UNIVERSITY CLINIC OF RESPIRATORY AND ALLERGIC DISEASES GOLNIK
SLOVENIAN ASSOCIATION OF PNEUMOLOGISTS
SLOVENIAN ASSOCIATION OF ALLERGOLOGY AND CLINICAL IMMUNOLOGY

4th Slovenian Pneumology and Allergology Congress 2008

Book of abstracts

Portorož, Slovenia, September 14-16, 2008

UNIVERSITY CLINIC OF RESPIRATORY AND ALLERGIC DISEASES GOLNIK
SLOVENIAN ASSOCIATION OF PNEUMOLOGISTS
SLOVENIAN ASSOCIATION OF ALLERGOLOGY AND CLINICAL IMMUNOLOGY

4th Slovenian Pneumology and Allergology Congress 2008

Book of abstracts

Portorož, Slovenia, September 14-16, 2008

Publisher
University Clinic of Respiratory
and Allergic Diseases Golnik

Editor
Izidor Kern

Reviewer
Viktorija Tomič

Prepress
Trajanus d.o.o., Kranj

Printing
Pro Grafika d.o.o., Žabnica

Portorož, Slovenia, September 14-16, 2008

CIP - Kataložni zapis o publikaciji
Narodna in univerzitetna knjižnica, Ljubljana

616.2(063)(082)
616.24-083(063)(082)

SLOVENIAN Congress of Pneumology and Allergology (4 ; 2008 ; Portorož)
4th Slovenian Congress of Pneumology and Allergology, Portorož, September 14-16 2008 / [editor Izidor Kern]. - Golnik : University Clinic of Respiratory and Allergic Diseases, 2008

ISBN 978-961-6633-17-8
1. Kern, Izidor
240100096

bolnišnica GOLNIK
KLINIČNI ODDELEK ZA PLJUČNE BOLEZNI IN ALERGIJO

BOLNIŠNICA GOLNIK - KLINIČNI ODDELEK ZA PLJUČNE BOLEZNI IN ALERGIJO
UNIVERSITY CLINIC OF RESPIRATORY AND ALLERGIC DISEASES GOLNIK

Golnik 36, 4204 Golnik, Slovenija **T:** +386 (0)4 25 69 100 **F:** +386 (0)4 25 69 117
E: kopa.tajnistvo@klinika-golnik.si **W:** www.klinika-golnik.si

Kazalo

Astma:
kaj lahko naredimo
na primarnem nivoju

Košnik M
Bolnišnica Golnik – Klinični oddelek za pljučne bolezni in alergijo, Slovenija

Astma je kronična bolezen, ki jo ima vsaj 5% populacije. V ambulanti splošnega zdravnika z 2.000 opredeljenimi bolniki naj bi jih približno 100 imelo astmo. Astma največkrat začne že v otroški dobi. Tri četrtine bolnikov ima blago (relativno lahko vodljivo) obliko bolezni in te bolnike večinoma vodijo zdravniki splošne in družinske medicine. Cilj vodenja astme je, da bolniki z astmo živijo normalno življenje, brez omejitev pri šoli, delu, vsakodnevnih in športnih aktivnostih. **Zelo pomembno je, da bolnika z astmo pridobimo za aktivno sodelovanje pri zdravljenju »njegove bolezni«, mi smo le svetovalci.**

Zdravljenje astme sledi postavitvi diagnoze
Pomembna je anamneza (epizode kašlja in/ali dušenja, tiščanja v prsnem košu, izraziteje po telesnem naporu, v zgodnjih jutranjih urah ali ob virusnih okužbah). Potrditev diagnoze temelji na funkcijskih preiskavah. Značilnost astme je variabilna obstrukcija. **Brez spirometrije ni obravnave bolnika z astmo**. Spirometrija v času simptomov pokaže obstrukcijo (razmerje FEV1/VC < 0,7). Obstrukcija se pomembno ublaži ali največkrat celo mine v obdobju brez težav, po inhalaciji bronhodilatatorja ali po večdnevnem zdravljenju s protivnetnimi zdravili. Variabilnost obstrukcije dokazujemo:
- Bronhodilatatorni test (za astmo je diagnostična normalizacija pljučne funkcije po bronhodilatatorju!!! Pozor: negativen bronhodilatatorni test astme ne izključi)
- Variabilnost meritev PEF (Kadar je izhodna spirometrija normalna)
- Metaholinski test (Kadar je izhodna spirometrija normalna. Dela naj ga izkušen laboratorij za pljučno funkcijo, oceni naj ga pulmolog).
- Glukokortikoidni test (Kadar se po bronhodilatatorju obstrukcija ne odpravi popolnoma, bronhodilatatorni test ponovimo še po mesecu dni prejemanja inhalacijskega glukokortikoida. Specialist pri refrakterni obstrukciji naredi glukokortikoidni test s sistemskim glukokortikoidom).

