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POLMONITI COMPLICATE

LA TERAPIA ANTIMICROBICA

DR.SSA ERIKA SILVESTRO
SS MALATTIE INFETTIVE OIRM

XXVIII CONGRESSO NAZIONALE SIMRI
Il respiro: scienza e terapia per la salute del bambino

Torino
10-12 ottobre 2024

POLMONITE COMPLICATA
Definizione

Site	Complication	Pathogens[a]
Local	Pleural effusion or empyema (~1%)	*Streptococcus pneumoniae* *Streptococcus pyogenes* *Staphylococcus aureus*
	Necrotizing pneumonia,[b]	*Streptococcus pneumoniae*
	Pneumatocele[b]	*Staphylococcus aureus*
	Lung abscess[b]	*Staphylococcus aureus* Anaerobes
Systemic (extra-pulmonary)	Bacteraemia, sepsis (~1%)[c]	*Streptococcus pneumoniae* *Streptococcus pyogenes* *Staphylococcus aureus*
	Rash, urticaria, mucositis (MIRM)[d]	*Mycoplasma pneumoniae*
	Haemolytic uraemic syndrome (HUS)[b]	*Streptococcus pneumoniae*
	Neurological symptoms (e.g., encephalitis)[b]	*Mycoplasma pneumoniae*

Patrick M. Meyer Sauteur, European Journal of Pediatrics (2024)

IDSA 2011

Table 2. Complications Associated With Community-Acquired Pneumonia

Pulmonary
Pleural effusion or empyema
Pneumothorax
Lung abscess
Bronchopleural fistula
Necrotizing pneumonia
Acute respiratory failure
Metastatic
Meningitis
Central nervous system abscess
Pericarditis
Endocarditis
Osteomyelitis
Septic arthritis
Systemic
Systemic inflammatory response syndrome or sepsis
Hemolytic uremic syndrome

Guidelines for the management of community acquired pneumonia in children: update 2011

British Thoracic Society Community Acquired Pneumonia in Children Guideline Group

GUIDELINES

ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia

Intensive Care Med (2023) 49:615–632

Esami colturali? SEMPRE!

Emocoltura
Esami su liquido pleurico
Escreato/espettorato
Tampone nasofaringeo
*Ag pneumococcico urinario**
Indagini molecolari

Recommendations

If the technology is available, we **suggest** sending a lower respiratory tract sample (either sputum or endotracheal aspirates) for multiplex PCR testing (virus and/or bacterial detection) whenever non-standard sCAP antibiotics are prescribed or considered.
Conditional recommendation, very low quality of evidence.

- Microbiological diagnosis should be attempted in children with severe pneumonia sufficient to require paediatric intensive care admission, or those with complications of CAP. [C]

BIOMARKERS

those who would not. Our data suggest that CRP and procalcitonin may be useful in predicting the development of specific severe outcomes, such as complicated pneumonia and sepsis. Given the higher negative predictive values (NPVs) of these markers in discriminating severe from nonsevere disease, it may be these markers have a role in ruling out the most severe outcomes.

Patrick M. Meyer Sauteur, European Journal of Pediatrics (2024)

Florin TA, et al. Pediatrics. 2020;145(6)

I PROTAGONISTI NELLA POLMONITE

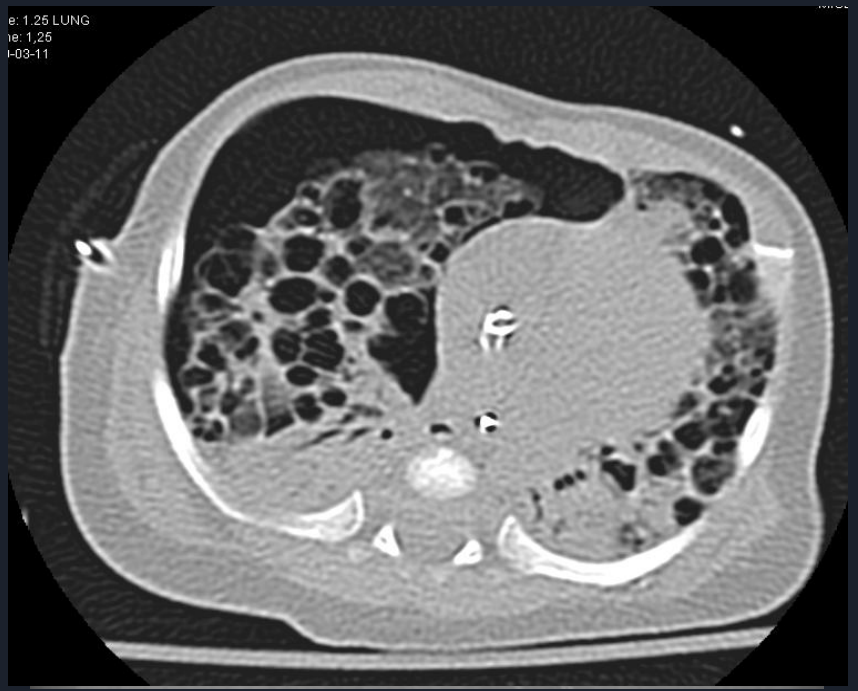
RSV, influenza
Adenovirus
Metapneumovirus
CMV, VZV, HSV

Influenza fattore di rischio per polmonite necrotizzante

- Overall, viruses account for 30–67% of CAP cases in childhood and are more frequently identified in children aged <1 year than in those aged >2 years. [II]

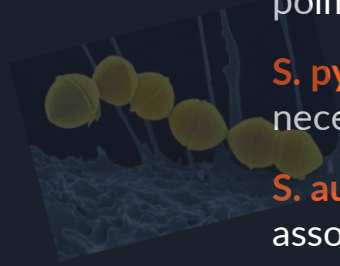
2019

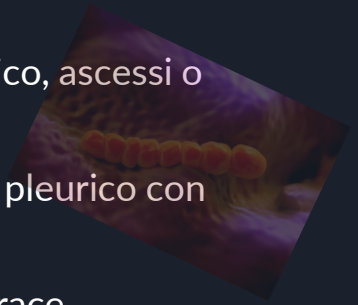
PERCH study.[33] The PERCH study found that the respiratory syncytial virus was the most common cause of pneumonia in children aged 1–59 months admitted to hospitals in Asia and Africa with severe or very severe pneumonia. Alone, viruses rarely cause complicated pneumonia, but viral and bacterial co-infection are common in the context of CAP.



Fernando M de Benedictis, Lancet 2020

I PROTAGONISTI NELLA POLMONITE

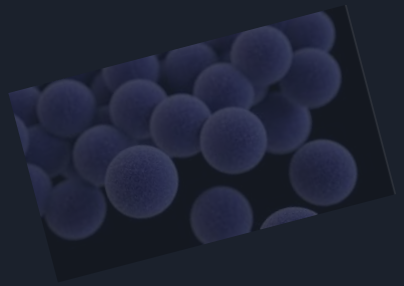




Alcuni sierotipi **di S. pneumoniae** possono essere associati a empiema pleurico, ascessi o polmonite necrotizzante; NB SEU (sierotipo 3)

S. pyogenes può determinare progressione a polmonite severa ed empiema pleurico con necessità di ICU.

S. aureus comunemente associato a pneumatocele con rischio di pneumotorace, associato ad aumentata mortalità in corso di influenza.



Pneumococco
S. pyogenes*
S. aureus*
H. influenzae
M. catarralis
Atipici
~~Legionella~~

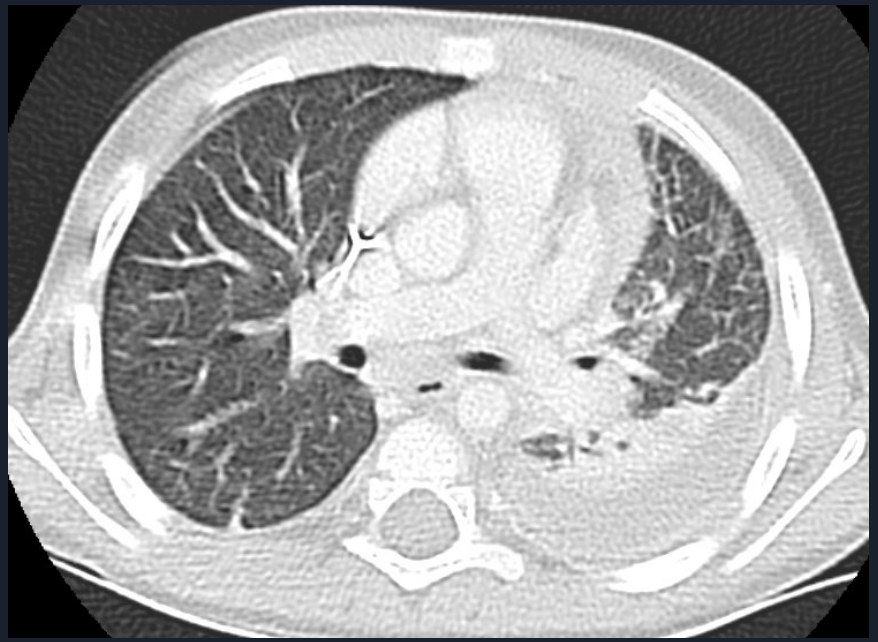
P. aeruginosa
S. agalactiae
E. coli
K. pneumoniae
A. baumanii
Aspergillo
P. jirovecii
M. tuberculosis

