Simposio SIGG-SIF
FARMACI CON AZIONE ANTICOLINERGICA
E DETERIORAMENTO COGNITIVO

Patologie pneumologiche nella persona affetta da decadimento cognitivo: quali problemi di trattamento

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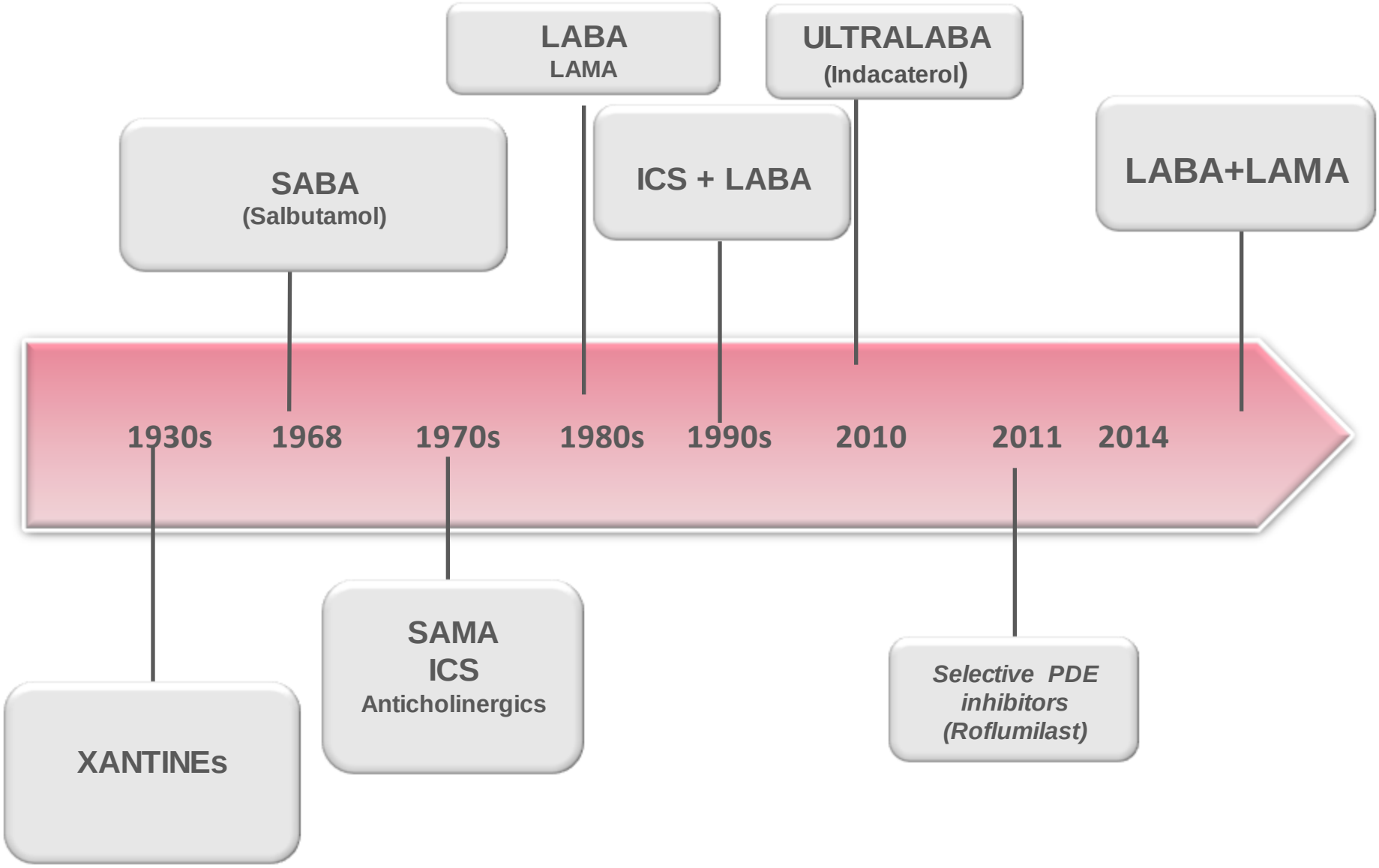
Istituto Clinico Città di Brescia

APPROPRIATEZZA SEC. BEERS
FARMACI DUPLICATI
DOSAGGIO
CARICO ANTICOLINERGICO
RISCHIO DI REAZIONI AVVERSE
INTERAZIONI
• ANTICOLINERGICI (SAMA, LAMA)
• BETA2 STIMOLANTI (SABA, LABA)
• CORTICOSTEROIDI
• TEOFILLINA

Pharmacotherapeutic options for COPD



Z. Diamant et al., New and existing pharmacotherapeutic options for persistent asthma and COPD, Nether J Med 2011

Available and Emerging Bronchodilators for COPD

Agents

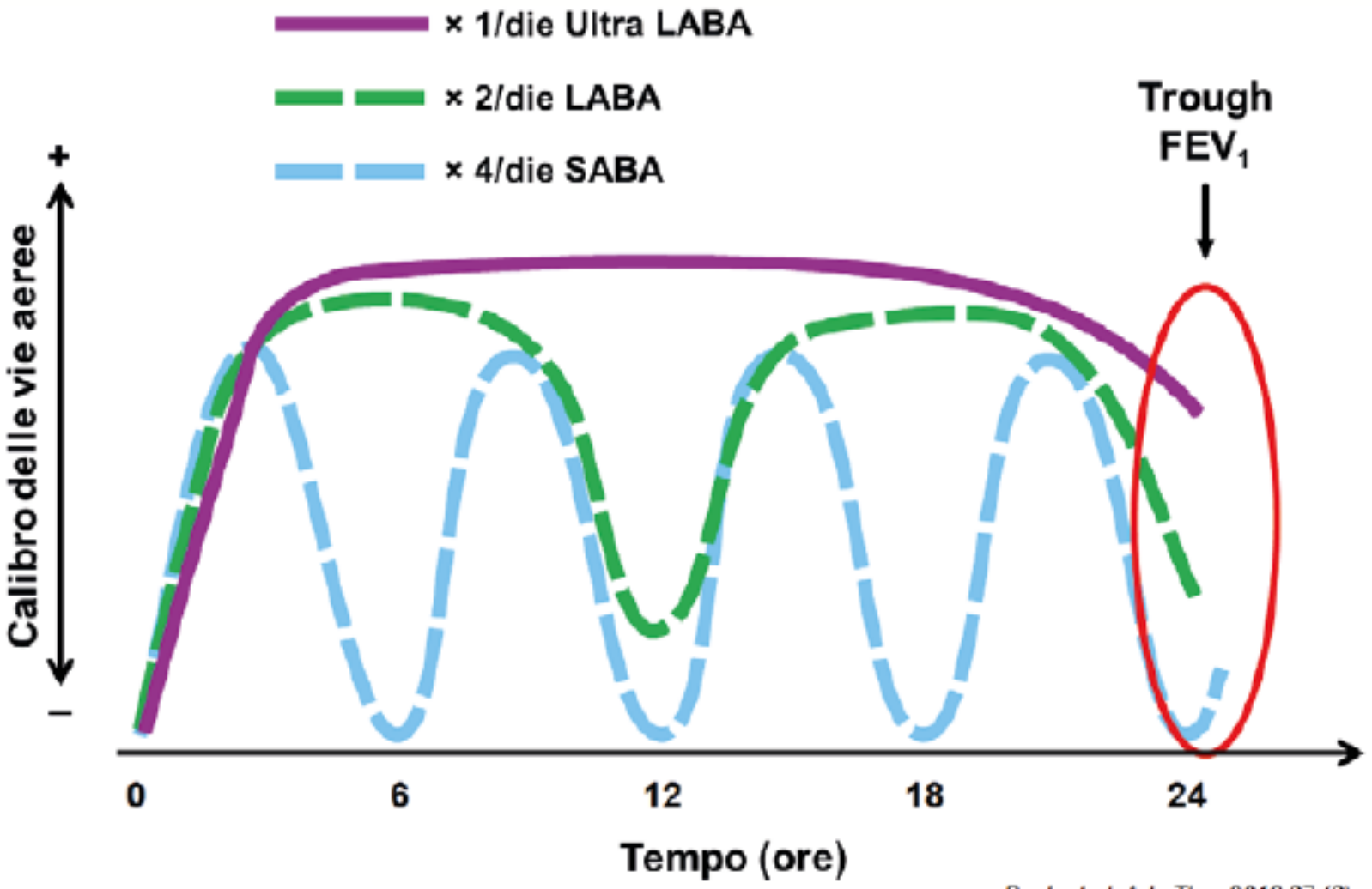
- LABAs (twice daily)
  - Formoterol
  - Salmeterol
- LAMAs (twice daily)
  - Aclidinium
- LABAs (once daily)
  - Indacaterol
  - Olodaterol*
  - Vilanterol*
- LAMAs (once daily)
  - Glycopyrronium
  - Tiotropium
  - Umeclidinium*

