3rd)	Cefuroxime (2nd)	Ceftibuten (3rd)		
	Amoxicillin	Cefpodoxime (3rd)	Cefdinir (3rd)	Ceftazidime (3rd)		
	Ampicillin	Ceftriaxone (3rd)	Cefditoren (3rd)	Cefoxitin (2nd)		
3-Position side chain						
Similar side chain/ cross-reactivity possible within group ^{b,d}	Similar side chain/ cross-reactivity possible within group	Similar Side chain/ cross-reactivity possible within group	Similar side chain/ cross-reactivity possible within group	Similar side chain/ cross-reactivity possible within group	Similar side chain/ cross-reactivity possible within group	Dissimilar side chain/unlikely cross-reactivity with each other ^{b,e}
Cefadroxil (1st)	Cefmetazole (2nd)	Cefotaxime (3rd)	Ceftibuten (3rd)	Cefuroxime (2nd)	Cefdinir (3rd)	Cefpodoxime (3rd)
Cephalexin (1st)	Cefoperazone (3rd)	Cephalothin (1st)	Ceftizoxime (3rd)	Cefoxitin (2nd)	Cefixime (3rd)	Cefprozil (2nd)
	Cefotetan (2nd)					Ceftibuten (3rd)
						Ceftriaxone (3rd)
						Cefepime (4th)
						Cefpirome (4th)
						Cefazolin (1st)
						Cefaclor (2nd)
						Ceftazidime (3rd)

Trattamento antibiotico della CAP lieve o moderata

- **Bambini > 5 anni,**

Amoxicillina 90 mg/kg/die in 3 somministrazioni

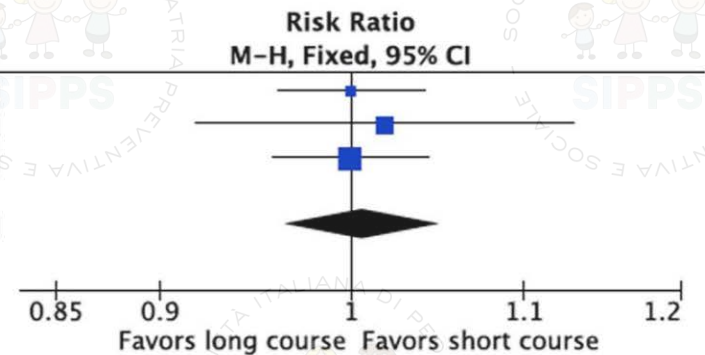
- I dati disponibili sono pochi e sembrano indicare che i macrolidi non sono superiori all'amoxicillina come farmaci di scelta iniziale
- La terapia con macrolide può essere considerato nel caso di bambini che non abbiano mostrato un miglioramento clinico dopo 48 ore di terapia antibiotica con amoxicillina ma che persistano in buone condizioni generali e non necessitino di ospedalizzazione

Clinical cure after short- (5 days) or long-term (10 days) of amoxicillin therapy in outpatient children with CAP

(from Marques IR, et al. Eur J Pediatr 2022)

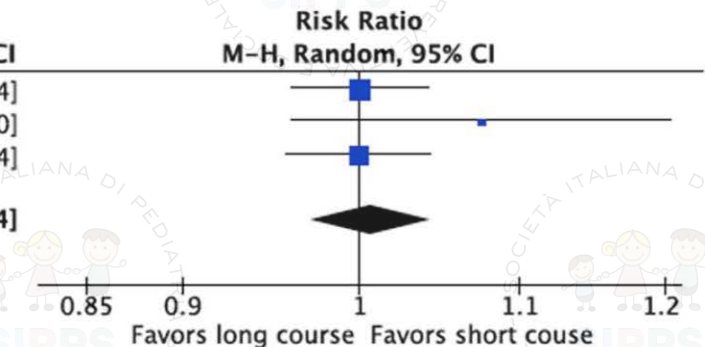
a

Study or Subgroup	Short course		Long course		Weight	Risk Ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI
Greenberg 2014	42	42	56	56	15.7%	1.00 [0.96, 1.04]
Pernica 2021	108	126	106	126	34.2%	1.02 [0.92, 1.13]
Williams 2022	154	160	156	162	50.1%	1.00 [0.96, 1.04]
Total (95% CI)		328		344	100.0%	1.01 [0.96, 1.05]
Total events	304		318			
Heterogeneity: $\text{Chi}^2 = 0.24$, $\text{df} = 2$ ($P = 0.89$); $I^2 = 0\%$						
Test for overall effect: $Z = 0.29$ ($P = 0.77$)						



b

Study or Subgroup	Short course		Long course		Weight	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI
Greenberg 2014	42	42	56	56	47.1%	1.00 [0.96, 1.04]
Pernica 2021	88	98	76	91	9.1%	1.08 [0.96, 1.20]
Williams 2022	154	160	156	162	43.8%	1.00 [0.96, 1.04]
Total (95% CI)		300		309	100.0%	1.01 [0.97, 1.04]
Total events	284		288			
Heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 2.71$, $\text{df} = 2$ ($P = 0.26$); $I^2 = 26\%$						
Test for overall effect: $Z = 0.35$ ($P = 0.72$)						



CONCLUSIONI

Il problema maggiore che ha il pediatra a fronte di un bambino nel quale sospetta una polmonite di lieve entità e che può rimanere a casa è quello di confermare la diagnosi e decidere se trattarlo o meno.

