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SIMRI
società italiana per le malattie respiratorie infantili

“Viaggio nelle pneumopatie croniche: DPC, FC e bronchiectasie non-FC”

Inquadramento microbiologico e trattamento in FC e DPC

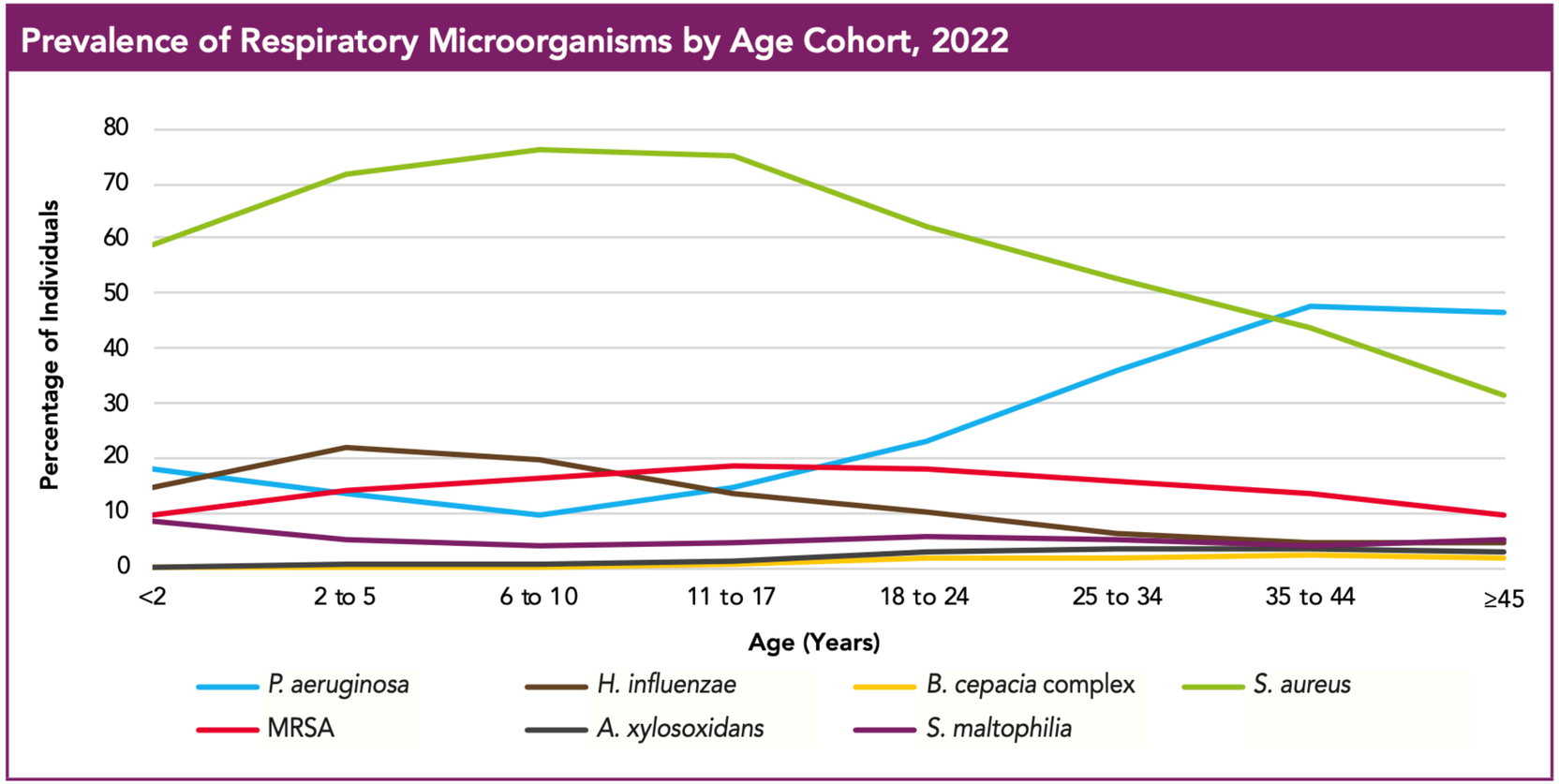
Dr.ssa Elena Spinelli
Centro Regionale Fibrosi Cistica ER
Ospedale “M.Bufalini” Cesena

NON conflitti di interesse
in relazione a questa presentazione

Rapporto collaborativi con le aziende farmaceutiche:

- Neupharma srl
- Viatris srl
- Chiesi spa

Colonizzazioni batteriche respiratorie in FC



Annual Data Report 2022
Cystic Fibrosis Foundation Patient Registry

"*Bacterial infections in patients with primary ciliary dyskinesia: comparison with cystic fibrosis*"

Christiaan DM Wijers, James F Chmiel, Bnejamin M Gaston

Chronic Respiratory Disease 2017, vol 14 (4) 392-406

Table 1. Summary of airway microbiology in patients with CF and patients with PCD.