LABA/LAMA Combinations

- Once daily
  - Indacaterol/glycopyrronium (QVA149)*
  - Vilanterol/umeclidinium*
  - Olodaterol/tiotropium*
- Twice daily
  - Formoterol/aclidinium*
  - Formoterol/glycopyrrolate*

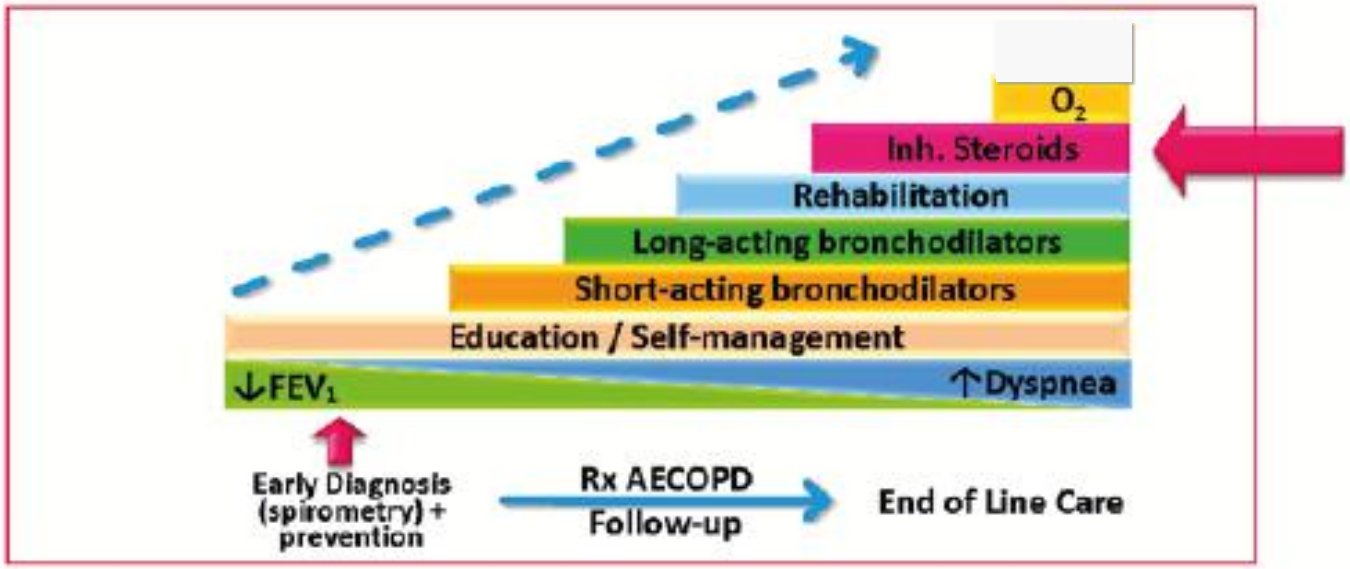
*Denotes under investigation in COPD in Europe

Effetto della broncodilatazione persistente: "stenting farmacologico"

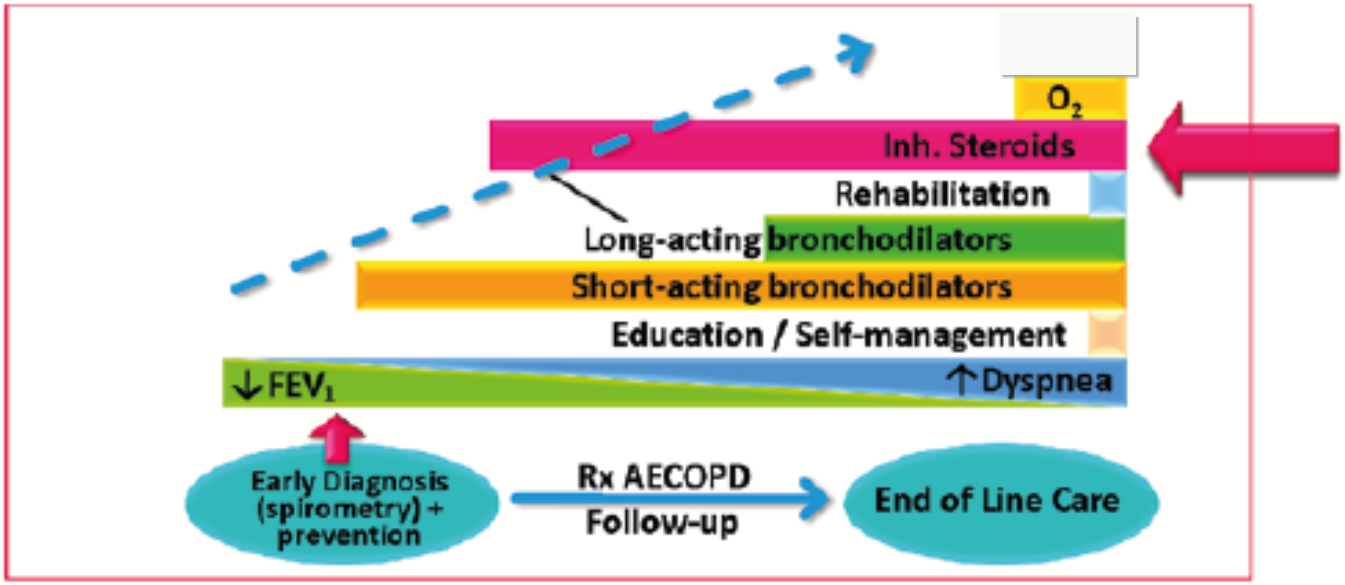


Beeh et al. Adv Ther 2010 27 (3)

A. Gestione della BPCO (Ideale)



B. Gestione della BPCO (Situazione attuale)



RESEARCH

Chronic Obstructive Pulmonary Disease: Prevalence, Characteristics, and Pharmacologic Treatment in Nursing Home Residents with Cognitive Impairment

Barbara J. Zarowitz, PharmD, CGP, FCCP, BCPS, FASCP, and Terrence O'Shea, PharmD, CGP

J Manag Care Pharm. 2012;18(8):598-606

22% of NH residents with COPD experienced at least 2 exacerbations of COPD /last year.

Over 55% were hospitalized at least once / last year

Nebulization is a common route of administration for respiratory medications

17% of patients with COPD received no medications

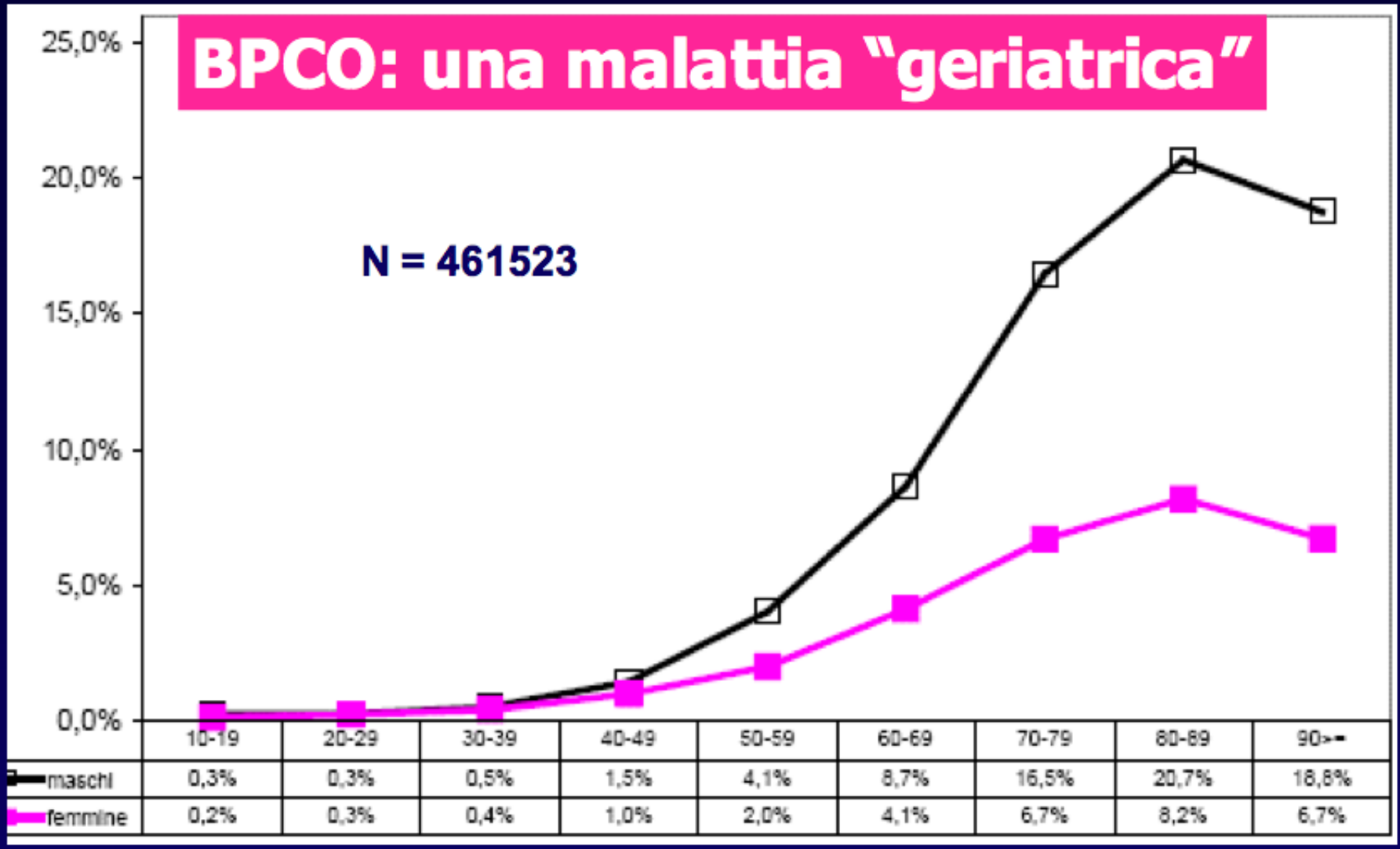
40% of residents with moderate to very severe cognitive impairment received SABA monotherapy