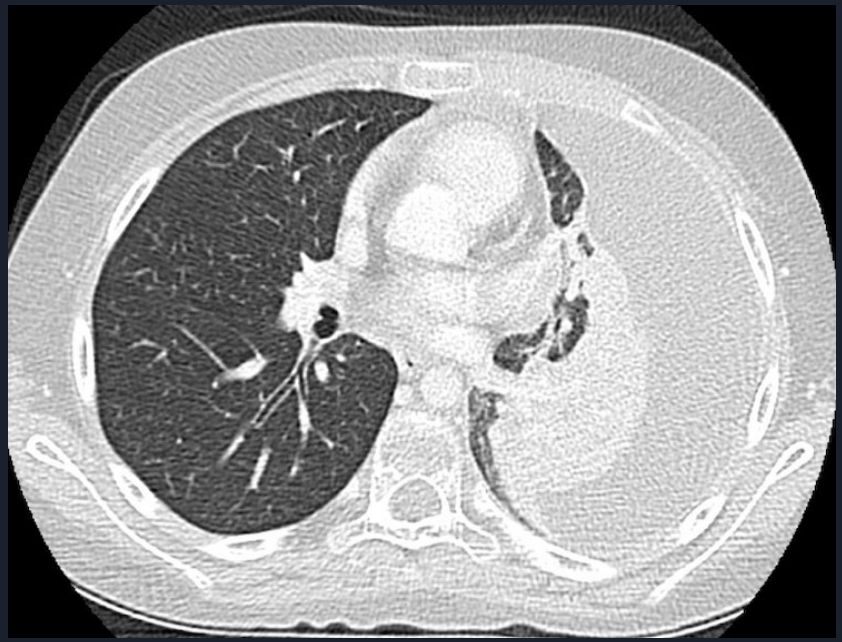
Fernando M de Benedictis, Lancet 2020

VERSAMENTO PLEURICO

Complicanza più comune nelle CAP.
Essudativo --> Fibrinopurulento --> Empiema

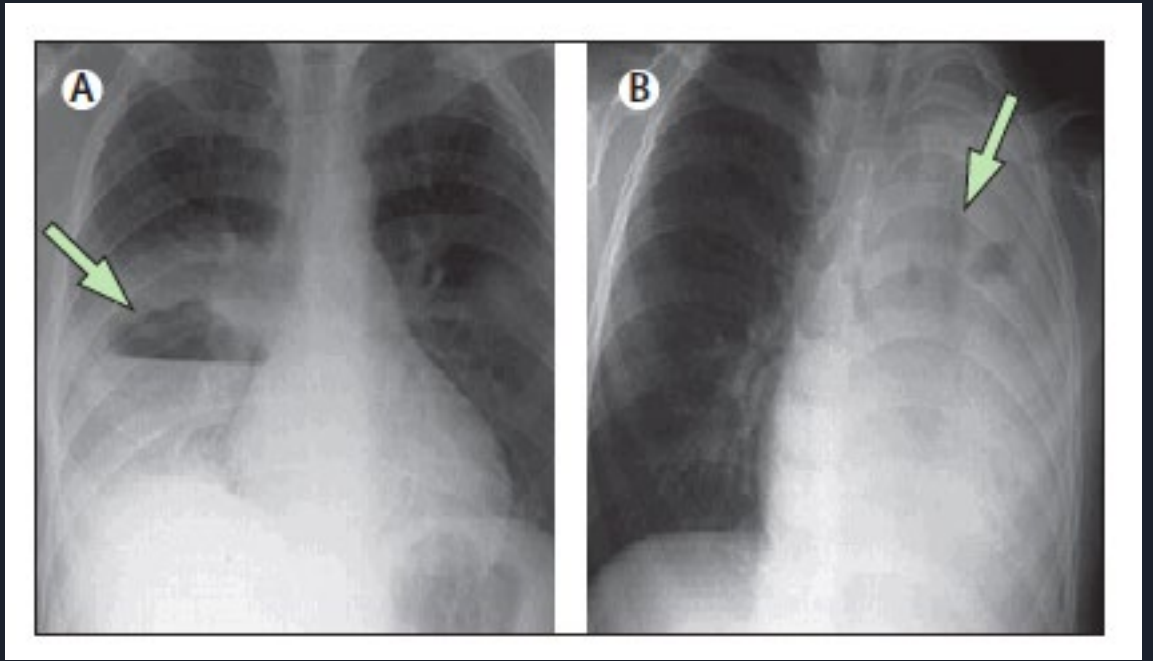
S. pyogenes





POLMONITE NECROTIZZANTE

Complicanza riscontrabile in fino al 7% delle CAP pediatriche.
S. pneumoniae la causa più frequente. Altri: *S. aureus*, *S. pyogenes*, *S. viridans*, *P. aeruginosa*, *anaerobi*.



Fernando M de Benedictis, Lancet 2020

ASCESSO POLMONARE

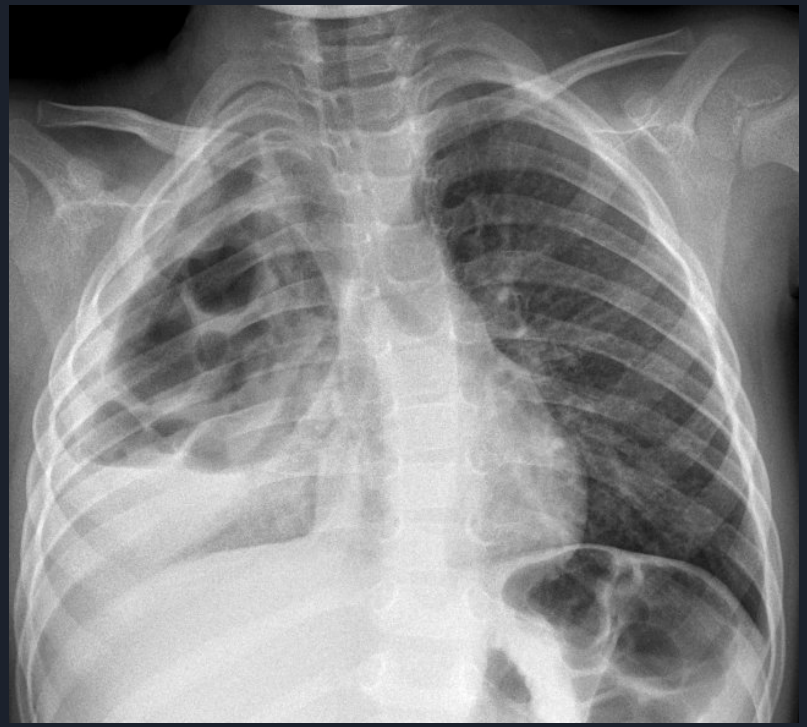
Singola cavità con parete ispessita contentente materiale purulento. Febbre prolungata a basso grado e tosse.

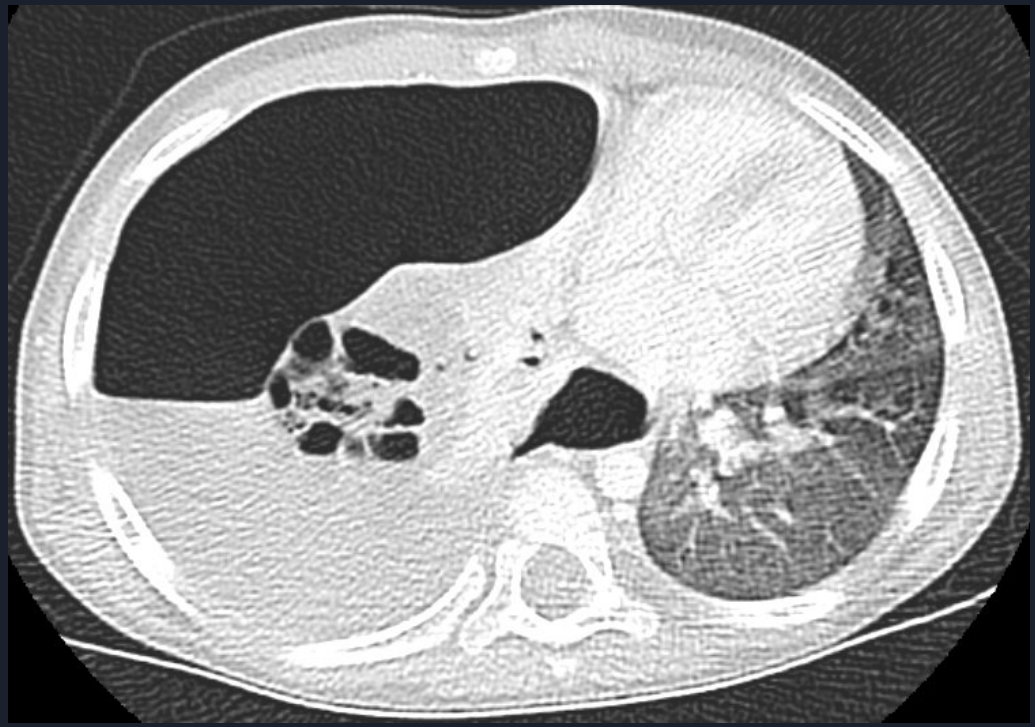
Cause più frequenti: *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *K. pneumoniae*, *anaerobi*.