	Common in pediatric patients		Common in adult patients		Associated with lung disease/ decline in lung function	
Airway pathogen	PCD	CF	PCD	CF	PCD	CF
Haemophilus influenzae	++[a]	+	+	±	Unclear	Y
Pseudomonas aeruginosa	+	++	++[a]	++[a]	Unclear	Y
Staphylococcus aureus	++/+	++[a]	+/±	++	Unclear	Y
Streptococcus pneumoniae	++/+	±/-	+	–	Unclear	Unclear
Moraxella catarrhalis	+/±	±/-	±/-	–	Unclear	Unclear
Achromobacter xylosoxidans	–	+/±/-	–	+/±/-	Unclear	Unclear
Ralstonia sp.	Unknown	–	Unknown	–	Unclear	Unclear
NTM	–/-	±/-	±/-	±/-	Unclear	Unclear
Burkholderia cepacia complex species	[b]	±/-	[b]	±/-	Unclear	Y
Anaerobes	Unknown	++	Unknown	++	Unclear	Unclear

PCD: primary ciliary dyskinesia; CF: cystic fibrosis; NTM: nontuberculous mycobacteria; sp.: species.
[a]Pathogens *most* commonly isolated from patients with this disease at this stage (pediatric/adult); ++ indicates very common pathogens (prevalence ~50% or greater); + indicates common pathogens (prevalence ~25%); ± indicates relatively common pathogens (prevalence ~10%); - indicates rare pathogens (prevalence ~5%); – indicates very rare pathogens (prevalence ~1% and less).
[b]Pathogen has to date not been isolated from the airways of this patient population.

Monitoraggio microbiologico nei centri FC

(almeno) ogni 3 mesi = 4 isolati/anno (criteri Leeds):
ricerca **BATTERI**

- coltura da aspirato ipofaringeo
- coltura escreato
- sputo indotto
- BAL

Almeno una volta/anno (adolescenti):
escreato per ricerca
Miceti e Micobatteri

non solo BATTERI…

"Revised ISHAM-ABPA working group clinical practice guidelines for diagnosing, classifying and treating allergic bronchopulmonary aspergillosis/mycoses"

Agarwal R, Sehgal IS, Muthu V, et al.
Eur Respir J. 2024 Apr 4;63(4):2400061.
doi: 10.1183/13993003.00061-2024.
PMID: 38423624; PMCID: PMC10991853

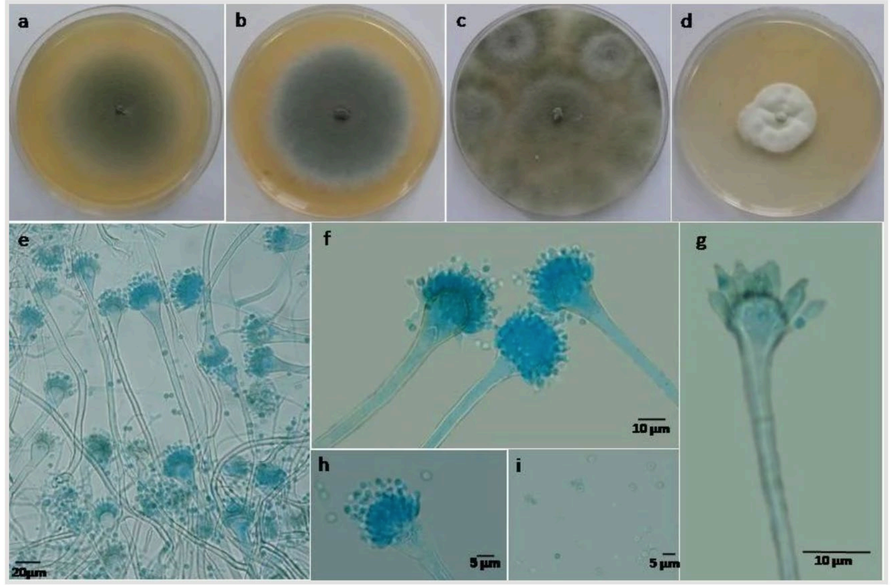


Figure: *Aspergillus fumigatus*. a, b. Seven days colonies of autumn (A.PZ1) and spring (A.BZ1) isolates on MEA; c, d. Seven days colonies of autumn (A.PZ1) and spring (A.BZ1) isolates on CYA; e, f. conidiophores; g. vesicle and phialides; h, i. conidiophores with conidia. Image Source: Mycologia Iranica