34-40% of patients with moderate to very severe cognitive impairment treated with SABA monotherapy exhibited SOB

Shortness of breath and exacerbations are common in NH and may be related to use of SABA in the absence of LABA or LAMA

J Manag Care Pharm. 2012;18(8):598-606

Prevalenza di BPCO in Italia, per sesso ed età



	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90>=
maschi	0,3%	0,3%	0,5%	1,5%	4,1%	8,7%	16,5%	20,7%	18,8%
femmine	0,2%	0,3%	0,4%	1,0%	2,0%	4,1%	6,7%	8,2%	6,7%

Melotti R, 2005. *HS Report 2002*

Journal of the
AMERICAN GERIATRICS SOCIETY

CRITERI DI BEERS VERSIONE 2012 - JAGS

Farmaci di uso potenzialmente inappropriato nell'anziano considerando la diagnosi

- Ritenzione urinaria: anticolinergici
- Stipsi: anticolinergici
- Glaucoma: ipratropio
- Disturbi cognitivi: anticolinergici (escluso SAMA e LAMA)
- Insonnia: teofillina
- Aritmie: teofillina

STARTing and STOPPing Medications in the Elderly

Drug or Drug Class	Potentially inappropriate use in elderly (i.e., 65 years and older) per STOPP[8]	Clinical concern[8]	Therapeutic alternative
Ipratropium, nebulized	• With narrow angle glaucoma	• Worsening glaucoma	• Use metered-dose inhaler and avoid getting drug in eyes
Theophylline	• Monotherapy for COPD	• Safer, more effective medications available	• For COPD: Inhaled corticosteroid and/or bronchodilator[6]

Anticholinergic Cognitive Burden List (ACB)

Developed by the Aging Brain Program at the IU Center for Aging Research
June 27, 2012

Drugs with ACB Score of 1

Generic Name	Brand Name
Alverine	Spasmonal™
Alprazolam	Xanax™
Atenolol	Tenormin™
Bupropion	Wellbutrin™, Zyban™
Captopril	Capoten™
Chlorthalidone	Diuril™, Hygroton™
Cimetidine	Tagamet™
Clorazepate	Tranxene™
Codeine	Contin™
Colchicine	Colcrys™
Diazepam	Valium™
Digoxin	Lanoxin™
Dipyridamole	Persantine™
Disopyramide	Norpace™
Fentanyl	Duragesic™, Actiq™
Furosemide	Lasix™
Fluvoxamine	Luvox™
Haloperidol	Haldol™
Hydralazine	Apresoline™
Hydrocortisone	Cortef™, Cortaid™
Isosorbide	Isordil™, Ismo™
Loperamide	Imodium™, others
Metoprolol	Lopressor™, Toprol™
Morphine	MS Contin™, Avinza™
Nifedipine	ardia™, Adalat™
Prednisone	eltasone™, Sterapred™
Quinidine	Quinaglute™
Ranitidine	Zantac™
Risperidone	Risperdal™
Theophylline	heodur™, Uniphyl™
Trazodone	Desyrel™
Triamterene	Dyrenium™
Warfarin	Coumadin™

Drugs with ACB Score of 2

Generic Name	Brand Name
Amantadine	Symmetrel™
Belladonna	Multiple
Carbamazepine	Tegretol™
Cyclobenzaprine	Flexeril™
Cyproheptadine	Periactin™
Loxapine	Loxitane™
Meperidine	Demerol™
Methotrimeprazine	Levoprome™
Molindone	Moban™
Oxcarbazepine	Trileptal™
Pimozide	Orap™

Scoring directions:

- Possible anticholinergics include those listed with a score of 1 in the column to the left
- Definite anticholinergics include those listed with a score of either 2 or 3 in the columns above and to the right

Scoring interpretation:

- Each definite anticholinergic may increase the risk of cognitive impairment by 46% over 6 years.[3]
- For each one point increase in the ACB total score, a decline in MMSE of 0.33 points over 2 years has been suggested.[4]
- Additionally, each one point increase in the ACB total score has been correlated with a 26% increase in the risk of death.[4]

COMPLETE REFERENCES:

1. Boustani MA, Campbell NL, Munger S, Maidment I, Fox GC. Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health*. 2008;4(3):311-20.
2. Campbell N, Boustani M, Limbil T, Ott C, et al. The cognitive impact of anticholinergics: a clinical review. *Clinical Interventions in Aging*. 2009;4(1):225-33.
3. Campbell N, Boustani M, Lane K, Gao S, Hendrie H, Khan B, Murrell J, Unverzagt F, Hake A, Smith-Gamble V, Hall K. Use of anticholinergics and the risk of cognitive impairment in an African-American population. *Neurology* 2010;75:152-159.
4. Fox C, Richardson K, Maidment, et al. Anticholinergic medication use and cognitive impairment in the older population: the Medical Research Council Cognitive Function and Ageing Study. *J Am Geriatr Soc* 2011; epub ahead of print.

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acb@agingbraincare.org

Drugs with ACB Score of 3

Generic Name	Brand Name
Amitriptyline	Elavil™
Amoxapine	Asendin™
Atropine	Sal-Tropine™
Benztropine	Cogentin™
Brompheniramine	Dimetapp™
Carbinoxamine	Histex™, Carbihist™
Chlorpheniramine	Chlor-Trimeton™
Chlorpromazine	Thorazine™
Clemastine	Tavist™
Clomipramine	Anafranil™
Clozapine	Clozaril™
Darifenacin	Enablex™
Desipramine	Norpramin™
Dicyclomine	Bentyl™
Dimenhydrinate	Dramamine™, others
Diphenhydramine	Benadryl™, others
Doxepin	Sinequan™
Flavoxate	Urispas™
Hydroxyzine	Atarax™, Vistaril™
Hyoscyamine	Anaspaz™, Levsin™
Imipramine	Tofranil™
Meclizine	Antivert™
Methocarbamol	Robaxin™
Nortriptyline	Pamelor™
Olanzapine	Zyprexa™
Orphenadrine	Norflex™
Oxybutynin	Ditropan™
Paroxetine	Paxil™
Perphenazine	Trilafon™
Promethazine	Phenergan™
Propantheline	Pro-Banthine™
Quetiapine	Seroquel™
Scopolamine	Transderm Scop™
Thioridazine	Mellaril™
Tolterodine	Detrol™
Trifluoperazine	Stelazine™
Trihexyphenidyl	Artane™
Trimipramine	Surmontil™

Farmaci inalati vengono considerati “topici”, ma:

- Frazione di dose inalata di formoterolo che viene deglutita varia 60-90%. Almeno 65% della dose deglutita è assorbita. Eliminato per via renale. Non ci sono dati disponibili sull’uso di formoterolo nei pazienti con GFR ridotta.
- Tiotropio ha un assorbimento sistemico e viene eliminato per via renale. Nei pazienti con insufficienza renale da moderata a grave deve essere utilizzato solo se i benefici attesi superano i potenziali rischi.

LESS IS MORE

Inhaled Anticholinergic Drug Therapy and the Risk of Acute Urinary Retention in Chronic Obstructive Pulmonary Disease

A Population-Based Study

Anne Stephenson, MD, PhD; Dallas Seitz, MD; Chaim M. Bell, MD, PhD; Andrea Gruneir, PhD; Andrea S. Gershon, MD, MSc; Pe… Paula A. Rochon, MD, MPH; Sud…

Background: Inhaled anticholin… are widely used treatments for … monary disease (COPD). The s… effects of IAC therapy have no… ied. This study sought to determ… nary retention (AUR) in seniors…

Methods: A nested case-control… COPD aged 66 years or older w… 1, 2003, to March 31, 2009, using… databases from Ontario, Canada. A hospitalization, same-day surgery, or emergency department visit for AUR identified cases, which were matched with up to 5 controls. Exposure to IACs was determined using a comprehensive drug benefits database. Conditional logistic regression analysis was conducted to determine the association between IAC use and AUR.

Conclusions: Use of short- and long-acting IACs is associated with an increased risk of AUR in men with COPD. Men receiving concurrent treatment with both short- and long-acting IACs and those with evidence of benign prostatic hyperplasia are at highest risk.