V času diagnostike naj bolnik prejema le kratkodelujoči bronhodilatator ob težavah (izjema je seveda težko poslabšanje astme).

Doseči urejenost astme
Cilj zdravljena astme je doseči čimboljši nadzor nad boleznijo.
Popolnoma urejena astma pomeni, da je jutranji PEF vedno več kot 80% bolnikove najboljše vrednosti, da bolnik nima nobenih simptomov astme, da nima nočnih prebujanj, nima poslabšanj, ne potrebuje olajševalcev, nima hospitalizacij, ne čuti neželenih učinkov zdravil.
Dobro urejena astma pomeni, da uporablja olajševalce 1x do 2x tedensko, da ima zelo blage simptome astme do 2x tedensko.

Popoln nadzor je mogoče doseči v 40%, dober nadzor pa v 80%. V veliko pomoč pri doseganju in vzdrževanju urejenosti astme sta vložni list za bolnika z astmo, ki je bil objavljen v ISIS-u, številka 1/2004, ali vprašalnik ACT (ISIS 2005;14,št. 7:48-52).
Osnovni princip trajnega zdravljenja astme je nadzor nad astmatskim vnetjem z nefarmakološkimi metodami (odstranjevanjem alergenov, dražljivcev, opustitev kajenja) in z zdravili - PREPREČEVALCI – (inhalacijski glukokortikoidi (IGK) so najmočnejše protivnetno zdravilo). Bolnik naj redno prejema protivnetno zdravilo v najmanjšem odmerku, ki še zadostuje za nadzor bolezni. Zdravljenje največkrat začnemo z zmernim odmerkom inhalacijskega glukokortikoida, dvakrat dnevno (npr. budezonid 2 X 400 g). Kadar ima bolnik malo simptomov, pridružen rinitis in/ali bi raje prejemal zdravila v obliki tablet, lahko začnemo z antilevkotrienom (preprečevalec začnemo vedno v monoterapiji!). Ob pojavu simptomov se dodatno inhalira OLAJŠEVALEC (hitrodelujoči beta agonist).

Vzdrževati urejenost astme
Odmerke zdravil je potrebno prilagajati:
- Korak navzgor, če v enem mesecu ni dobre stabilnosti astme. Prej seveda preverimo pravilnost diagnoze, zavzetost in sodelovanje bolnika, ali zdravila pravilno jemlje, ali se izogiba sprožilcem simptomov. Če po enem mesecu astma ni **dobro urejena**, naj se bolnika napoti k specialistu.
- Korak navzdol, če je astma urejena. Odmerke IGK razpolavljamo vsake 3 mesece. Majhen odmerek IGK (400 g budezonida ali manj) bolnik lahko prejema 1x dnevno. Najmanjši odmerek, ki ga na primarni ravni ne ukinjamo, je 200 g budezonida.

Pomembni orodji vodenja astme sta **zdravstvena vzgoja** bolnikov in **partnersko vodenje** bolezni. Zdravstveno vzgojo bolnika večinoma izvajajo specializirane medicinske sestre. Seveda cilje za vsakega bolnika postavi zdravnik. Medicinska sestra pomaga, da se bolnik tem ciljem približuje in izvede tudi nekatere ukrepe, ki so bili predvideni kot možni scenariji na poti k cilju. Sem sodi npr. prilagajanje odmerkov zdravil, ko bolnik doseže določeno stopnjo stabilnosti bolezni. Bolnika moramo naučiti samozdravljenja, kar pomeni, da ga poučimo, da je astma kronična, dinamična bolezen, stalno ga poučujemo o ukrepih in postopkih, s katerimi obdrži bolezen stabilno ter o prepoznavanju in ukrepih v primeru poslabšanja bolezni. Bolnik naj ima pisni načrt vzdrževalnega zdravljenja in ukrepanja ob poslabšanju astme.
Partnersko vodenje: Koristen pristop je pogost telefonski ali e-mail kontakt, preko katerega medicinska sestra (npr. mesečno) preverja in spodbuja bolnika k rednemu jemanju preprečevalnih zdravil in preverja stabilnost bolezni. Pri tem lahko uporablja vprašalnik za nadzor astme in bolniku svetuje v skladu z njegovim načrtom zdravljenja astme, ki ga je pripravil zdravnik.