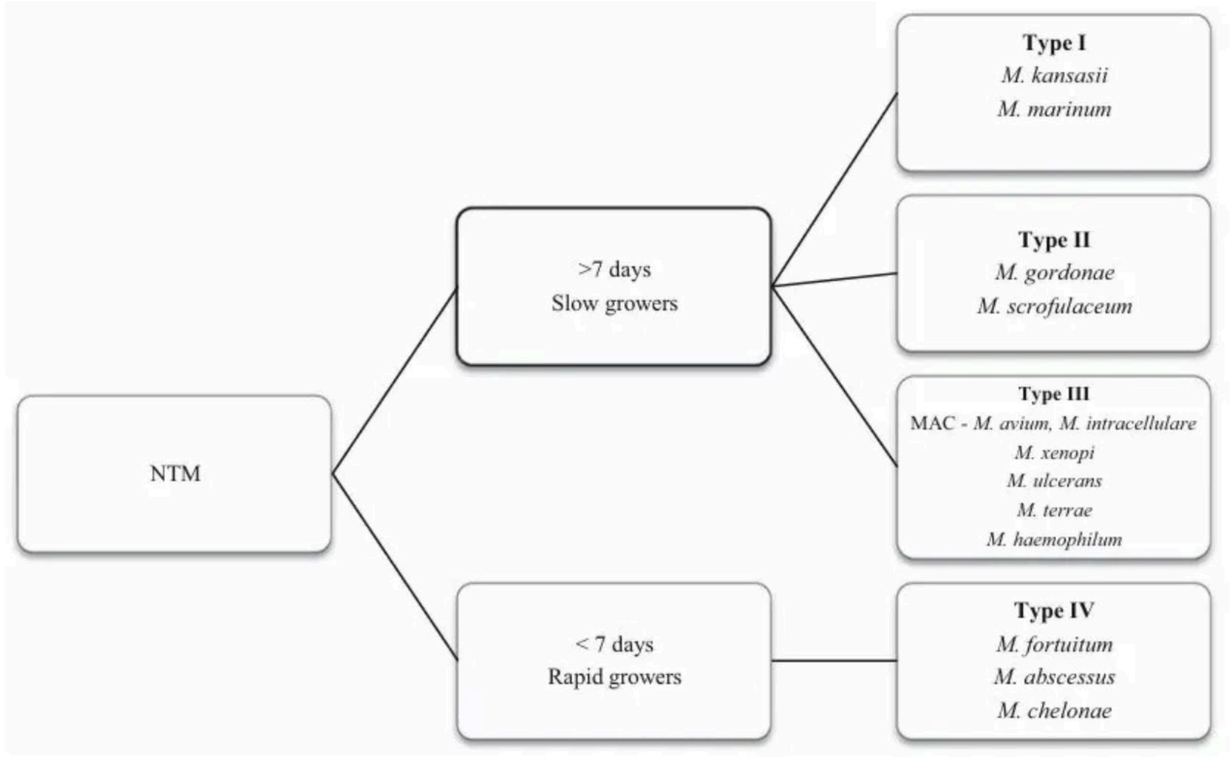
non solo BATTERI…

Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline

Daley CL, Iaccarino JM, Lange C, et al.

Clin Infect Dis. 2020 Aug 14;71(4):e1-e36.

doi: 10.1093/cid/ciaa241



Monitoraggio microbiologico nei centri FC

1 Staphylococcus aureus Carica approssimativa: 1000 CFU/ml.

Stafilococco aureo meticillino-resistente (MRSA) resistente a beta lattamici, cefemi e carbapenemi. GERME SENTINELLA: potrebbero insorgere problemi di diffusione e terapia. Per il controllo della diffusione fare riferimento alle procedure aziendali.

2 Pseudomonas aeruginosa Carica approssimativa: 1000 CFU/ml.

Ceppo 1 Staphylococcus aureus

Antibiotici		*MIC*	*MIC Breakpoint S<=*	*R>*
Penicillina G	R	>=0.5	0.125	0.125
Ceftaroline	S	0.25	1	2
Clindamicina	R		0.25	0.25
Daptomicina	S	<=0.12	1	1
Eritromicina	R	>=8	1	2
Levofloxacina	SE	0.25	0.001	1
Linezolid	S	2	4	4
Mupirocina	S	<=1		
Oxacillina	R	>=4	2	2
Rifampicina	S	<=0.03	0.06	0.06
Teicoplanina	S	1	2	2
Tetraciclina	S	<=1	1	2
Tigeciclina	S	<=0.12	0.5	0.5
Trimetoprim/sulfametoxazolo	S	<=10	20	40
Vancomicina	S	<=0.5	2	2
Ac. fusidico	S	<=0.5	1	1
Gentamicina	S	<=0.5	2	2

MIC = Concentrazione Minima Inibente (mg/L)
Antibiogramma interpretato secondo criteri Eucast:
R= Resistente
S = Sensibile, a regime di dosaggio standard
SE o I = Sensibile a elevata esposizione all'antibiotico, in funzione del dosaggio, modalità e tempistica di somministrazione, distribuzione nel sito di infezione, metabolismo ed escrezione.