Arch Intern Med. 2011;171(10):914-920

- Anticolinergici, specie nebulizzati e in soggetti con IPB, aumenta 40% rischio di ritenzione urinaria acuta
- Effetto maggiore all' dose dipendente
- No differenza tra ipratropio e tiotropio

Anticholinergic Medication Use and Cognitive Impairment in the Older Population: The Medical Research Council Cognitive Function and Ageing Study

Chris Fox, MD,[a] Kathryn Richardson,* MSc,[b] Ian D. Maidment, MA,[cd] George M. Savva, PhD,[e] Fiona E. Matthews, PhD,[f] David Smithard, MD,[gh] Simon Coulton, MSc,[d] Cornelius Katona, MD,[i] Malaz A. Boustani, MD, MPH,[jklm] and Carol Brayne, MD[be]*

OBJECTIVES: To determi
tions with possible and def
creases the risk of cognitiv
older people and whether r
DESIGN: A 2-year longi
enrolled in the Medical Re
tion and Ageing Study betv
SETTING: Community-dv
participants.
PARTICIPANTS: Thirteen
aged 65 and older.
MEASUREMENTS: Basel
anticholinergics determine
cholinergic Cognitive Burden Scale and cognition determined using the Mini-Mental State Examination (MMSE). The main outcome measure was decline in the MMSE score at 2 years.
RESULTS: At baseline, 47% of the population used a medication with possible anticholinergic properties, and

nergic properties.
level, social class,
ions, number of
ve performance at
te anticholinergic
greater decline in
(CI) = 0.03–0.64,
whereas the use of
ot associated with
11, $P = .79$). Two-
taking definite
001) and possible
1) anticholinergics.
CONCLUSION: The use of medications with anticholinergic activity increases the cumulative risk of cognitive impairment and mortality. J Am Geriatr Soc 59:1477–1483, 2011.

Key words: anticholinergic activity; cognitive impairment; elderly

Possible anticholinergic properties (ACB score 1) most frequently reported: furosemide, atenolol, nifedipine

Moderate activity (ACB 2): carbamazepine

Severe activity (ACB 3): amitriptyline

EXTRA
Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2011;1:43–50
DOI: 10.1159/000322883
Published online: January 19, 2011
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www.karger.com/dee

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Original Research Article

Anticholinergic Drugs and Their Effects on Delirium and Mortality in the Elderly

M.J. Luukkanen[a, c] J. Uusvaara[a] J.V. Laurila[b] T.E. Strandberg[d]
M.M. Raivio[a, e] R.S. Tilvis[b] K.H. Pitkälä[a]

Abstract

Aim: To investigate the use of drugs with anticholinergic properties (DAPs) and their associations with delirium and mortality among elderly patients with comorbidities. ***Methods:*** 425 patients (≥70 years of age) in geriatric wards and nursing homes were assessed. The use of DAPs was retrieved from their medical records. Delirium was diagnosed according to the DSM-IV criteria. ***Results:*** Of the 341 patients (80.2%) treated with multiple DAPs (≥2), 92 patients (27.0%) suffered from delirium, whereas 14 of 84 patients (16.7%) without DAP treatment had delirium ($p = 0.050$). In a logistic regression analysis with age, gender, and Charlson Comorbidity Index as covariates, DAP treatment did not predict delirium (odds ratio 1.67, 95% confidence interval 0.87–3.21). The 2-year mortality was 49.3% (n = 168) in DAP users and 35.7% (n = 30) in non-users, respectively ($p = 0.026$). In the Cox proportional hazard model adjusted for age, gender, and comorbidity, DAPs did not predict mortality (hazard ratio 1.12, 95% confidence interval 0.75–1.68). ***Conclusion:*** The use of DAPs is very frequent among frail inpatients with comorbidities, but their use has no independent prognostic significance.

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Combination of Inhaled Corticosteroid and Bronchodilator-Induced Delirium in an Elderly Patient With Lung Disease.

Moss JM, Kemp DW, Brown JN. J Pharm Pract. 2013

Steroid psychosis has been well described with oral glucocorticoids, however, our search of the literature did not identify an association between delirium and the combination of inhaled glucocorticoids and long-acting beta-agonists.

The onset of delirium was likely due to the systemic absorption of the glucocorticoid from lung deposition, complicated in an individual with several predisposing risk factors for delirium.

ADVERSE EFFECT INHALED ANTICHOLINERGIC DRUG

Antimuscarinic effects:

- common (≥1%): dry mouth and/or throat irritation
- Rarely (<0.1%): urinary retention, constipation, acute angle closure glaucoma, palpitations (notably SVT and AF), rash, angioedema, anaphylaxis)

ADVERSE EFFECT INHALED ANTICHOLINERGIC DRUG

Tiotropium and ipratropium are linked to increased risk of heart attacks, stroke and cardiovascolare death.

The FDA requested turther trials; these are now compete,and adequately resolve the previous safety concerns.

Tiotropium is inhaler has been found to be associated with an increase of all cause mortality in people with COPD.

CHEST

Original Research

COPD

The Impact of Tiotropium on Mortality and Exacerbations When Added to Inhaled Corticosteroids and Long-Acting β-Agonist Therapy in COPD

Philip M. Short, MBChB; Peter A. Williamson, MBChB; Douglas H. J. Elder, MBChB; Samuel I. W. Lipworth, BSc; Stuart Schembri, MD; and Brian J. Lipworth, MD

Background: **Tiotropium has been shown to improve lung function, quality of life, and exacerbations and reduce mortality when compared with placebo in COPD. It remains unclear whether benefits are seen when tiotropium is used in conjunction with inhaled corticosteroids (ICSs) plus long-acting β-agonists (LABAs).**

Methods: **We performed a retrospective cohort study using a National Health Service database of patients with COPD in Tayside, Scotland, between 2001 and 2010 that is linked with databases regarding hospital admissions, pharmacy prescriptions, and death registries. The impact of the addition of tiotropium (Tio) to ICS + LABA therapy on all-cause mortality, hospital admissions for respiratory disease, and emergency oral corticosteroid bursts was evaluated. Adjusted hazard ratios (HRs) were calculated by Cox regression after inclusion of the following covariates: cardiovascular and respiratory disease, diabetes, smoking, age, sex, and deprivation index.**

Results: **A total of 1,857 patients were given ICS + LABA + Tio, and 996 were given ICS + LABA. Mean follow-up was 4.65 years. The adjusted HR for all-cause mortality for ICS + LABA + Tio vs ICS + LABA was 0.65 (95% CI, 0.57-0.75; $P < .001$). Adjusted HRs for hospital admissions and oral corticosteroid bursts were 0.85 (95% CI, 0.73-0.99; $P = .04$) and 0.71 (95% CI, 0.63-0.80; $P < .001$), respectively.**

Conclusions: **The study suggests that the addition of tiotropium to ICSs and LABA therapy may confer benefits in reducing all-cause mortality, hospital admissions, and oral corticosteroid bursts in patients with COPD. Triple therapy is widely used in the real-life management of COPD, with only limited scientific support. The study supports the use of triple therapy in COPD and provides a platform for randomized controlled trials specifically addressing this topic.**

CHEST 2012; 141(1):81–86

Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; HR = hazard ratio; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LAMA = long-acting antimuscarinic; NHS = National Health Service; TARDIS = National Health Service Tayside Respiratory Disease Information System; Tio = tiotropium UPLIFT = Understanding Potential Long-term Impacts on Function with Tiotropium

ADVERSE EFFECT INHALED BETA2 AGONIST DRUG

Apart from the occasional episode of tachycardia and tremor, both SABAs and LABAs are well tolerated.

It has also been suggested that tolerance/ tachyphylaxis would render LABAs less efficacious over time. Data from TORCH has refuted this by demonstrating that the bronchodilator effect of LABA therapy is maintained at 3 years.

Inappropriate ICS Use in Clinical Practice

- **Inappropriately prescribed in 15%-20% of patients[a,b]**
- **Most frequently overprescribed for mild to moderate disease, often guided by exacerbations[b]**
- **Overprescription in COPD increases risk for adverse events → lower self-reported health status, increased risk for poor patient adherence[b,c]**
- **Failure to use medications according to established guidelines increases the burden of COPD[d]**

a. Corrado A, et al. *Respir Med*. 2012;106(7):989-997.
b. de Miguel-Diez J, et al. *Lung*. 2011;189(3):199-206.
c. Fletcher MJ, et al. *BMC Public Health*. 2011;11:612.
d. Miravitlles M, et al. *Respir Med*. 1999;93(3):173-179.