Poslabšanje astme
Vzroki
Poslabšanje astme nastane, kadar se okrepi astmatsko vnetje. Poslabšanje je največkrat le posledica premalo aktivnega zdravljenja s preprečevalnimi zdravili. Ob ustreznem vzdrževalnem zdravljenju se astma poslabša ob virusnih okužbah (prehladih, gripi). Astma se poslabša, če je bolnik izpostavljen večji koncentraciji alergena, za katerega je občutljiv.
Bolezen se praviloma slabša počasi (nekaj dni) le redkokdaj kar nenadoma. Bolnik čuti dušenje, dražeče kašlja, tišči ga v prsih in piska. Pogosteje kot ponavadi potrebuje olajševalno zdravilo (bronhodilatator). Simptomi so izrazitejši ponoči. Poslabša jih telesni napor in tudi govorjenje ali smeh. Poslabšanje astme prikažemo tudi z meritvijo pljučne funkcije (PEF).
Ločiti je treba med poslabšanjem astme (simptomi zaradi nenadno povečanega astmatskega vnetja) in slabo urejeno astmo (simptomi zaradi slabo nadzorovanega astmatskega vnetja).

Zdravljenje
Bolnik mora vedeti, da se ob poslabšanju astme lahko (mora?) posvetuje z osebnim zdravnikom tudi po telefonu.
Če se astma slabša počasi, naj bolnik takoj ko opazi znake slabšanja bolezni, vsaj početveri odmerek inhalacijskega glukokortikoida (za 1-2 tedna) in o tem obvesti svojega zdravnika.

Pri nenadnem hudem poslabšanju astme so najprej potrebni bronhodilatatorji v inhalaciji: agonisti beta-2 sami ali v kombinaciji s parasimpatikolitiki. Začetni odmerek agonista beta-2 lahko znaša tudi 10 do 25 vdihov iz pršilnika ali 2 do 6 ml raztopine Berodual v inhalaciji. Če se stanje ne popravi v 20 minutah po inhalaciji bronhodilatatorja, odmerek ponovimo (tudi večkrat). Pri hudem poslabšanju astme bolnik potrebuje dodatek kisika prek vsaj 35% maske ali 6 litrov na minuto po nosnem katetru. Če se po bronhodilatatorju PEF ne izboljša na vsaj 75% najboljše vrednosti ali če se po prehodnem izboljšanju čez 2 do 3 ure zopet zmanjša, damo peroralni glukokortikoid (32 mg metilprednizolona 3 - 7 dni).
Napotitev v bolnišnico je potrebna, če je poslabšanje zelo hudo (PEF <33% predvidene vrednosti) ali se slabo odzove na zdravljenje (npr. bolnik že potrebuje bronhodilatator na 2 do 3 ure). Za bolnišnično zdravljenje se odločimo tudi pri bolnikih, za katere že iz prejšnjih izkušenj vemo, da se slabo (počasi) odzovejo na zdravljenje ali da imajo katastrofalna poslabšanja astme. Bolnik mora med transportom v bolnišnico prejemati inhalacije bronhodilatatorjev in kisik.
Pri zdravljenju poslabšanj astme ne uporabljamo antibiotikov, mukolitikov, in antitusikov.

Sodelovanje med zdravnikom splošne medicine in pnevmologom
Priporočamo tesno sodelovanje med osebnim zdravnikom in pulmologom in ne zgolj napotovanja bolnika. V partnerski odnos pri obravnavi astme je koristno pritegniti tudi bolnika in druge zdravstvene delavce (medicinsko sestro, farmacevta v lekarni). Dokončno diagnozo astme lahko postavi sam zdravnik splošne medicine, največkrat pa dokončno diagnozo postavi specialist pnevmolog, ki opravi tudi alergološko diagnostiko. Kasnejša obravnava bolnika z astmo je načeloma prepuščena zdravniku splošne medicine.
V obravnavo bolnika z astmo se mora vključiti specialist pnevmolog v naslednjih primerih:
- slab odziv na začetno zdravljenje (indikacijo za dolgodelujoče $beta_2$ agoniste ali za kombinacijo preprečevalnih zdravil ali za predpis teofilina naj vedno naredi specialist),
- dvom v diagnozo (starejši, kadilci),
- hkratni sistemski simptomi (n.pr. sum na sindrom Churg-Straussove),
- dodatna opredelitev etiologije (aspirinska intoleranca, gastroezofagealni refluks),
- sum na poklicno astmo, ocena delovne sposobnosti povezane z astmo,
- ob nosečnosti,
- razvoj astme v smer krhke astme ali drugih oblik življenja ogrožujoče astme.