Ceppo 2 Pseudomonas aeruginosa

Antibiotici		*MIC*	*MIC Breakpoint S<=*	*R>*
Amikacina	S	<=8	16	16
Cefepime	SE	1	0.001	8
Ceftazidima	SE	1	0.001	8
Cloramfenicolo	R	>8		
Ciprofloxacina	SE	<=0.25	0.001	0.5
Colistina	S	<=2	4	4
Fosfomicina	R	64		
Imipenem	SE	<=1	0.001	4
Levofloxacina	SE	0.25	0.001	2
Meropenem	S	1	2	8
Piperacillina/Tazobactam	SE	<=4	0.001	16
Tobramicina	S	<=2	2	2

MIC = Concentrazione Minima Inibente (mg/L)
Antibiogramma interpretato secondo criteri Eucast:
R= Resistente
S = Sensibile, a regime di dosaggio standard
SE o I = Sensibile a elevata esposizione all'antibiotico, in funzione del dosaggio, modalità e tempistica di somministrazione, distribuzione nel sito di infezione, metabolismo ed escrezione.

- **Antibiogramma**: utile, ma…
- **R** in vitro vs in vivo?
- **MIC** per concentrazioni ematiche! E quelle polmonari?

Pseudomonas aeruginosa:

ERADICARE!

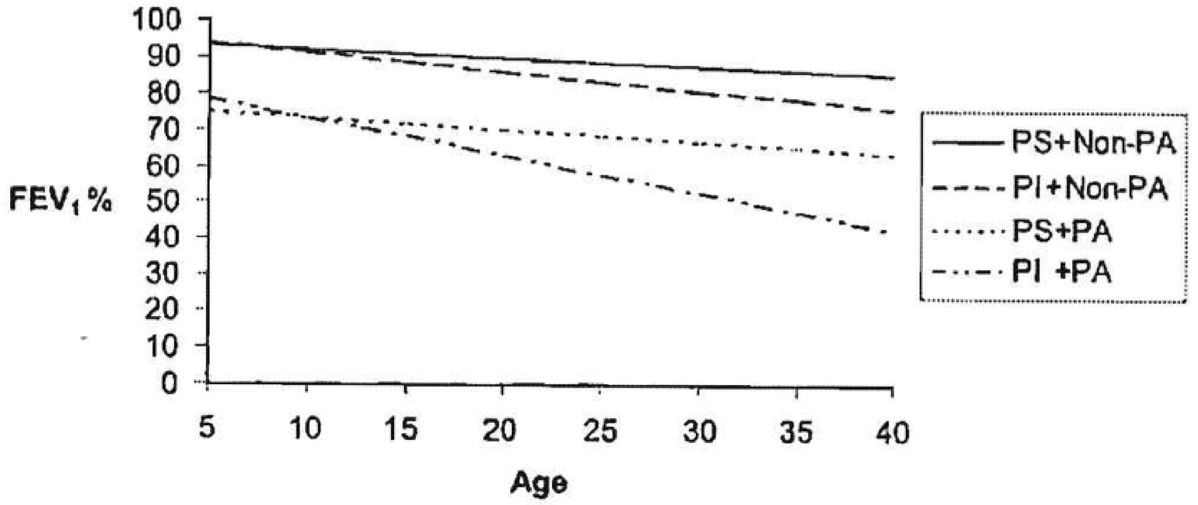


Fig. 5. Mixed model regression lines of FEV_1 vs. age in years for PI and PS patients with chronic *Pseudomonas aeruginosa* colonization (PA) and those without (Non-PA).