INHALED GLUCORTICOIDS SIDE EFFECTS

EFFECTS OF LOCAL DEPOSITION

-Dysphnia

-Topical candidiasis

SYSTEMIC SIDE EFFECTS

-Osteoporosis

-Adrenal suppression

-Intraocular pressure: no reports of glaucoma associated with prolonged continuous use of lower dosages of inhaled steroides. If the cumulative dose of sterroids is in excess of 1500microg beclomethasone/die (or equivalent), consider monitoring introcular pressure

-Psychiatric effects **(psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression)**

-Effects on glucose and lipid metabolism

-Infection

Side Effects of ICS

- Increased risk for pneumonia seen in studies with fluticasone/salmeterol[a-c]
- 2-year probability of pneumonia reported as an adverse event: 8% for fluticasone/salmeterol vs 4% for tiotropium group (P = .008)[b]
- Increased incidence of pneumonia did not translate into overall worsening in health status or mortality[a,b]
- Risk for fracture and diabetes also reported[d,e]

a. Calverley PM, et al. *N Engl J Med*. 2007;356(8):775-789.
b. Wedzicha JA, et al. *Am J Respir Crit Care Med*. 2008;177(1):19-26.
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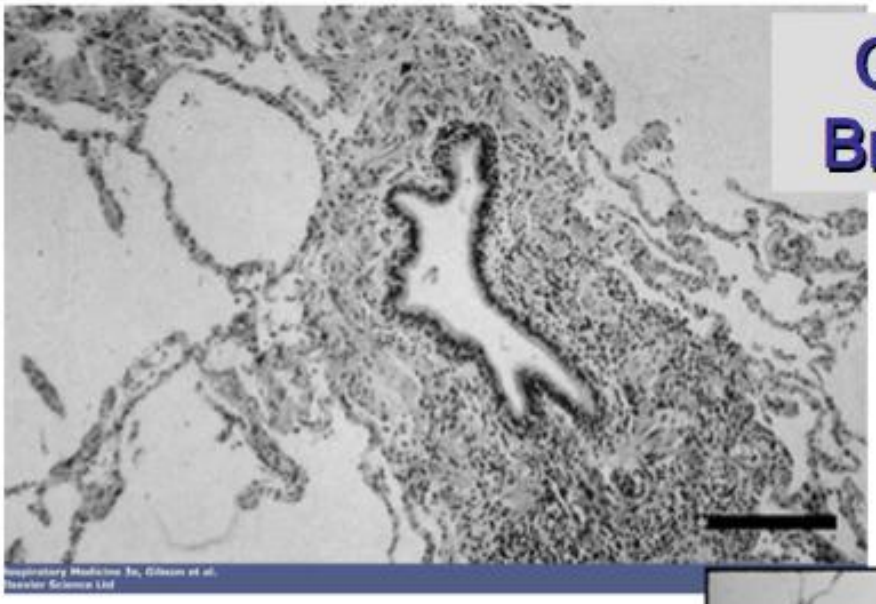
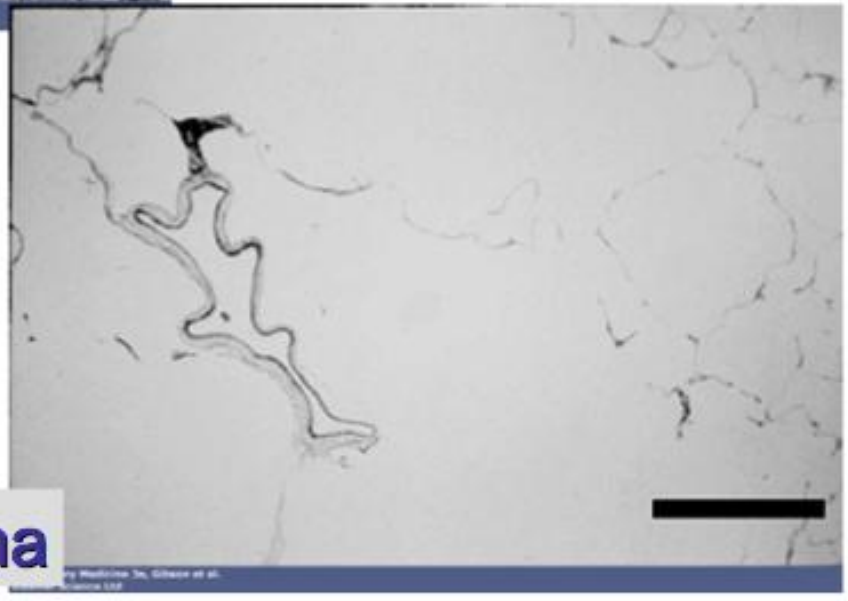
d. Suissa S, et al. *Am J Med*. 2010;123(11):1001-1006.
e. Loke YK, et al. *Thorax*. 2011;66(8):699-708.



Chronic Bronchitis

Emphysema



Eur Respir J 2010; 35: 913–922
DOI: 10.1183/09031936.00125109
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REVIEW

Cognitive function in COPD

J.W. Dodd, S.V. Getov and P.W. Jones

- 30-70%
- There may be a pattern of cognitive dysfunction (CD) specific to COPD (executive memory, motor functions) (If MMSE < 24 and 1/5 IADL lost: Mental Deterioration Battery; *Antonelli-Incalzi 2007*)
- Cognitive function is only mildly impaired in patients without hypoxaemia
- CD has been reported to worsen over time
- Hypoxaemia, hypercapnia, smoking and comorbidities (such as vascular disease) are unlikely to account for all of the CD
- CD may be associated with increased mortality and disability
- There is limited evidence for a significant effect of treatment on CD

REVIEW

Cognitive dysfunction in patients with chronic obstructive pulmonary disease – A systematic review

Lone Schou [a,*], Birte Østergaard [b], Lars S. Rasmussen [c], Susan Rydahl-Hansen [d], Klaus Phanareth [a]

Respiratory Medicine (2012) 106, 1071–1081

Significant relationship between the severity of COPD and cognitive dysfunction only in patients with severe to very severe COPD.

Level of functioning appears to be better than in patients with Alzheimer's disease.

Hypoxia can worsen confusion and pulmonary medications (e.g., theophyline, steroids, and sympathomimetic agents) may worsen behavioral symptoms.

International Journal of Chronic Obstructive Pulmonary Disease

open access to scientific

Open Access Full Text Article

ORIGINAL

COPD and cognitive impairment: the role of hypoxemia and oxygen therapy

Neeta Thakur, et al.

COPD was associated with a substantive risk of cognitive impairment compared (OR 2.4; 95%[CI] 1.04–6.64).
No COPD severity measures were associated with the risk of cognitive impairment (CI).

Low baseline oxygen saturation (<88%) was related to increased risk of CI (OR 5.5; 95% CI 1.01–29.2; P=.048).

Regular use of oxygen therapy decreased the risk for CI (OR 0.14; 95% CI 0.07–0.27; P=.0001).

Among patients with COPD regular use of home oxygen is protective.

International Journal of Chronic Obstructive Pulmonary Disease 2010:5 263–9

SPIROMETRY (before and after bronchodilation)

- Age-related decline in the **FEV1/FVC** ratio
- **40%** of COPD patients over 65y are not able to properly perform spirometry (fatigue, lack of coordination, cognitive impairment)
- In elderly individuals classified as COPD by using a pure spirometric criterion, the diagnosis should be confirmed only when **symptoms and/or risk factors for COPD** are present
- **FEV6** showed good accuracy in classifying patients and predicting prognosis (but a diagnosis of COPD cannot be ascertained in about 20% of patients, in whom it remains eminently clinical)

(Pistelli, 2011)