FdR: malformazione cistica congenita, immunodeficit (IperIgE)

POLMONITE NECROTIZZANTE

Pneumococco

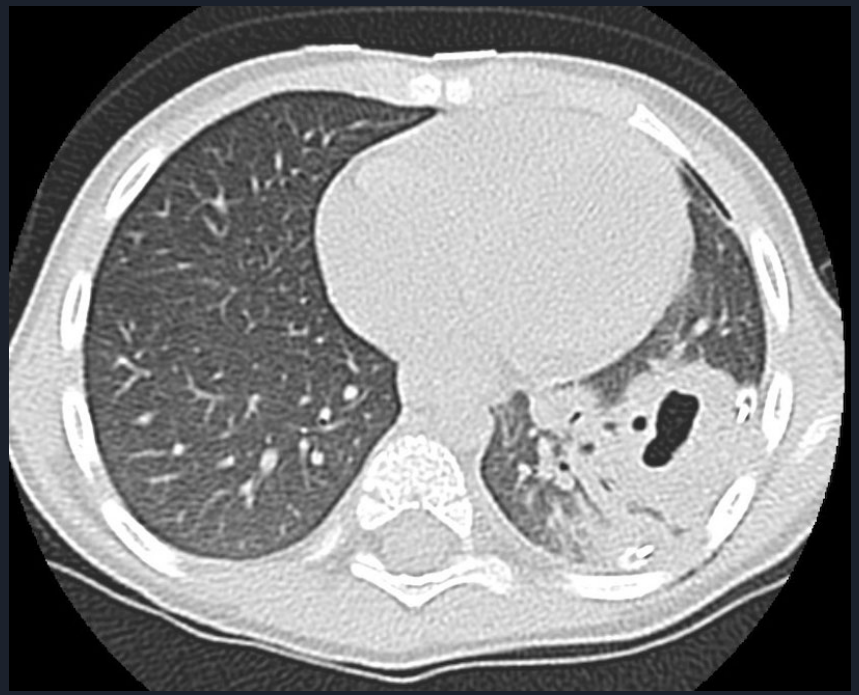


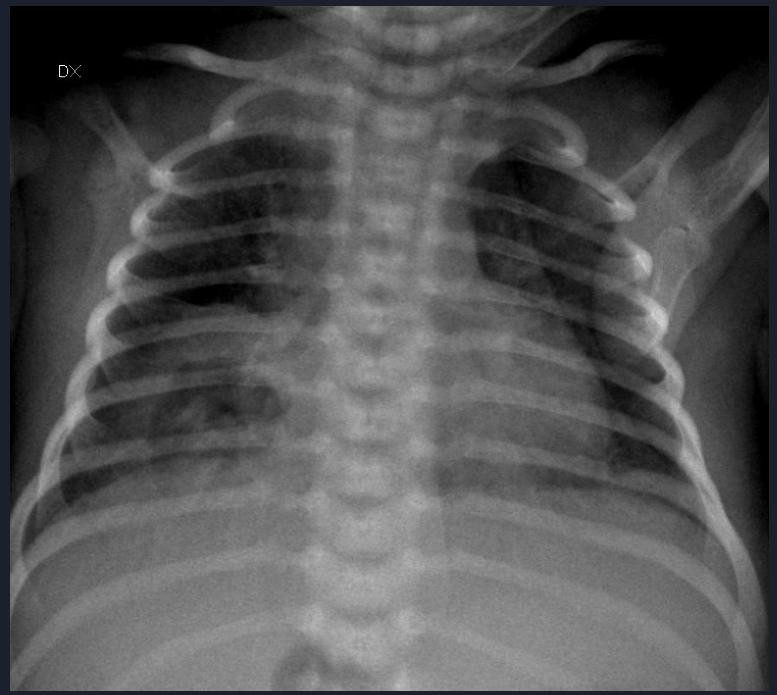


POLMONITE NECROTIZZANTE

S. pyogenes

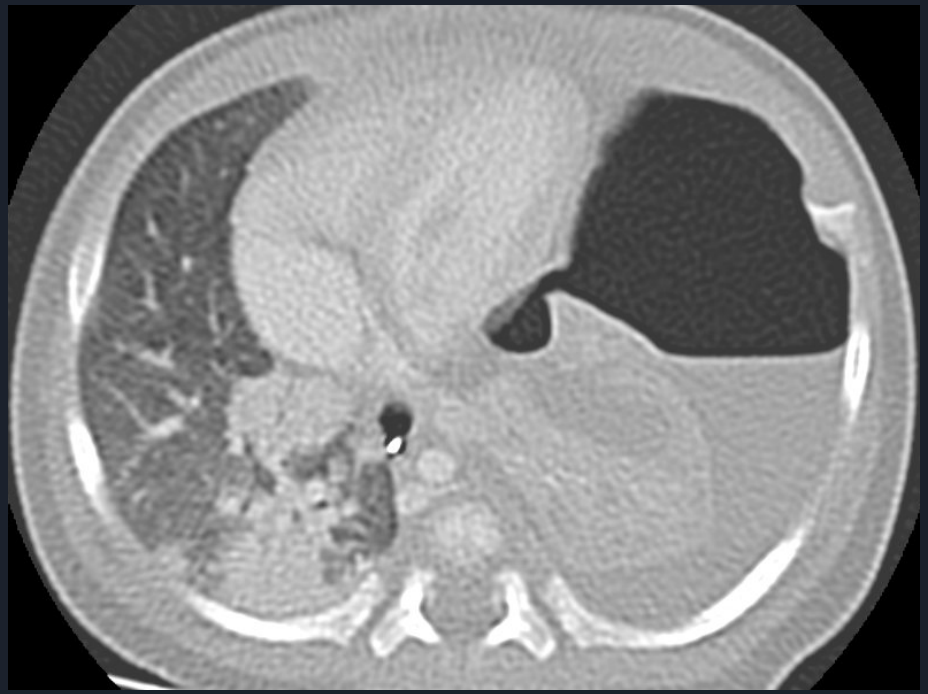
E. coli





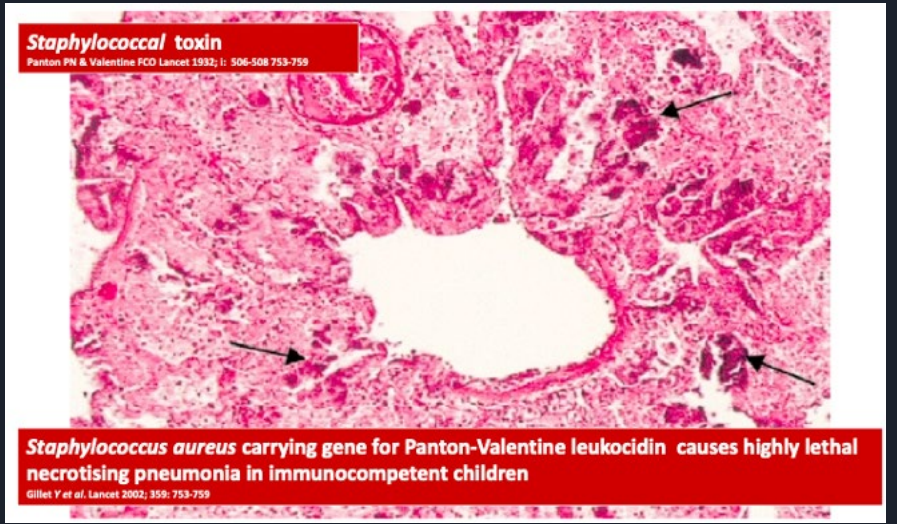
ASCESSO POLMONARE

MRSA pvl+



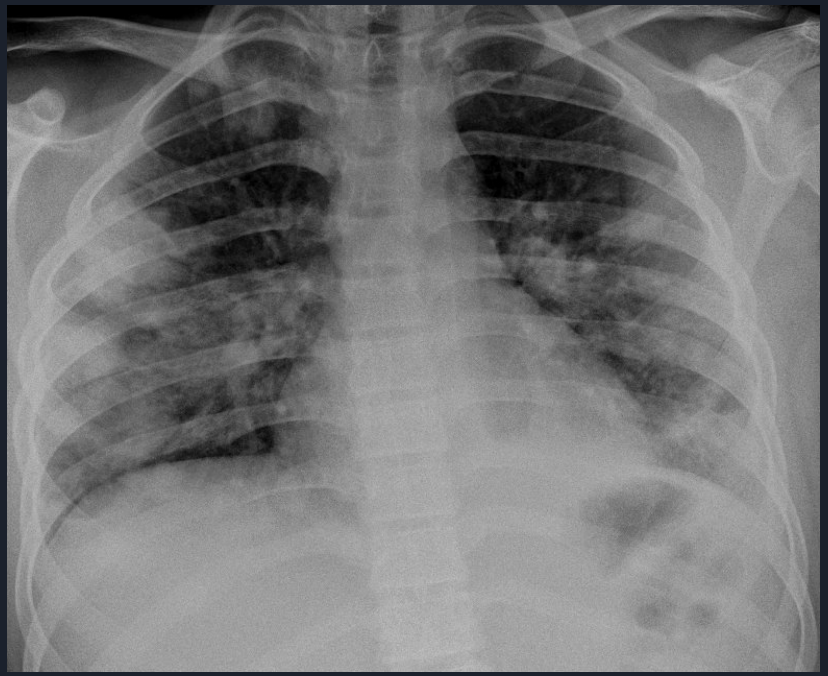
LEUCOCIDINA DI PANTON VALENTINE

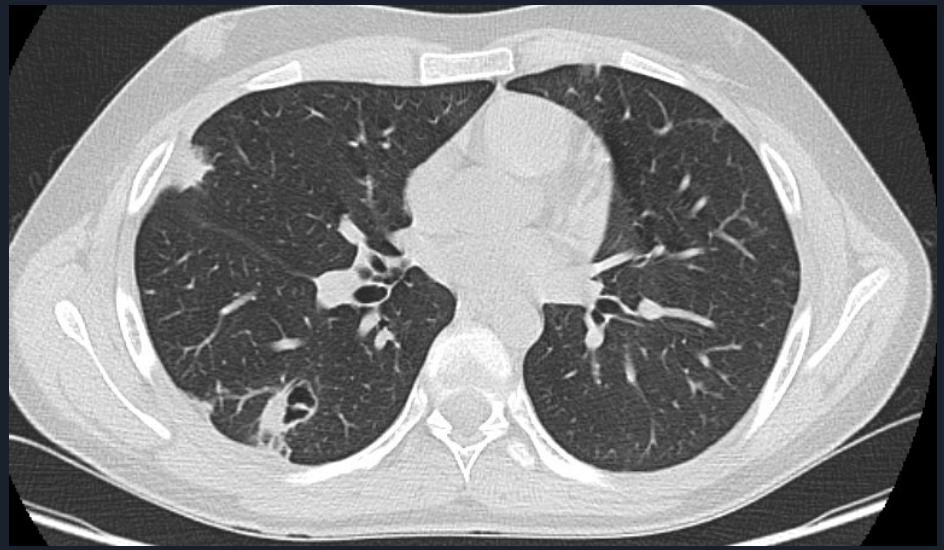
Esotossina che porta a lisi cellulare, rilasciando proteasi che danneggiano il tessuto parenchimale. Ceppi di *S. aureus PVL+* hanno maggiore affinità verso l'epitelio danneggiato delle vie aeree (NB: infezioni virali pregresse!) rispetto a ceppi PVLneg.