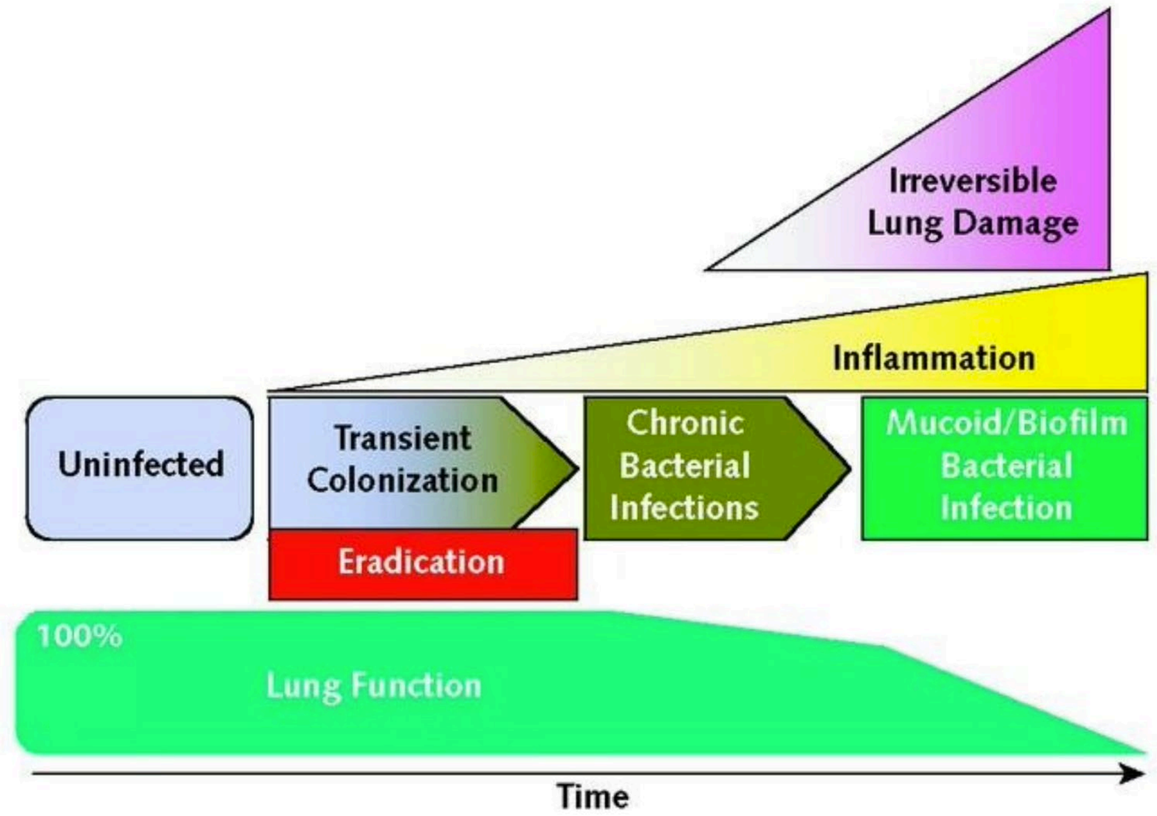
Schaedel, C., de Monestrol, I., Hjelte, L., Johannesson, M., Kornfält, R., Lindblad, A., Strandvik, B., Wahlgren, L. and Holmberg, L.

*"**Predictors of deterioration of lung function in cystic fibrosis**"*

Pediatr. Pulmonol. 2022, 33: 483-491. https://doi.org/10.1002/ppul.10100

Pseudomonas aeruginosa:

ERADICARE!