FEV6 NOT UNIVERSAL SOLUTION *(Bellia, Thorax 2008)*

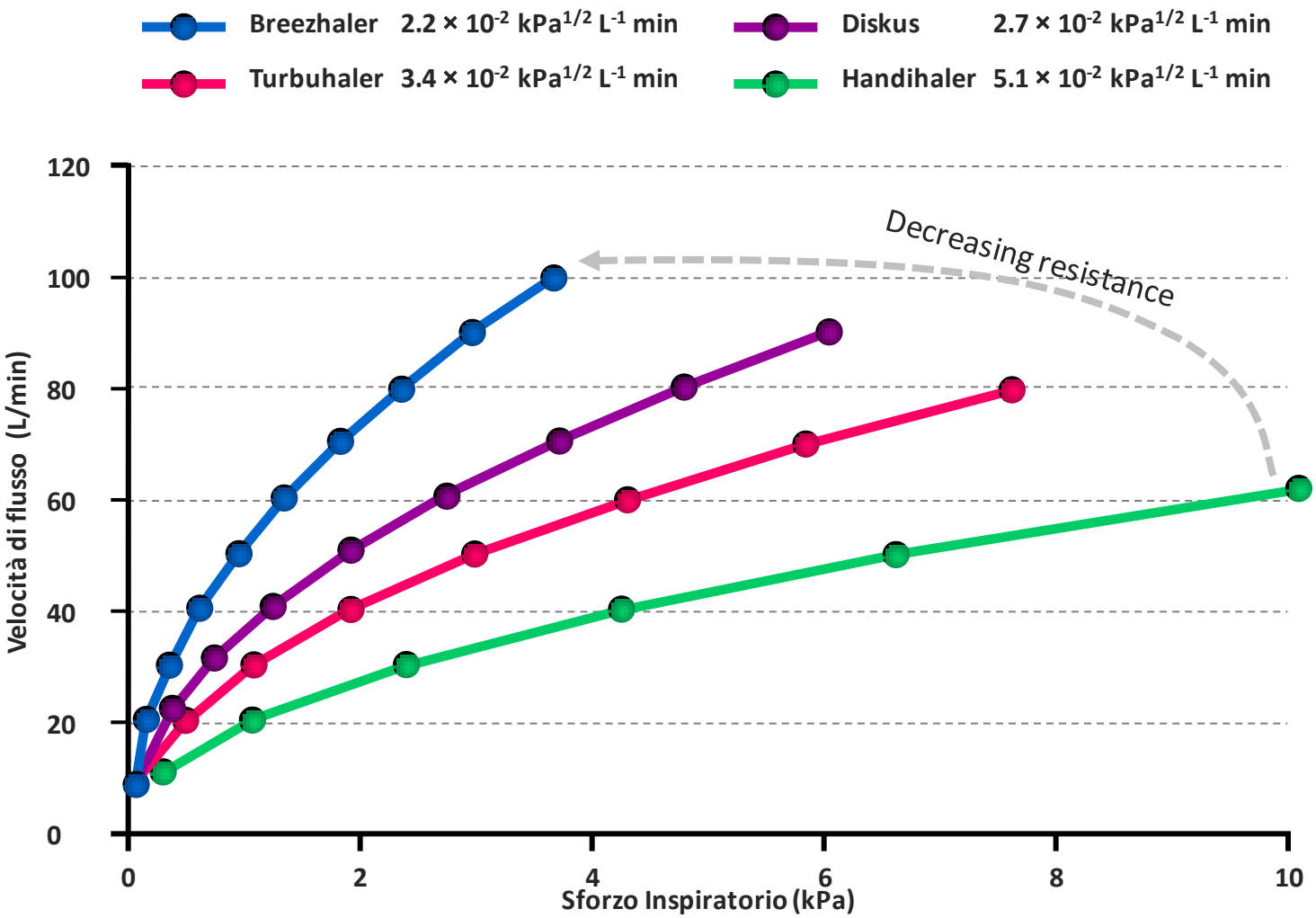
Table 3 Factors negatively influencing achievement of valid FEV_6 measurement: multivariable logistic analysis on 1531 subjects with a satisfactory start-of-test criterion

	Odds ratio	p Value	95% confidence interval
Older age (every 5 years)	1.42	<0.001	1.25 to 1.59
Female sex	1.58	0.022	1.08 to 2.31
Lower education*	1.77	0.001	1.25 to 2.51
Depression†	1.54	0.045	1.12 to 2.13
Cognitive impairment‡	1.61	0.009	1.09 to 2.37
Spirometric restriction§	1.98	<0.001	1.37 to 2.86

PRINCIPALI DEVICE - CARATTERISTICHE

CLASSE FARMACETICA	NOME DEVICE	NOME FARMACO	PRINCIPIO ATTIVO	PREZZO	AZIENDA	STEP PER INALARE	PRE CARICATO	PRE DOSATO	FACILE ALL'USO	CONTA DOSI	FEEDBACK AL PAZIENTE	SICUREZZA OVERDOSE	BLOCCO FINALE
LAMA	GENUIAR	EKLIRA / BRETARIS	ACLIDINIO	€ 45,85	ALMIRALL / G.MENARINI	2	SI	SI	SI	SI	SI	SI	SI
	BREEZHALER	SEEBRI	GLICOPIRRONIO	€ 48,26	NOVARTIS	8	NO	NO	SI	NO	NO	CPS	CPS
	HANDIHALER	SPIRIVA	TIOTROPIO	€ 50,80	PFIZER-BOERIGHER	8	NO	NO	SI	NO	NO	CPS	CPS
	RESPIMAT					9	NO	SI	NO	NO	NO	?	?
LABA	BREEZHALER	ONBREZ / HIROBRIZ	INDACATEROLO	€ 35,75	NOVARTIS / CHIESI	8	NO	NO	SI	NO	NO	CPS	CPS
ICS LABA	DISKUS	SERETIDE / ALIFLUS	SALMETEROLO+ FLUTICASONE	€ 75,59	GLAXO / MENARINI	4	SI	SI	SI	SI	NO	NO	NO
	TURBOHALER	SIMBYCORT	FORMOTEROLO+ BUDESONIDE	€ 65,70	ASTRAZENECA	2	SI	SI	NO	NO	NO	NO	NO

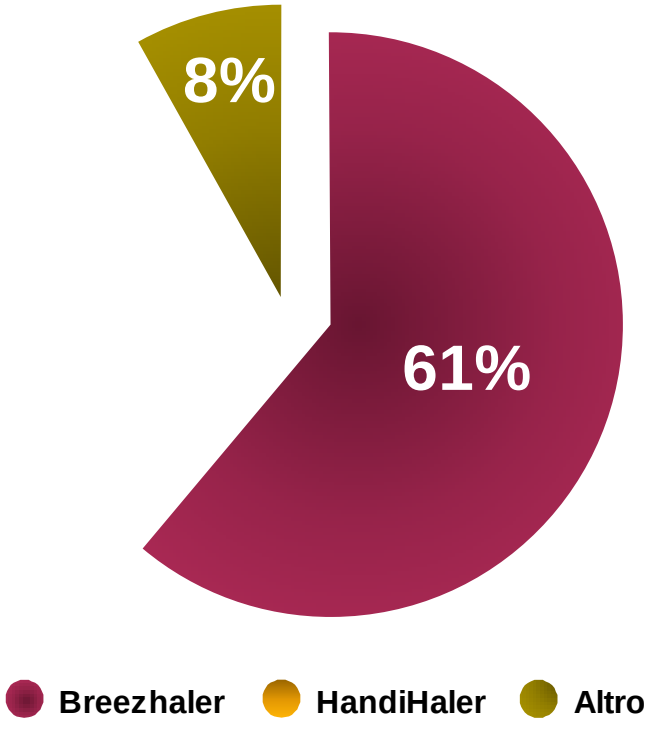
Inalatore esercita una minore resistenza al flusso rispetto ad altri dispositivi



Singh D et al. ATS 2010

2/3 dei pazienti preferiscono Breezhaler®

Breezhaler® preferito dai pazienti rispetto a HandiHaler ®: 61% vs 31%



Breezhaler® preferito in termini di:

- Facilità d'apertura/chiusura
- Comodità d'inalazione
- Maneggevolezza
- Controllo dell'inalazione
- Sicurezza nell'aver assunto il farmaco

Studio crossover, a due periodi, in aperto e della durata di 14 giorni, in 82 pazienti affetti da BPCO

Chapman KR et al. *Int J COPD* 2011; 6:353–363

SPRAY

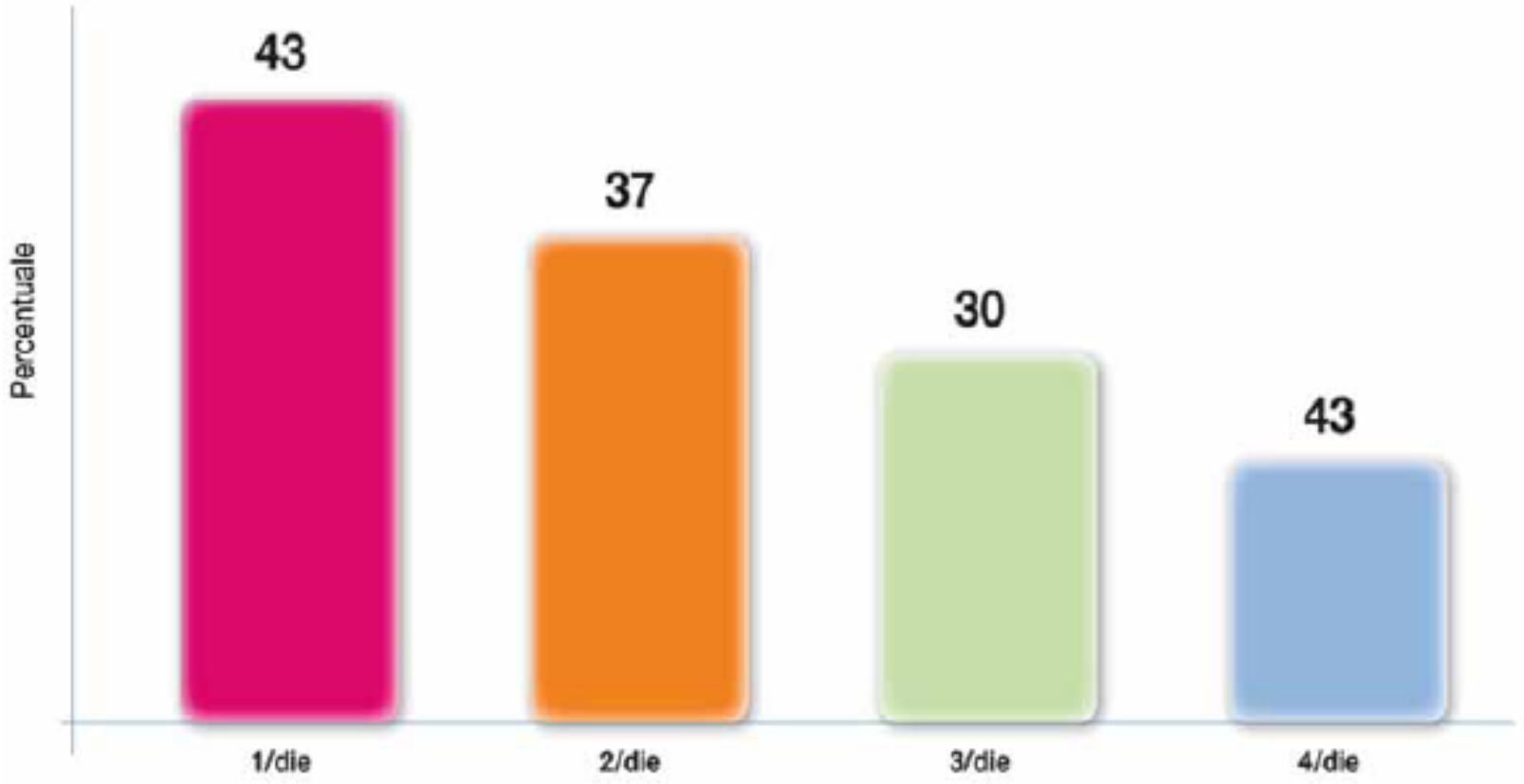
- Negli anziani poco indicati gli spray dosati perchè non sempre riescono a coordinare l'inspirazione con la pressione manuale sulla bomboletta (Allen, 2003).
- Distanziatori facilitano l'impiego degli spray dosati