Zakaj astme včasih ne moremo urediti?
Težko vodljiva astma:
- Napačna diagnoza (bolnik nima astme): psihogena dispneja, disfunkcija glasilk, pljučni embolizmi, tumor v traheji ali zgornjem mediastinumu
- Slaba zavzetost za zdravljenje
- Kajenje cigaret
- Komorbidnosti, ki slabšajo astmo (kronični sinuzitis, GERB, debelost, psihiatrične bolezni, zdravila)
- Refrakterna astma (5% vseh astem)

Astma s pridruženim rinitisom
Preko 80% bolnikov z astmo boluje za rinitisom. Simptomi rinitisa in astme se nekoliko prepletajo, zato se nam rado zgodi, da pri postavitvi ene diagnoze vse bolnikove težave pripišemo tej diagnozi. Korektno zdravljenje trajnega alergijskega rinitisa torej pomembno zmanjšuje težave bolniku z astmo, poleg tega pa tudi pogostnost poslabšanj astme.

Literatura

1. http://www.ginasthma.com/Guidelineitem.asp??l1=2&l2=1&intId=60
2. Stališče Bolnišnice Golnik, Združenja pnevmologov Slovenije in Katedre za družinsko medicino do obravnave odraslega bolnika z astmo. *Zdrav Vestn* 2007;76,369-79.

Bronhokonstrikcija ob naporu

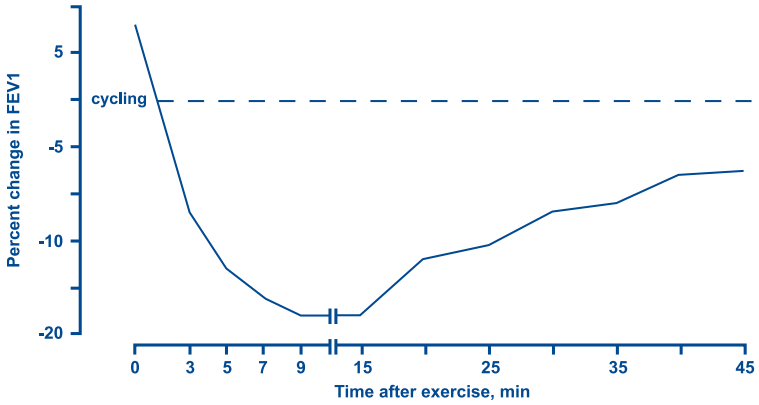
Šorli J
Bolnišnica Golnik – Klinični oddelek za pljučne bolezni in alergijo, Slovenija

Abstract. The term "exercise-induced asthma" is often used to describe episodic bronchoconstriction following exercise in asthmatic patients. This wording is potentially misleading, since exercise is not an independent risk factor for asthma, but rather a trigger of bronchoconstriction in patients with underlying asthma. In fact, there is some speculation that decreased physical activity is a risk factor for asthma, and that exercise may be helpful in preventing the onset of asthma in children. Thus, the term exercise-induced bronchoconstriction (EIB) is a more accurate reflection of the underlying pathophysiology, and is generally preferred. Therapy of EIB varies somewhat with the clinical setting. The first priority in patients with uncontrolled asthma is treatment of the underlying disease. If asthma is controlled or EIB is the only manifestation of airway hyperresponsiveness, EIB should be treated prophylactically with inhaled beta-2 agonists or cromoglycates. Patients with persistent exercise-induced symptoms should be treated with inhaled glucocorticoids. Leukotriene-modifying agents can be used in patients who refuse, or fail to respond to inhaled steroid treatment.