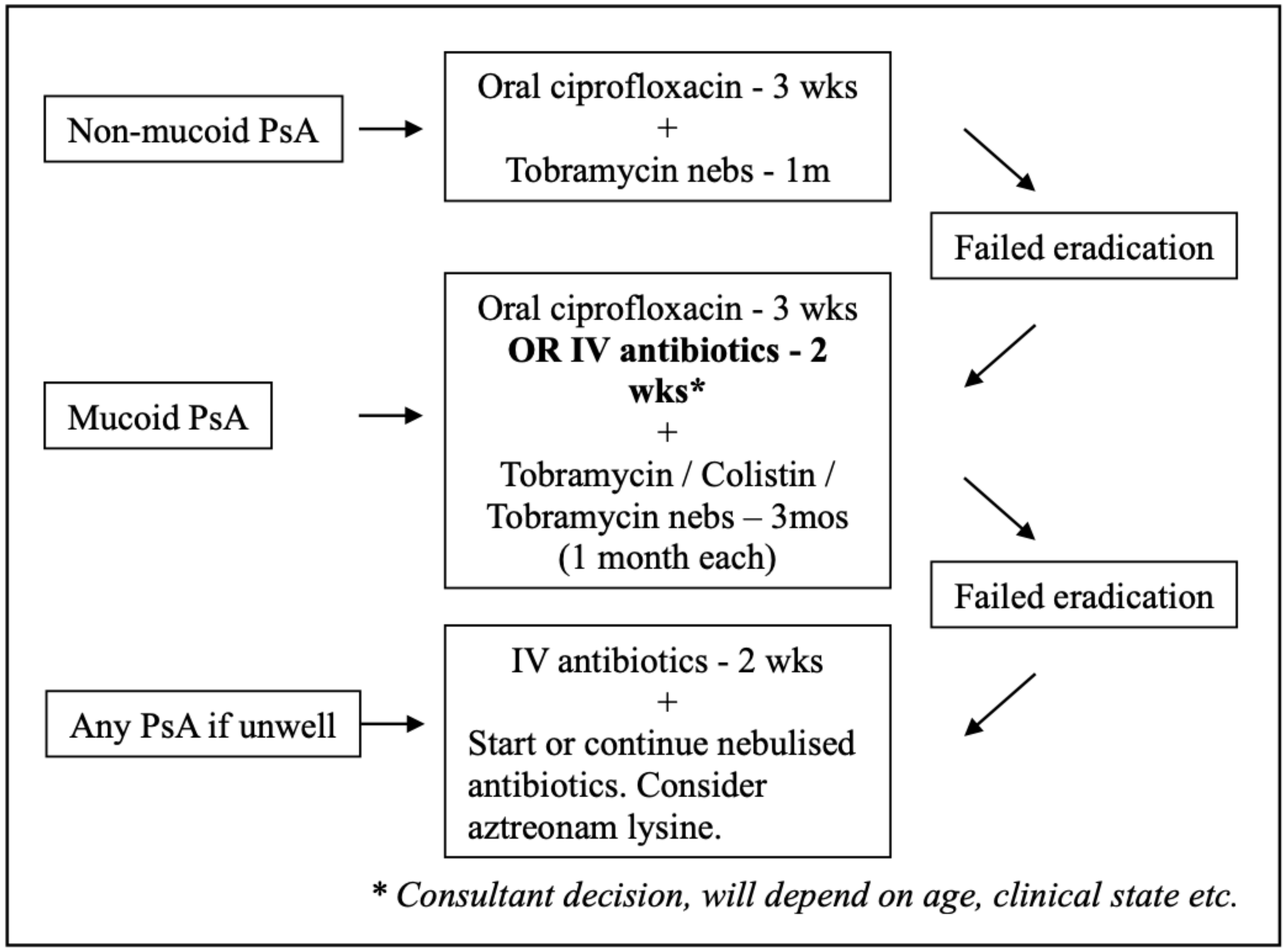
Starner TD, McCray PB Jr; American College of Physicians; American Physiological Society.

"Pathogenesis of early lung disease in cystic fibrosis: a window of opportunity to eradicate bacteria"

Ann Intern Med. 2005 Dec 6;143(11):816-22. doi: 10.7326/0003-4819-143-11-200512060-00010. PMID: 16330793.

Pseudomonas aeruginosa:

ERADICARE!



Clinical Guidelines:
Care of Children
with
Cystic Fibrosis

Royal Brompton Hospital

Part of Guy's and St Thomas' NHS Foundation Trust

Available on
www.rbht.nhs.uk/childrencf

& APP download

2023

Piatti G, De Santi MM, Farolfi A, Zuccotti GV, D'Auria E, Patria MF, Torretta S, Consonni D, Ambrosetti U.

"Exacerbations and Pseudomonas aeruginosa colonization are associated with altered lung structure and function in primary ciliary dyskinesia"

BMC Pediatr. 2020 Apr 13;20(1):158. doi: 10.1186/s12887-020-02062-4. PMID: 32284045; PMCID: PMC7153224.

Pseudomonas aeruginosa: ERADICARE anche in DCP

Methods: We retrospectively analyzed data from 58 patients with PCD, 37 adults and 21 children. The demographic and clinical data, forced expiratory volume at 1 s (FEV_1) and forced vital capacity (FVC), sputum microbiology and imaging results (chest CT scores-modified Bhalla) were recorded. Patients were stratified according to the number of exacerbations (< 2/year vs ≥ 2/year) and chronic Pseudomonas aeruginosa (PA) colonization. The possible correlations between lung function and chest CT scores were assessed; we also evaluated the correlation between these parameters and the severity scores for bronchiectasis (BSI, FACED and e-FACED).

Results: Chest CT scores showed a significant correlation with FEV_1 ($p = 0.0002$), age ($p < 0.0001$), BMI ($p = 0.0002$) and number of lung lobes involved ($p < 0.0001$). PA colonization had an overall prevalence of 32.6%: no significant difference in FEV_1 between PA colonized and non-colonized patients was found ($p = 0.70$), while chest CT score was significantly worse in chronic PA colonized patients ($p = 0.009$). Patients with a high number of exacerbation (≥ 2/year) were older ($p = 0.01$), had lower FEV_1 ($p = 0.03$), greater number of lobes involved ($p < 0.001$) and worse CT score than patients with low number of exacerbations ($p = 0.001$); they also had higher prevalence of PA chronic bronchial infection (33.3% versus 13.6%, $p = 0.10$). Multivariable linear regression analyses adjusted for gender, age and BMI showed positive associations between PA colonization and number of exacerbations with severity of disease (number of lobes involved, CT score, BSI, FACED, and e-FACED).