  dell'

  le dimensioni delle goccioline

  dell'aerosol mentre le particelle più grosse - non respirabili - vengono trattenute all'interno del dispositivo, diminuendo la percentuale di farmaco che si deposita in orofaringe).
- Utilizzo di questi dispositivi diminuisce l'incidenza degli effetti indesiderati locali dei corticosteroidei inalati (candidosi orofaringea) e riduce la quantità di farmaco che viene deglutita ed assorbita nel tratto gastrointestinale (beclometasone a livello intestinale non viene inattivato al 1° passaggio epatico e può quindi essere responsabile di effetti sistemici).

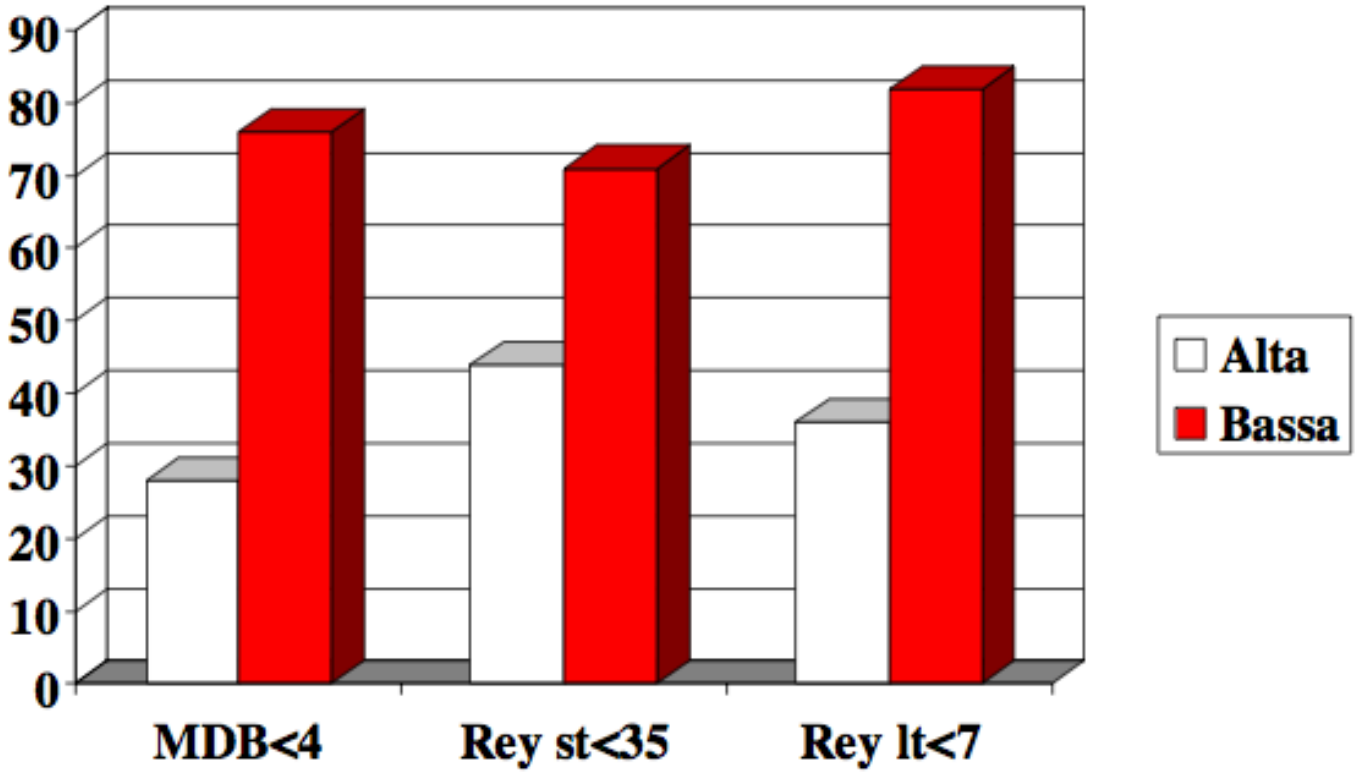
La monosomministrazione comporta un incremento della compliance e dell'assunzione del trattamento



Percentuale di giorni in terapia in funzione del numero di somministrazioni in pazienti con patologia ostruttiva cronica

Toy et al. Respir Med 2011

Cognitive impairment and adherence to therapy in COPD



*Low compliance: the patient omits to take the drug at least twice for week

Antonelli Incalzi et al, Chest 1997; 112: 1506

Review

Pneumonia in the very old

Jean-Paul Janssens and Karl-Heinz Krause

Lancet Infect Dis 2004: 4: 112–24

Not implementation of guidelines lead to an overuse of antibiotics

without proven benefit.

RESISTENZE ANTIOBIOTICI

Carbapenemi:
- Pseudomonas aeruginosa multidrug resistant
- Acinetobacter baumannii multidrug resistant

Cefalosporine 3a generazione:
- Enterobacteriaceae ESBL
- Clostridium difficile
- Staphylococcus aureus (MRSA)

Vancomicina

- Enterococchi resistenti (VRE)

Chinoloni:
- Pseudomonas aeruginosa multidrug resistant
- Clostridium difficile
- Staphylococcus aureus (MRSA)

Tabella 4 • *Sensibilità (in percentuale) di Klebsiella pneumoniae ai diversi antibiotici.*

	Media Ospedali	Media RA
Amoxicillina/clavulanico	89,6	84,6
Piperacillina/tazobactam	92,9	89,7
Cefotaxime	92,1	86,3
Ciprofloxacina	91,6	84,9
Gentamicina	95,0	95,6
Imipenem	98,8	100
Meropenem	95,9	100
Cotrimoxazolo	89,1	83,5
Fosfomicina	76,1	72,1
Nitrofurantoina	47,3	56,7

Studio Provincia di Trento 2007-2010.

Tabella 5 • *Sensibilità (in percentuale) di Proteus mirabilis ai diversi antibiotici.*

	Media Ospedali	Media RA
Ampicillina	52,7	28,3
Amoxicillina/clavulanico	86,4	80,3
Piperacillina/tazobactam	93,6	88,0
Cefotaxime	81,7	50,0
Ciprofloxacina	72,2	33,1
Gentamicina	80,6	70,7
Meropenem	100	97,3
Cotrimoxazolo	54,8	22,5
Fosfomicina	78,5	52,7

Studio Provincia di Trento 2007-2010.

Tabella 6 • *Sensibilità (in percentuale) di Staphilococcus aureus a meticillina*

	Media Ospedali	Media RA
Meticillina	71,2	41,9

Studio Provincia di Trento 2007-2010.

Original Investigation

Calcium-Channel Blocker–Clarithromycin Drug Interactions and Acute Kidney Injury

Sonja Gandhi, BSc; Jamie L. Fleet, BHSc; David G. Bailey, BScPhm, PhD; Eric McArthur, MSc; Ron Wald, MD; Faisal Rehman, MD; Amit X. Garg, MD, PhD

IMPORTANCE Calcium-channel blockers are metabolized by the cytochrome P450 3A4 (CYP3A4; EC 1.14.13.97) enzyme. Blood concentrations of these drugs may rise to harmful levels when CYP3A4 activity is inhibited. Clarithromycin is an inhibitor of CYP3A4 and azithromycin is not, which makes comparisons between these 2 macrolide antibiotics useful in assessing clinically important drug interactions.