Una attenta valutazione della sintomatologia clinica può essere utile a sottrarre qualche caso alla terapia antibiotica

Se decide di trattare, la scelta è sempre sull'amoxicillina con qualche problema nella valutazione del dosaggio e del frazionamento giornaliero

La durata è di 5 giorni ma è richiesta una attenta osservazione per evidenziare i casi che non rispondono in modo adeguato e richiedere il cambio di terapia o il ricovero.

Episodes of Rx-confirmed CAP with viruses in children aged 0-12 months

(Esposito S et al., Influenza Other Respir Viruses. 2013)

VIRUS	2007-08		2008-09		2009-10		Total episodes	
	No. (%)*	Coinf. No.(%) ^	No. (%)*	Coinf. No.(%)^	No. (%)*	Coinf. No.(%)^	No. (%)*	Coinf. No.(%)^
RSV	14 (33.3)	3 (21.4)	26 (44.8)	13 (50.0)	22 (22.2)	10 (45.4)	62 (36.8)	26 (41.9)
Rhinovirus	17 (40.4)	11 (64.7)	15 (25.8)	10 (66.6)	15 (15.1)	7 (87.5)	47 (28.1)	28 (59.5)
Bocavirus	7 (16.6)	6 (85.7)	2 (3,4)	2 (100)	5 (5,0)	5 (100)	14 (10.1)	13 (92.8)
Influenza	2 (4.7)	1 (50.0)	5 (8.6)	1 (20.0)	3 (3.0)	2 (66.6)	10 (7.2)	4 (40.0)
Metapneu.	10 (23.8)	3 (30.0)	5(8.6)	1 (20.0)	2 (2.0)	1 (50.0)	17 (12.2)	5 (29.4)
Coronavirus	2 (4.7)	2 (100)	0 (0.0)	0	5 (5.0)	5 (100)	7 (5.0)	7 (100)
Parainfluenza (1-4)	0 (0)	0	1 (1.7)	0 (0.0)	1 (1.0)	1 (100)	2 (1.4)	1 (50.0)
Adenovirus	0 (0)	0	0 (0.0)	0 (0.0)	1 (1.0)	1 (100)	1 (0.7)	1 (100)
Episodes with viruses	38/42 (90.4)	12/38 (31.5)	43/58 (74.1)	16/43 (37.2)	37/39 (94.8)	15/37 (40.5)	118/139 (84.9)	43/118 (36.4)

•% among the total number of CAP investigated;

•^ % of the total number of infections in which the virus was identified

Episodes of Rx-confirmed CAP with viruses in children aged 13-36 months

(Esposito S et al., Influenza Other Respir Viruses. 2013)

2007-08

2008-09

2009-10

Total episodes

VIRUS	No. (%) *	Coinf. No.(%)^	No. (%)*	Coinf. No.(%)^	No. (%)*	Coinf. No.(%)^	No. (%)*	Coinf. No.(%)^
RSV	35 (41.1)	16	58 (38.6)	21	30 (30.3)	10	123 (36.8)	47
Rhinovirus	26 (30.5)	15	44 (29.3)	21	24 (24.2)	7	94 (28.1)	43
Bocavirus	12 (14.1)	9	15 (10.0)	11	12 (12.1)	6	39 (11.6)	26
Influenza	4 (4.7)	1	16 (10.6)	6	10 (10.1)	1	39 (11.6)	8
Metapneumo.	12 (14.1)	5	13(8.6)	4	6 (6.1)	0	31 (9.2)	9
Coronavirus	3 (3.5)	2	7 (5.8)	3	5 (5.0)	4	15 (4.5)	9
Parainfluenza (1-4)	0 (0)	0	4 (2.6)	2	6 (6.1)	2	10 (3.0)	4
Adenovirus	1 (1.1)	0	4 (2.6)	3	2 (2.0)	1	7 (2.1)	4
Episodes with viruses	68/85 (80.0)	20/68 (29.4)	122/150 (81.3)	36/122 (29.5)	78/99 (78.8)	14/78 (17.9)	268/334 (80.2)	70/268 (26.1)

•% among the total number of CAP investigated;

•^ % of the total number of infections in which the single virus was identified

PRINCIPAL BACTERIA CAUSING CHILDHOOD CAP BY AGE

(From Principi N & Esposito S, Thorax 2011)

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

Agents of Community Acquired Pneumonia in Children

(from Jain S, et al. NEJM 2015)