Conclusions: In our PCD population the number of exacerbations (≥ 2/year) and PA colonization were the two most relevant factors associated with severity of disease.

Gatt D, Shaw M, Wee W, Solomon M, Dell SD, Ratjen F.

"Efficacy of Antibiotic Eradication Therapy of Early Pseudomonas aeruginosa Infection in Children with Primary Ciliary Dyskinesia"

Ann Am Thorac Soc. 2023 Jun;20(6):854-860. doi: 10.1513/AnnalsATS.202210-858OC. PMID: 36753426.

Rationale: Chronic infection with *Pseudomonas aeruginosa* (PsA) negatively impacts lung disease in patients with primary ciliary dyskinesia (PCD). There is currently limited evidence regarding the efficacy of PsA antibiotic eradication therapy (AET) in children with PCD. **Objectives:** To assess the effectiveness of AET of early PsA infection in children with PCD. **Methods:** This retrospective study included pediatric patients with a confirmed PCD diagnosis according to the American Thoracic Society guidelines at the Hospital for Sick Children between 2010 and 2022. Children with newly acquired PsA infection underwent AET using a stepwise protocol. The protocol included the following steps: step 1, 28 days of tobramycin inhalation solution (TIS); step 2, repeat TIS if culture positive after step 1; and step 3, 14 days of intravenous antibiotics followed by 28 days of TIS if culture positive after step 2. Step 3 was also used for patients who presented with pulmonary exacerbation symptoms. The main outcome was a PsA-negative culture result based on the microbiological results of the first culture after completion of each step of treatment. **Results:** During the study period, 31 children had a new PsA infection and underwent AET. Of the 27 children who had been asymptomatic at the time of the PsA infection, negative PsA culture results were achieved in 20 (74%) of 27, 1 (14%) of 7, and 5 (83%) of 6 after steps 1, 2, and 3 of AET, respectively. All four symptomatic patients who initially were treated with step 3 had successful clearance of PsA. The overall cumulative success rate of the protocol for negative culture results after AET was 97% (30 of 31). For patients in whom AET was successful, the probability of staying PsA free for at least 1 year was 70%. **Conclusions:** AET for early PsA infection is highly effective in PCD, with sustained efficacy in most individuals. These data suggest that AET should be considered in all children with PCD who have early PsA infection.

per approfondire:

Marthin JK, Lucas JS, Boon M, Casaulta C, Crowley S, Destouches DMS, Eber E, Escribano A, Haarman E, Hogg C, Maitre B, Marsh G, Martinu V, Moreno-Galdó A, Mussaffi H, Omran H, Pohunek P, Rindlisbacher B, Robinson P, Snijders D, Walker WT, Yiallouros P, Johansen HK, Nielsen KG.

International BEAT-PCD consensus statement for infection prevention and control for primary ciliary dyskinesia in collaboration with ERN-LUNG PCD Core Network and patient representatives.

ERJ Open Res. 2021 Aug 2;7(3):00301-2021. doi: 10.1183/23120541.00301-2021. PMID: 34350277; PMCID: PMC8326680.

- Segregazione dei pazienti (in base ai germi)

- Gli operatori vanno dal paziente (e non viceversa)

TABLE 1 Final 20 suggested BEAT-PCD consensus statements included in the infection prevention and control for primary ciliary dyskinesia (PCD) statements