INFEZIONI BATTERIEMICHE - METASTATICHE

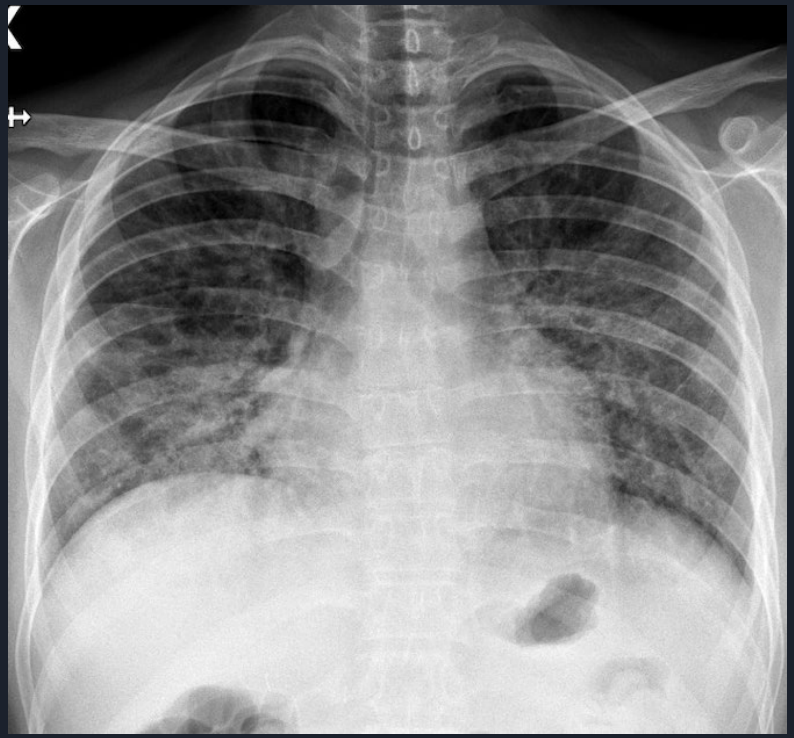
MSSA PVL+

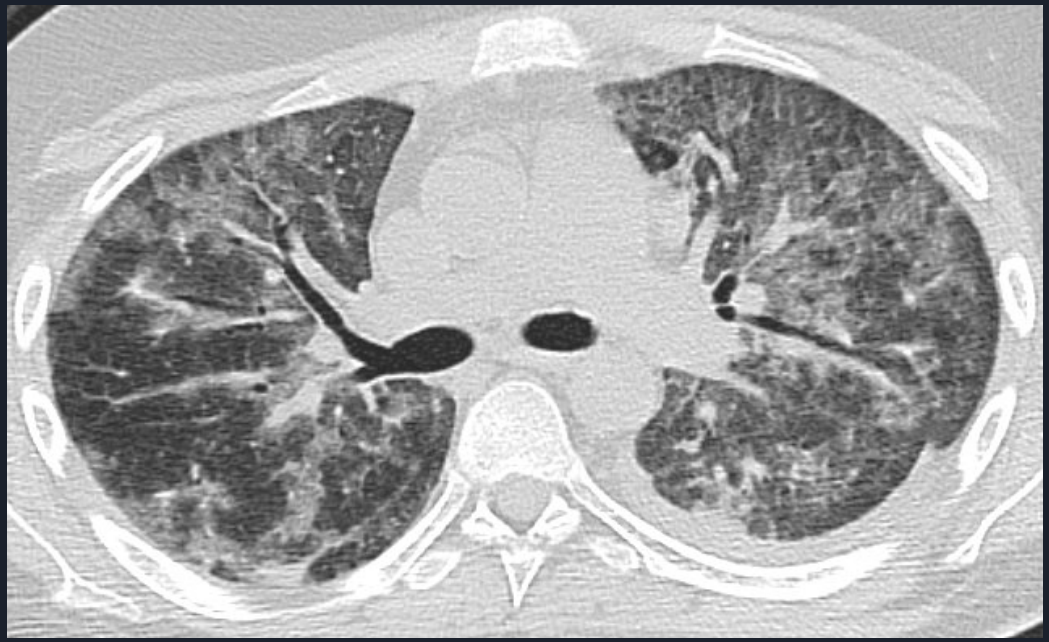




POLMONITI NELL'IMMUNOCOMPROMESSO

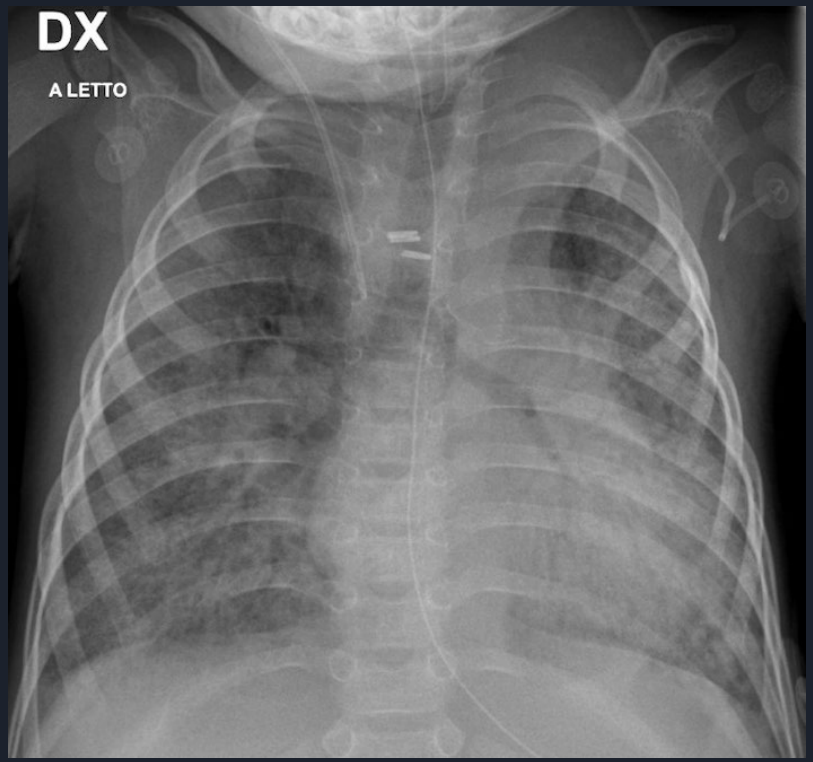
Pneumocystis jirovecii



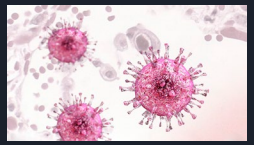


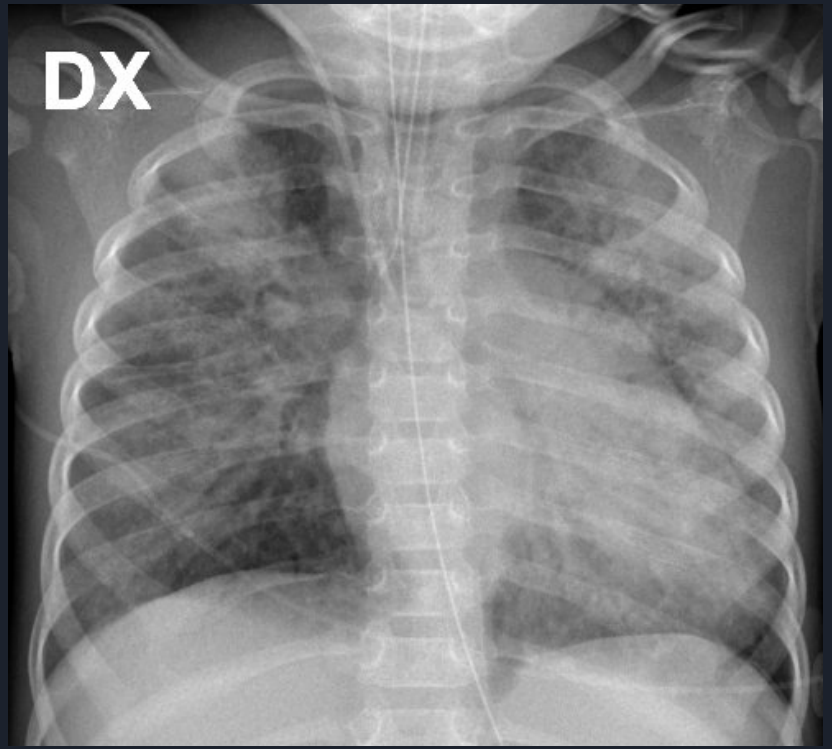
POLMONITI NELL'IMMUNOCOMPROMESSO

P. jirovecii



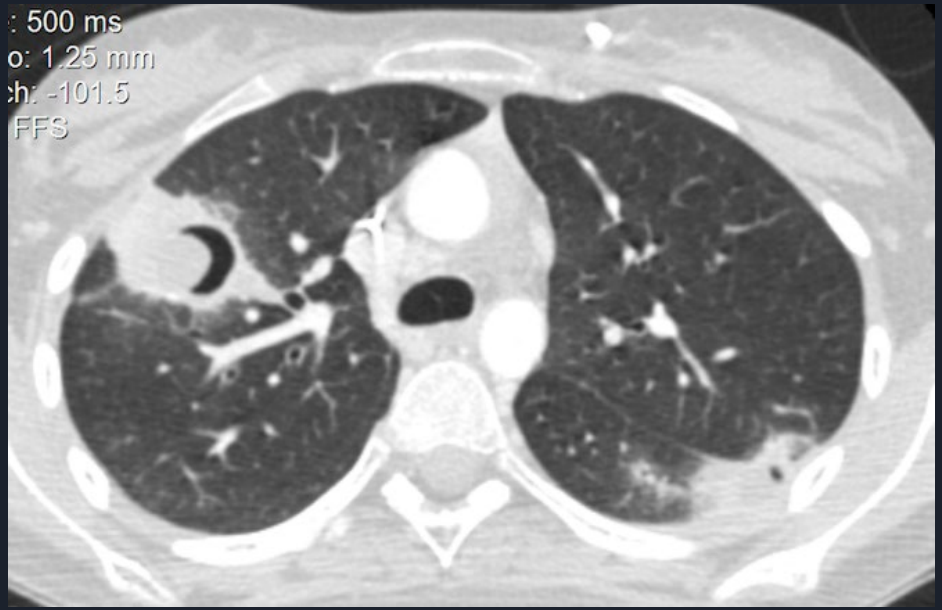
cmv



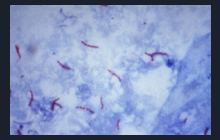


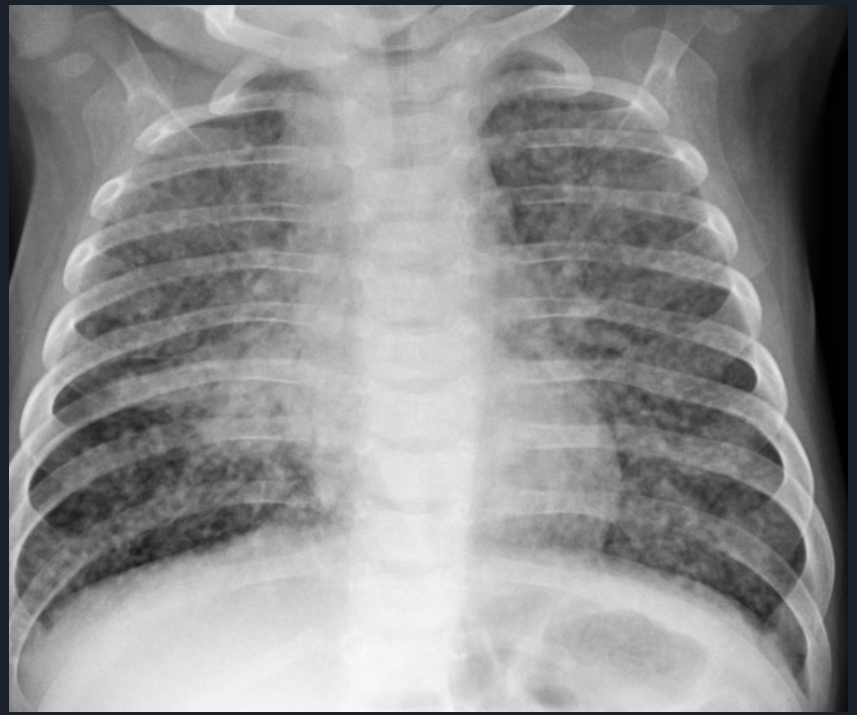
POLMONITI NELL'IMMUNOCOMPROMESSO

Aspergillus



M. tuberculosis





PERCHé L'ANTIBIOTICO?

BTS 2011

All children with a clear clinical diagnosis of pneumonia should receive antibiotics as bacterial and viral pneumonia cannot reliably be distinguished from each other.

IDSA 2019

As bacterial pathogens often coexist with viruses and there is no current diagnostic test accurate enough or fast enough to determine that CAP is due solely to a virus at the time of presentation, our recommendations are to initially treat empirically for possible bacterial infection or coinfection.

disease and the start of therapy; indeed, the early initiation of appropriate antibiotics might, in some cases, prevent the development of effusion and restrict the progression to empyema.[122] Antibiotic treatment

Fernando M de Benedictis, Lancet 2020

QUALI ANTIBIOTICI?