Supplemental content at jama.com

Pneumonia in the Elderly: A Review of Severity Assessment, Prognosis, Mortality, Prevention, and Treatment

Carol P. Chong, FRACP, and Philip R. Street, FRACP

Southern Medical Journal • Volume 101, Number 11, November 2008

Predictive indices:

- PSI
- CURB-65
- ATS modified
- SOAR

Pneumonia severity index scoring system[4]

Characteristic	Points
Age	
Men	Age (yr)
Women	Age (yr-10)
Nursing home resident	10
Coexisting illness	
Neoplastic disease	30
Liver disease	20
Congestive heart failure	10
Cerebrovascular disease	10
Renal disease	10
Physical examination findings	
Altered mental status	20
Respiratory rate >30 min	20
Systolic blood pressure <90 mm Hg	20
Temperature <35 or >40°C	15
Pulse >125/min	10
Laboratory and radiographic findings	
Arterial pH <7.35	30
Blood urea nitrogen >30 mg/dL	20
Serum sodium <130 mmol/L	20
Serum glucose >250 mg/dL	10
Hematocrit <30%	10
Partial pressure of oxygen <60 mm Hg	10
Pleural effusion	10

PSI (Fine 1997)
Severity of CAP presentation.
Identify patients at low risk of mortality that can be treated at home.

Class 1-2= 0-70 home

Class 3= 71-90 home/H

Class 4-5= >91 H

Modified British Thoracic Society guidelines (CURB-65)[5]

Confusion (defined as Mental Test Score of 8 or less, or new disorientation in person, place or time)

Urea >7 mmol/L

Respiratory rate ≥30/min

Blood pressure (systolic <90 mm Hg or diastolic ≤60 mm Hg

Age ≥65 yr

CURB-65 (Lim 2003)
Predict mortality in hospitalized patients at 30d (high risk mortality)

Mortality risk:
score 0-1= low (1.5%) home
score 2= intermediate (9.2%) H
score >3= high (22%) ICU

American Thoracic Society guidelines[6]

Criteria for severe community-acquired pneumonia

Presence of 1 major or 2 minor criteria

Major

- Septic shock
- Need for ventilation

Minor

- Multilobar disease (>2 lobes)
- Systolic BP <90, diastolic BP <60
- PaO_2/FiO_2 ratio <250

ATS guidelines modified (Niederman 2001)

Predict which patients with CAP should be treted in ICU

SOAR prediction rule for elderly patients[7]

One point for each of the following:

- Systolic blood pressure <90 mm Hg
- Oxygentation (PaO2: FiO2 <250)
- Age ≥65 yr
- Respiratory rate ≥30 breaths/min

(Myint 2007)

END-OF-LIFE PNEUMONIA

(in severely demented patients, in terminally ill patients, and in dying patients)

- Pneumonia in older individuals without terminal disease has to be distinguished from EOLP.
- Death from pneumonia is associated with severe suffering.
- Rate of discomfort is higher in patients dying from pneumonia than in patients dying from other causes.
- Severity of dementia critically establishes the outcome of pneumonia.
- Survival is probably not prolonged by antibiotic treatment of EOLP.

END-OF-LIFE PNEUMONIA

(in severely demented patients, in terminally ill patients, and in dying patients)

- Attributable mortality of pneumonia is low and antibiotics have little effect on life expectancy and should be used only if they provide the best means to alleviate suffering.

- Presently we do not know whether antibiotics are superior to symptomatic treatment alone for the relief of this suffering.

END-OF-LIFE PNEUMONIA

(in severely demented patients, in terminally ill patients, and in dying patients)

Specific symptoms and concerns that may arise in the comfort care of end-of-life pneumonia include:

1. Dyspnea (shortness of breath; air hunger)
2. Respiratory congestion
3. Agitated delirium
4. Pain (eg. pleuritic pain, discomfort from immobility, or pain due to pre-existing conditions such as arthritis or malignancy)
5. Supporting and addressing concerns of families – such as decreased intake of food/fluids, concerns about medications such as opioids, need for sedation in terminal delirium, rapid deterioration.

PNEUMONIA AND ADMISSION TO THE ICU

- Decision to admit very old patients with pneumonia to the ICU should be taken very cautiously.
- Very old patients with CAP are now commonly admitted to the ICU (and/or subjected to invasive ventilation) (CAP: 20–25% for the 80–89y, and around 15% for those aged over 90; mortality approximates 25% for the 80–89y, and is close to 30% for those aged over 90).

- Patients with pneumonia and terminal disease certainly should not be admitted.
- Patients with significant comorbidities should not be admitted since their likelihood to survive ICU treatment is low.
- In very old CAP patients without significant comorbidities, ICU admission may be considered, but only after careful consideration of all aspects (autonomy, beneficence, non-maleficence).

NIV INDICAZIONI

Le attuali indicazioni si basano sui livelli di evidenza di efficacia:

Evidenza elevata: BPCO riacutizzata
EPA cardiogeno

Evidenza medio-bassa: asma
pz immunodepresso
ARDS
polmonite
post-operatorio
post-estubazione

-Crummy F, et al: Int Med Journal 2007 (37) 112-118
-Liesching T, et al : Chest 2003 (124) 699-713

Results of noninvasive ventilation in very old patients

Schortgen F, Follin A, Piccari L, Roche-Campo F, Carteaux G, Taillandier-Heriche E, Krypciak S, Thille AW, Paillaud E, Brochard L. Ann Intensive Care 2012 21;2(1):5

•Efficacia NIV nei ultra80enni con IRA specie se correlata a “pump-failure” da riacutizzazione di BPCO, analoga ai soggetti più giovani

•NIV principale indicazione negli ultra80enni (40%) dato il loro alto rischio di sviluppare complicanze durante VMI

•Identikit sottogruppo di "ultra-anziani": "fragili", dipendenti ADL, comorbilità, in stadi molto avanzati della m.respiratoria cronica di base, spesso già in ventilo terapia domiciliare

British Thoracic Society
2002

NIV nella polmonite come alternativa alla intubazione

•CPAP migliora ossigenazione, in pazienti con polmoniti diffuse che rimangono ipossici, nonostante trattamento medico adeguato (C)

•NIV può evitare intubazione in alcuni pazienti, specialmente quelli con COPD

•IRA ipercapnica da polmonite: candidati alla intubazione se NIV fallisce, dovrebbero essere ricoverati solo in UTI, dove è possibile IOT, in tempo reale, appena necessario (C)

British Thoracic Society
2002

NIV nella polmonite come trattamento massimale

'ceiling of treatment' per pazienti che non verranno intubati

DNI deve essere presa, prima di iniziare NIV in ogni paziente. Ciò deve essere verificato da intensivisti e rimanere documentato nella cartella clinica

Pazienti dovrebbero essere ricoverati non in UTI, ma nelle U.O.Medicina / Pneumologia (D)

Necessita chiaro piano di cura alternativo nel caso di fallimento NIV (palliazione), se non si ottengono miglioramenti entro 12 ore, per evitare che una terapia non confortevole (NIV) sia continuata più del necessario

2 tipi NIV

UTI: IRA da "lung failure" o "pump failure"

"escalation therapy" (O2, NIV, VMI), personale qualificato, adeguato monitoraggio, possibilità di rapida transizione alla IOT in caso di fallimento

U.O.MEDICHE: NIV nell'"end-of-life"

setting più appropriato per la cura dei "pazienti DNI" (fuori da UTI; costi, relazione familiari)

Nulla da perdere tentare trial NIV in pazienti in cui senza un supporto ventilatorio la mortalità è vicino al 100%

Fallimento NIV richiede rapide misure di controllo dei sintomi più adeguatamente eseguibili in luoghi di cura "aperti" (ward) con supporto familiari

Lung (2012) 190:597–603
DOI 10.1007/s00408-012-9403-y

REVIEWS

Noninvasive Positive Pressure Ventilation for Acute Respiratory Failure in Delirious Patients: Understudied, Underreported, or Underappreciated? A Systematic Review and Meta-analysis

Michael Charlesworth · Mark W. Elliott · John D. Holmes

Delirium is a relative contraindication

If delirium were precipitated by respiratory failure, as is quite likely, NPPV would encourage delirium resolution

Delirium is associated with NPPV failure and the risk of this is 112 % more than that in nondelirious patients

NIV can trigger refusal of NPPV

LETTERS TO THE EDITOR

JAGS 60:1576–1598, 2012

CASE REPORTS

NONINVASIVE POSITIVE PRESSURE VENTILATION IMPROVED REFRACTORY BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA IN AN ELDERLY ADULT WITH TYPE 2 RESPIRATORY FAILURE

Use of a High-Flow Oxygen Delivery System in a Critically Ill Patient With Dementia

Tatjana P Calvano DO, Joshua M Sill MD, Kenneth R Kemp MD, and Kevin K Chung MD

[Respir Care 2008;53(12):1739–1743]

CONCLUSIONI

- BPCO:
  - Migliorare appropriatezza terapia farmacologica
  - Effetti collaterali sistemici minori (eventi CV ?)
  - Causa peggioramento performance cognitive
  - O2 terapia recupero funzioni cognitive (?)
  - Demenza= limitazione diagnostica e terapeutica

- POLMONITI:
  - Migliorare appropriatezza terapia antibiotica
  - End of life pneumonia
  - NIV

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