No.	Aspect	Statement	Consensus %	E-survey voters
1	DM	"The BEAT-PCD network suggests to culture on selective media for *Pseudomonas aeruginosa* routinely in every airway secretion sample[#]"	100	18
2	DM	"The BEAT-PCD network suggests that all PCD Centres have access to bacterial typing"	100	14
3	DM	"The BEAT-PCD network suggests to culture airway secretion samples[#] from patients at least 4 times annually"	94.4	18
4	DM	"The BEAT-PCD network suggests to culture for NTM at least annually and in addition at any unexplained deterioration of lung function"	92.9	14
5	DM	"The BEAT-PCD network suggests routine bacterial typing at first positive culture of *Burkholderia cepacia*"	92.9	14
6	DM	"The BEAT-PCD network suggests the use of modified Leeds criteria [5] when defining chronicity of *Pseudomonas aeruginosa*"	83.3	18
7	IT	"The BEAT-PCD network suggests that treatment of NTM relies on 1) Pulmonary symptoms and 2) Nodular or cavitary processes on chest radiograph and/or bronchiectasis with small nodules on HRCT scan and 3) Positive culture results from at least two separate airway secretion samples[#] or positive culture results from at least one bronchial wash or lavage or mycobacterial histological findings in either transbronchial or lung biopsy material together with positive microbiological culture according to 2020 ATS/IDSA criteria" [27]	100	18
8	IT	"The BEAT-PCD network suggests that cultured *Pseudomonas aeruginosa* is treated regardless of symptoms and microscopy"	100	18
9	IT	"The BEAT-PCD network suggests that *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Staphylococcus aureus* (MSSA) are treated, if the patient is symptomatic"[¶]	94.4	18
10	IT	"The BEAT-PCD network suggests that cultured Multi-Resistant *Staphylococcus aureus* (MRSA) is treated regardless of symptoms and microscopy"	86	14
11	IT	"The BEAT-PCD network suggests that cultured *Burkholderia cepacia* complex is treated regardless of symptoms and microscopy"	83.3	18
12	S	"The BEAT-PCD network suggests that patients with *Pseudomonas aeruginosa* infection should be segregated in outpatient and in-patient settings"	100	18
13	S	"The BEAT-PCD network suggests that patients with NTM infection should be segregated in outpatient and in-patient settings"	94.4	18
14	S	"The BEAT-PCD network suggests that patients with MRSA infection should be segregated in outpatient and in-patient settings"	88.9	18
15	S	"The BEAT-PCD network suggests that patients with *Burkholderia cepacia* complex infection should be segregated in outpatient and in-patient settings"	88.9	18
16	S	"The BEAT-PCD network suggests that all PCD centres have written guidelines for segregation that are adapted to the facilities of the individual centres and to the best standards"	94.4	18
17	S[+]	"During the COVID-19 Pandemic concerning arrangements outside the hospital: The BEAT-PCD network suggests (*e.g.*, BEAT-PCD Conferences) that if more than one patient with PCD is attending indoor events they should keep at least a 2-m distance and wear a mask regardless of infection status"	93.8	16 e-mail respondents
18	S	"The BEAT-PCD network suggests that patients with identified viral infection or 'clinically having a cold' should be temporarily segregated in outpatient and in-patient settings, or at least wear a mask"	88.2	17
19	S	"The BEAT-PCD network suggests a cleaning procedure between patients and at the end of the day to include registered hospital-grade disinfectant/detergent"	83.3	18
20	S	"The BEAT-PCD network suggests that the following bacteria do not need specific considerations regarding segregation: *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Staphylococcus aureus* (MSSA)"	82.4	17

DM: diagnostic microbiology aspects; NTM: nontuberculous mycobacteria; IT: infection treatment aspects; HRCT: high-resolution computed tomography; S: segregational aspects; COVID-19: coronavirus disease 2019; MSSA: methicillin-susceptible *Staphylococcus aureus*. Voters: 18 PCD experts responded to the E-surveys; 16 voted by e-mail for consensus statement #15. [#]: Airway secretion sample defined as: sputum sample or oropharyngeal cough swab or laryngeal suction. [¶]: "Symptomatic" = increased symptoms judged at the discretion of the treating physician. [+]: Accepted consensus after re-evaluation due to COVID-19 pandemic. Accepted consensus was based on the decisions from an international PCD expert panel. Each proposed statement was presented for the expert panel using a Likert scale offering five possible response options: "Strongly agree", "Agree", "Neutral", "Disagree", "Strongly disagree". Consensus for a proposed statement was defined where at least 80% agreement ("Strongly agree" or "Agree") was obtained within the PCD expert panel.

Azitromicina in FC e DCP

- proprietà batteriostatiche
- effetto antiinfiammatorio
- immunomodulatorio
- protegge contro la crescita del biofilm (Pseudomonas a.)

- in FC: significativo miglioramento funzionale (FEV1) e riduzione delle esacerbazioni polmonari (1)

- risultati simili in adulti con bronchiectasie non-FC (2)

- 90 pz DCP: azitromicina 3 vv/settimana vs placebo (6 mesi)
Azitromicina ben tollerata ed efficace : dimezzata la frequenza delle riesacerbazioni, ridotto il riscontro di batteri (3)

(1)Southern K.W., Barker P.M., Solis-Moya A., Patel L. ***Macrolide antibiotics for cystic fibrosis***. *Cochrane Database Syst. Rev.* 2012;11:Cd002203. doi: 10.1002/14651858.CD002203
(2) Wong C., Jayaram L., Karalus N., Eaton T., Tong C., Hockey H., Milne D., Fergusson W., Tuffery C., Sexton P., et al. ***Azithromycin for prevention of exacerbations in non-cystic fibrosis br***
(3) Kobbernagel H.E., Buchvald F.F., Haarman E.G., Casaulta C., Collins S.A., Hogg C., Kuehni C.E., Lucas J.S., Moser C.E., Quittner A.L., et al. ***Efficacy and safety of azithromycin maintenan***

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respiratorie infantili

Grazie!

Domande?