AMOXICILLINA

AMOXI/CLAVULANATO

CEFTRIAXONE/CEFOTAXIME

Pneumo, haemophilus, moraxella, MSSA

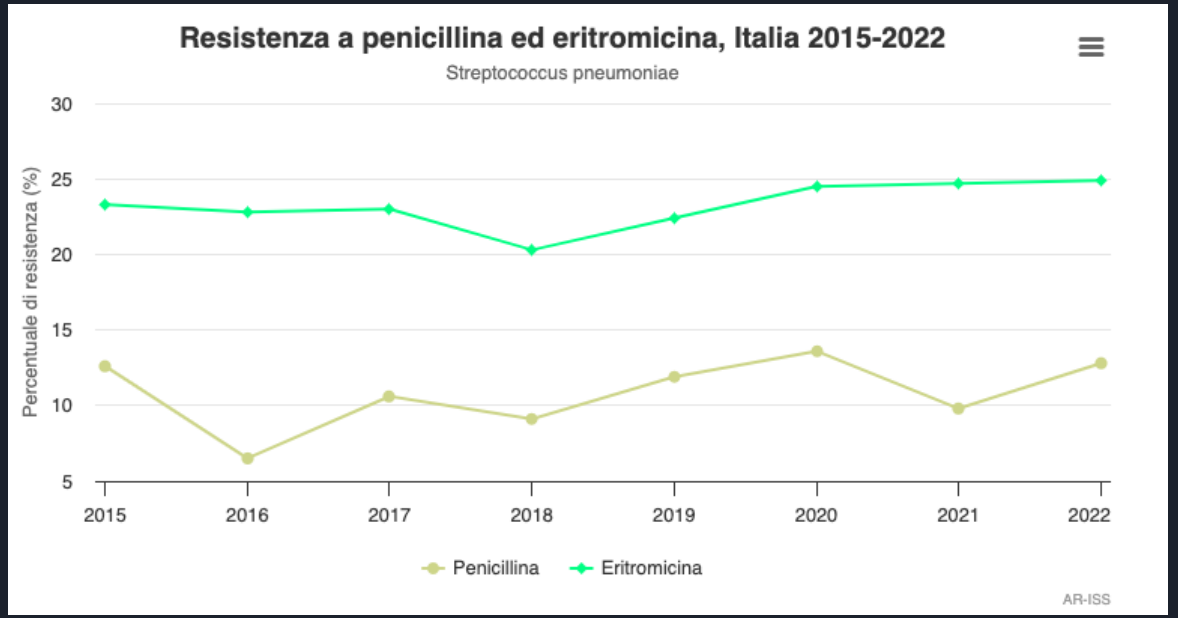
AZITROMICINA

CLARITROMICINA

CHINOLONICI

DOXICICLINA

Atipici, intracellulari



QUALI ANTIBIOTICI?

~~AMOXICILLINA~~

~~AMOXI/CLAVULANATO~~

CEFTRIAXONE/CEFOTAXIME

Pneumo, haemophilus, moraxella, MSSA

VANCOMICINA/TEICOPLANINA

CLINDAMICINA

LINEZOLID

CEFTAROLINA

MRSA, PVL

AZITROMICINA

CLARITROMICINA

CHINOLONICI

DOXICICLINA

Atipici, intracellulari

PIPERACILLINA/TAZOBACTAM

MEROPENEM

CEFTAZIDIME/AVIBACTAM

CEFTOLOZANO/TAZOBACTAM

Gram neg, anaerobi, MDR

QUALI ANTIBIOTICI?

any underlying comorbidities. Initial therapy must be effective against *S pneumoniae* (the commonest cause of CCAP) and *S aureus*, guided by local bacteriological knowledge. High-dose penicillin or ampicillin, amoxi-

Pneumococco
MSSA

AMPICILLINA
CEFALOSPORINA

vancomycin in children with CCAP.[126] In areas where there is a high prevalence of meticillin-resistant *S aureus*, vancomycin should be used as an additional first-line agent until culture results are available. However, one

MRSA

ANTI-MRSA,
eventuale
copertura PVL

resistance.[128] Coverage of anaerobic organisms with metronidazole should be added for patients with lung abscesses when aspiration is suspected. Children with

Anaerobi

Recommendation. We suggest not routinely adding anaerobic coverage for suspected aspiration pneumonia unless lung abscess or empyema is suspected (conditional recommendation, very low quality of evidence).

IDSA 2019

time of an outpatient visit. Because early antiviral treatment has been shown to provide maximal benefit, treatment should not be delayed until confirmation of positive influenza test results.

ANTIVIRALE per Influenza

Fernando M de Benedictis, Lancet 2020; CID 2011

S. aureus

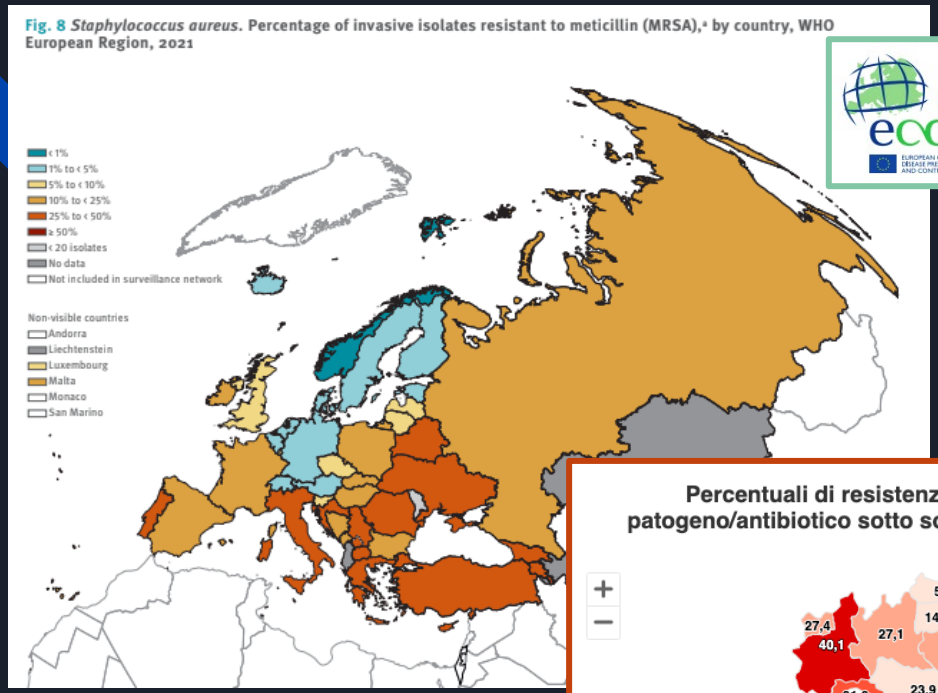
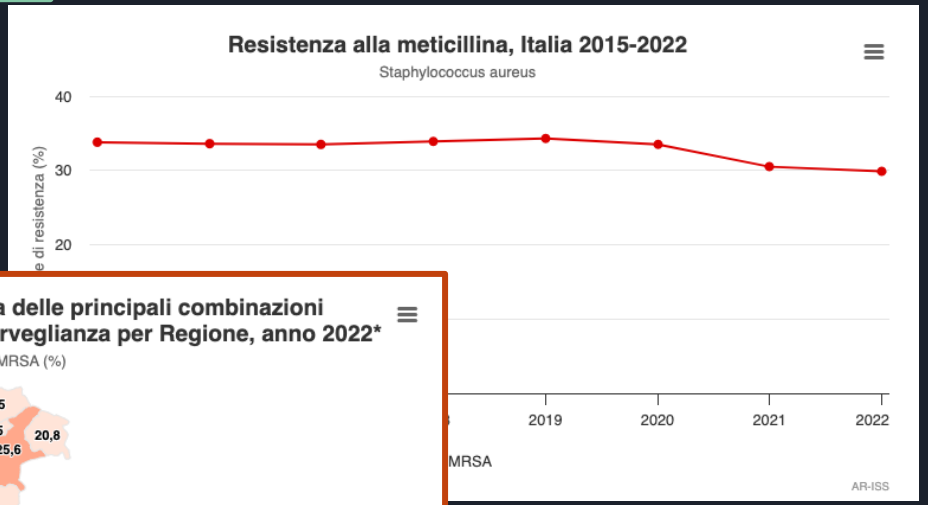
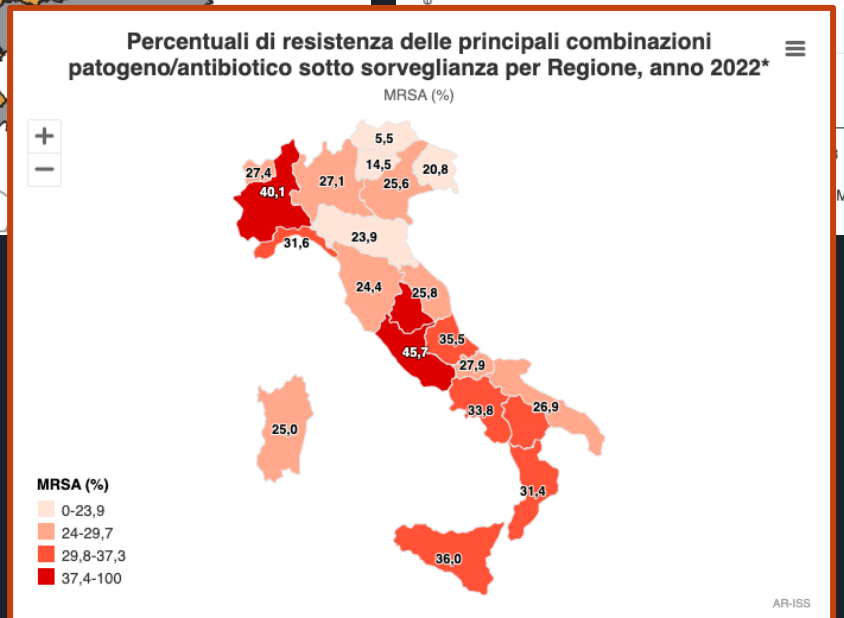


Fig. 8 Staphylococcus aureus. Percentage of invasive isolates resistant to meticillin (MRSA),[a] by country, WHO European Region, 2021
< 1%
1% to < 5%
5% to < 10%
10% to < 25%
25% to < 50%
≥ 50%
< 20 isolates
No data
Not included in surveillance network
Non-visible countries
Andorra
Liechtenstein
Luxembourg
Malta
Monaco
San Marino


Resistenza alla meticillina, Italia 2015-2022
Staphylococcus aureus
40
30
20
2019
2020
2021
2022
MRSA
AR-ISS


Percentuali di resistenza delle principali combinazioni patogeno/antibiotico sotto sorveglianza per Regione, anno 2022*
MRSA (%)
5,5
27,4
40,1
27,1
14,5
25,6
20,8
31,6
23,9
24,4
25,8
45,7
35,5
27,9
33,8
26,9
25,0
31,4
36,0
MRSA (%)
0-23,9
24-29,7
29,8-37,3
37,4-100
AR-ISS

Epitelial lining fluid (ELF), comparto polmonare considerato il sito di localizzazione degli organismi extracellulari responsabili di polmonite o riacutizzazioni respiratorie.
Si ottiene attraverso procedura broncoscopica e BAL.

Gli antibiotici che hanno un miglior rapporto ELF/plasma (>1) sono i macrolidi, fluorochinolonici (levo e moxi) e linezolid.

Keith A. Rodvold et al. Clin Pharmacokinet 2011; 50 (10)

CEFALOSPORINE

I beta-lattamici non si accumulano a livello dei macrofagi alveolari (AM), pertanto non sono attivi vs i patogeni intracellulari.

t/MIC

26.69 mg/L, respectively. Ceftriaxone concentration in ELF was 12.18 ± 5.15 (mean ± standard deviation) times higher than that in plasma, ranging from 1.29 to 20.44.

Yi-Ning Dong et al. Br J Clin Pharmacol. 2023

CEFTRIAXONE

S. pneumoniae
H. influenzae

GLICOPEPTIDI

VANCOMICINA: si concentra meglio nell'ELF in caso di infiammazione polmonare, rispetto a tessuto polmonare sano.

Keith A. Rodvold et al. Clin Pharmacokinet 2011; 50 (10)

TEICOPLANINA
Studio su 13 adulti con VAP

fraction of only 10% [10]. Interestingly, median ELF and unbound serum concentrations of teicoplanin were close to each other.

t/MIC

Olivier Mimoz et al. Intensive Care Med (2006)

CLINDAMICINA

Già in uno studio del 1980 sulla capacità di alcuni antibiotici di concentrarsi a livello dei macrofagi alveolari, la Clindamicina ha mostrato ottime performance con una diffusione a livello cellulare 50x rispetto al comparto extracellulare dopo soli 30 min dall'infusione.

JD Johnson et al. Antibiotic uptake by alveolar macrophages. J Lab Clin Med 1980

LINEZOLID

Linezolid promptly diffused into the ELF that was collected from 16 VAP patients [106]. The ELF/plasma ratio was 1X for both peak and through concentrations, being effective against most bacterial strains with MIC values of 2–4 mg/L. In 12 VAP patients, the admin-

B. Viaggi et al. Antibiotics 2022, 11, 1193

Plasma and bronchopulmonary concentrations of linezolid were measured in 25 healthy adult subjects for up to 48 hours after the fifth oral dose of 600 mg every 12 hours.[135] The mean concentrations and systemic exposure of linezolid in ELF (range 64.3 µg/mL at 4 hours to 0.7 µg/mL at 48 hours; AUC_{24} 672 µg • h/mL) exceeded those in plasma (range 15.5–0.2 µg/mL;

Keith A. Rodvold et al. Clin Pharmacokinet 2011; 50 (10)

shown in Figure 1. The concentrations of linezolid in the ELF were significantly higher than those in plasma at 1, 2, 3, 6, and 12 hours after administration of the first dose (*P* values are shown in Table S1). At steady state, the concentrations of linezolid in the ELF were almost twice as high as those in plasma at 1, 2, and 3 hours when the fifth dose was administered ($P < .0001$; Table S1). It was also found that the maximum

t/MIC

ChangdeWu et al. The Journal of Clinical Pharmacology. 2022

MACROLIDI

Marcata concentrazione a livello dell'ELF e dei macrofagi alveolari rispetto al plasma. Numerosi studi riportano un'elevata concentrazione di Azitromicina e Claritromicina nell'ELF.

white blood cells [86]. Furthermore, single and repeated doses of azithromycin had a preferential distribution in AM (>100X), with a progressive increase up to 24–120 h after the last dose [89–91].

CHINOLONI

Ottima diffusione a livello dell'ELF e delle cellule alveolari.

up to 10X [43,44]. In healthy volunteers (HV) at the steady state, oral levofloxacin 0.5–0.75 g achieved tissue/plasma ratios that were greater than 2X in ELF and 10X in AM 24 h post-dose [45]. The different penetration rates between ciprofloxacin and levofloxacin

B. Viaggi et al. Antibiotics 2022, 11, 1193

CEFTAROLINA

Cefalosporina ad ampio spettro (V gen) con attività in vitro vs Gram negativi (no Pseudomonas) e Gram positivi, compreso MRSA. Battericida.
Maggiore affinità di legame per le PBP. Inattivata da AmpC e ESBL.
Ridotto legame con le proteine --> rapida diffusione tissutale

in plasma and ELF. At an MIC of 1 µg/mL for *S. aureus*, approximately 14% and 53% of patients receiving ceftaroline fosamil 600 mg every 12 h and every 8 h, respectively, were predicted to achieve 42% *f*T>MIC in ELF. The PK/PD

where this microorganism is prevalent. A multicentre, randomised trial showed that ceftaroline produced similar clinical response rates to ceftriaxone plus vancomycin in children with CCAP.[126] In areas where

0-2 mesi	6 mg/kg	8 ore	60 min
2m-2aa	8 mg/kg	8 ore	
2-18aa (<33 kg)	12 mg/kg	8 ore	
2-18aa (>33 kg)	400 mg	8 ore	
	600 mg	12 ore	

Approvata dall'età neonatale per SSTI e CAP

Drwiega EN, et al. Clin Pharmacokinet. 2022.
Fernando M de Benedictis, Lancet 2020

PIPERACILLINA/TAZOBACTAM

tively. Assessment of target attainment for a dosage regimen of 4 g of piperacillin every 8 h as a 30-min intravenous infusion predicted > 95% of healthy subjects and patients had adequate exposure in both serum and ELF to treat organisms with an MIC of 1 µg/mL. Approximately 50% of critically

Dagli studi PK/PD sembra che la penetrazione di Pip/tazo a livello polmonare sia maggiore nel paziente critico rispetto al soggetto sano.

MEROPENEM

La penetrazione nell'ELF ha un grande range di variabilità nel paziente critico con HAP.

[56]. Noncompartmental PK estimates based on mean values of plasma and ELF concentrations at each sampling time demonstrated a higher AUC_{24} in plasma (502 µg•h/mL vs. 422 µg•h/mL, $p = 0.082$) and ELF (150 µg•h/mL vs. 80.3 µg•h/mL, $p = 0.010$) for the 3-h versus 30-min infusion groups.

In summary, we found that meropenem PK/PD target attainment within the lung was variable and that CrCL >115 mL/min reduced the impact on the likelihood of achieving >50% $T_{>4xMIC}$ in both plasma and ELF. Notably, we observed suboptimal target attainment within ELF even among patients who achieved maximal target attainment in plasma. Simulations in both plasma and ELF support the importance of loading doses to improve first 24-hour target attainment when prolonged or continuous infusion doses

Roxane Rohani et al. Antimicrobial Agents and Chemotherapy. 2023

VORICONAZOLO

In conclusion, the present study is the first human study to show that voriconazole is rapidly absorbed into the systemic circulation after inhalation of an aqueous solution, although concentrations of voriconazole remain considerably higher in ELF than in plasma. However, voriconazole also accumulates in ELF compared to in plasma after oral treatment. More stud-

Charlotte U. Andersen et al. Basic & Clinical Pharmacology & Toxicology, 2017

NUOVI ANTIBIOTICI?

LEFAMULINA

Lefamulin is the first truly new antibiotic class since the oxazolidinone linezolid. The mechanism of action of lefamulin is via protein synthesis inhibition, and lefamulin is approved for the treatment of CAP based on equivalence to moxifloxacin[297,298]. This drug can be used as a single agent to target MRSA and other CAP pathogens resistant to macrolide, β-lactam and fluoroquinolone antibiotics, and possibly in cases of treatment failure and/or in patients with multiple drug allergies. Unfortunately, lefamulin does not have substantial activity against ESBL-producing gram-negative pathogens, which is an unmet need in CAP.

Antoni Torres et al.
Nature Review 2021

CEFTOBIPROLE

Autorizzazione pediatrica per CAP e HAP

QUANDO AGGIUNGERE UN **SECONDO ANTIBIOTICO**?

BTS 2011

- 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]

Intensive Care Med (2023) 49:615–632

Recommendation

We **suggest** the addition of macrolides, not fluoroquinolones, to beta-lactams as empirical antibiotic therapy in hospitalised patients with sCAP.
Conditional recommendation, very low quality of evidence.

Remark: The task force also considered the duration of treatment of macrolides being between 3 and 5 days. This would be a reasonable timing especially in the context of de-escalation therapy.

PER QUANTO TRATTARE?

IDSA 2011

VII. What Is the Appropriate Duration of Antimicrobial Therapy for CAP?

Recommendations

CAP non complicata

54. Treatment courses of 10 days have been best studied, although shorter courses may be just as effective, particularly for more mild disease managed on an outpatient basis. *(strong recommendation; moderate-quality evidence)*

55. Infections caused by certain pathogens, notably CA-MRSA, may require longer treatment than those caused by *S. pneumoniae*. *(strong recommendation; moderate-quality evidence)*

71. The duration of antibiotic treatment depends on the adequacy of drainage and on the clinical response demonstrated for each patient. In most children, antibiotic treatment for 2–4 weeks is adequate. *(strong recommendation; low-quality evidence)*

Pleuropolmonite

The duration of intravenous antibiotic therapy to prescribe is controversial, and oral antibiotic therapy should be started as soon as possible.[130–132] A course of 2–3 weeks of intravenous antibiotic therapy is usually sufficient, often with a transition to oral therapy when fever has abated for at least 24–48 h, there is no respiratory distress or evidence of uncontrolled sepsis, the child is tolerating enteral feeds and has an improved mood and playfulness, and when inflammatory markers are reducing.[133]

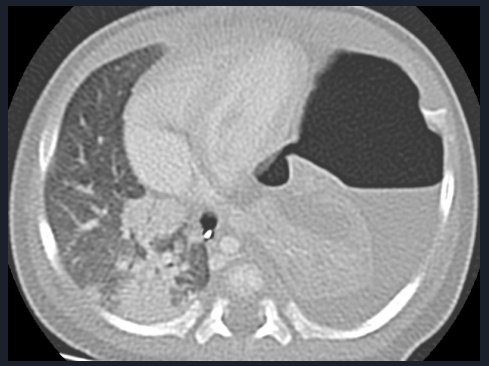
negative.[121] More prolonged therapy might be necessary for lung abscesses, which are typically slow to resolve.

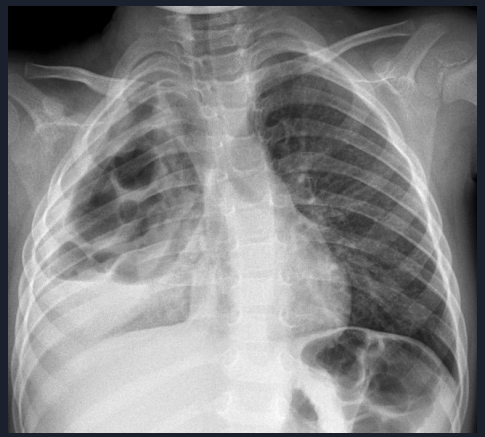
Fernando M de Benedictis, Lancet 2020

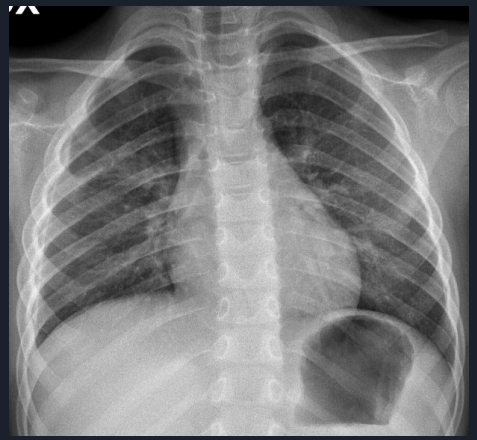
Follow-up

- Children with severe pneumonia, empyema and lung abscesses should be followed up after discharge until they have recovered completely and their chest x-ray has returned to near normal. [D]

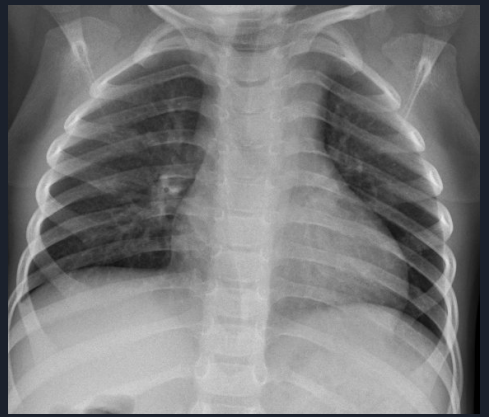
reviews. Those with residual cavitary lesions should also have a repeat chest radiograph 2–4 weeks after discharge to ensure that these residual lesions have resolved.





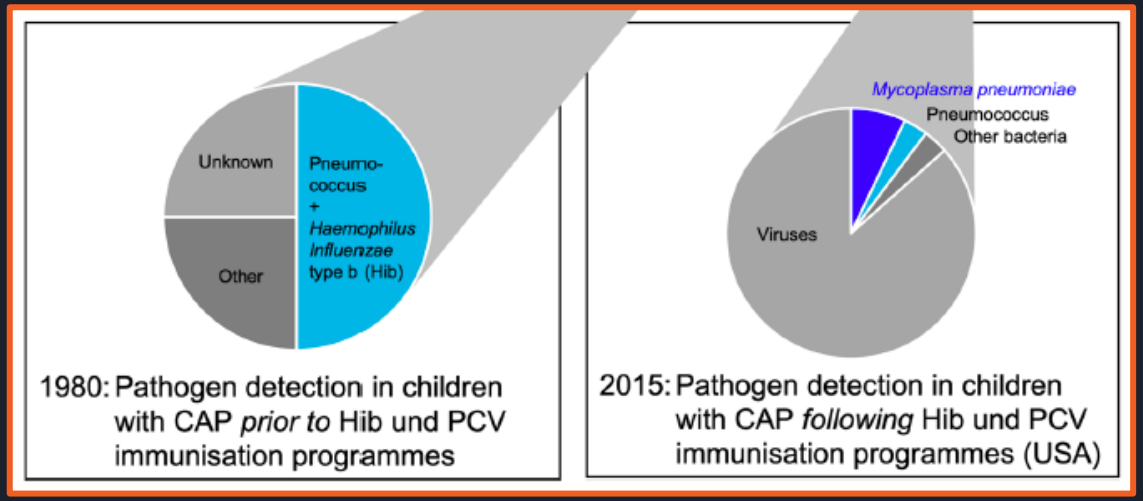


5 mesi da stop ATB



3 anni dall'infezione

VACCINI



Patrick M. Meyer Sauteur, European Journal of Pediatrics (2024)

BTS 2011

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

La *vaccinazione antipneumococcica PCV13* associata a riduzione della malattia invasiva pneumococcica e ad un aumento relativo delle infezioni da S. pyogenes e S. aureus.

Three European studies found that vaccination with the PCV13 reduced the incidence of parapneumonic effusion and empyema in children, without causing serotype shifting.[20–22] Serotypes 1, 3, and 19A, all of which are covered by the PCV13, accounted for most of the *Streptococcus pneumoniae* strains detected in studies from

Fernando M de Benedictis, Lancet 2020

VACCINI

RSV

XX. Can Pediatric CAP Be Prevented?

Recommendations

88. Children should be immunized with vaccines for bacterial pathogens, including *S. pneumoniae*, *Haemophilus influenzae* type b, and pertussis to prevent CAP. *(strong recommendation; high-quality evidence)*

89. All infants ≥6 months of age and all children and adolescents should be immunized annually with vaccines for influenza virus to prevent CAP. *(strong recommendation; high-quality evidence)*

90. Parents and caretakers of infants <6 months of age, including pregnant adolescents, should be immunized with vaccines for influenza virus and pertussis to protect the infants from exposure. *(strong recommendation; weak-quality evidence)*

Il quarto segreto della felicità è coltivare la voglia di imparare, come un bellissimo orto.

(Alberto Pellai)

Grazie