Razlogov, zakaj se pri sicer zdravem človeku pojavlja težka sapa ob naporu je veliko. Še več je razlogov, zaradi katerih se težka sapa pojavlja pri osebah z različnimi, zlasti internističnimi obolenji. Vsako tako stanje moramo obravnavati pozorno in po potrebi tudi ukrepati.
Izraz z naporom povzočena astma se običajno uporablja za opis ponavljajočih bronhokonstrikcij, ki so vezane na telesno aktivnost pri bolnikih z astmo. Sam izraz je pogosto zavajajoč, saj napor sam astme ne povzroča in je samo eden od neodvisnih dejavnikov za slabšanje slabo urejene astme. Vsaka bronhokonstrikcija, ki se pojavi ob povečani telesni obremenitvi tudi ni astma, zato je izraz bronhokonstrikcija povzročena z naporom (BPN) bolj pravilen.
BPN se pojavlja v 7 do več kot 20 odstotkih populacije in je hkrati prisotna pri okrog 80% simptomatskih astmatikih. Tesno je povezana z bronhialno preodzivnostjo, vendar se ne pojavlja pri vseh ljudeh z omenjenim stanjem.
Domneva se, da je glavni sprožilni mehanizem vdihavanje večje količine suhega mrzlega zraka, kot posledica povečane minutne ventilacije ob naporu. Ob tem pride do spremembe v osmolalnosti površine dihalnih poti. Ob tem opažajo tudi povečanje prisotnosti različnih vnetnih mediatorjev (LTC4, LTD4, histamin, IL-8), aktivacijo TH2 limfocitov in občasno povečanje količine eozinofilcev.

Simptomi, ki jih bolniki zaznajo so lahko zelo različni in obsegajo kašelj, piskanje, stiskanje v prsnem košu in težko sapo. Simptomi se lahko pojavijo takoj po začetku telesne obremenitve, še pogostejši pa so takoj po končani obremenitvi. Naravni potek sprememb v dihalih med telesnim naporom vodi

v bronhodilatacijo, ki traja še nekaj minut po končani obremenitvi. Pri bolnikih z BPN pa začetni bronhodilataciji sledi bronhokonstrikcija, ki se pojavi v nekaj minutah, doseže svoj vrh v 10 - 15 minutah in nezdravljena traja približno eno uro. Pri večini bolnikov z BPN začetnemu obdobju sledi refraktarna faza, v kateri dodatna obremenitev ne povzroča dodatne bronho-konstrikcije in traja do štiri ure po začetku napora. To obdobje izkoriščamo pri zdravljenju, saj s počasnim in temeljitim ogrevenjem pred pričakovano obremenitvijo dosežemo refraktarno obdobje z minimalno bronhokonstrikcijo.
Nekateri avtorji opisujejo tudi kasno bronhokonstrikcijo, ki se pojavi več ur po končani obremenitvi, vendar je intenzivnost tega pojava manjša.



Diagnozo potrdimo s pomočjo obremenilnega testiranja na ergometru, s čimer dosežemo obremenitev do 85 % predvidene maksimalne zmogljivosti. Doseženo stopnjo obremenitve vzdržujemo 6 - 8 minut. Spirometrijo opravimo pred obreme-nitvijo in nato vsakih 10 - 15 minut. Test je pozitiven, če FEV1 pade za 20% ali več glede na izhodiščno vrednost.

V samem poteku obravnave je v diferencialni diagnostiki potrebno pomisliti še na disfunkcijo glasilk, obstrukcijo velikih dihalnih poti, traheomalacijo, intersticijske pljučne bolezni, GERB in srčno popuščanje.

Glavni namen zdravljenja BPN je zagotoviti, da se bolniki ne izogibajo telesnim aktivnostim. Bolnike z astmo moramo spodbujati, da so telesno aktivni ne glede na simptomatsko astmo. Pri zdravljenju kombiniramo tako farmakološke, kot nefarmakološke ukrepe. Pri nefarmakoloških ukrepih se zlasti opiramo na odstranjevanje razlogov za pojav BPN. Z dobro telesno zmogljivostjo zmanjšamo potrebno minutno ventilacijo pri enaki stopnji obremenitve, z vdihavanjem ogretega toplega zraka pa še dodatno zmanjšamo draženje dihal, zato bolnikom svetujemo dihanje preko šala oziroma posebnih mask ob hladnem vremenu.

Med farmakološke ukrepe sodi v prvi vrsti dobro urejena in zdravljena astma. To dosegamo z uporabo inhalacijskih steroidov in entilevkotrieni. S slednjimi predvsem takrat, ko z inhalacijskimi steroidi ne dosežemo želene urejenosti bolezni, oziroma jih bolnik noče prejemati. Beta-2 agonisti neposredno pred pričakovanim naporom (5 - 10 minut), običajno v obliki kratko delujočega pripravka, se uporabljajo kadar je BPN edina manifestacija preodzivnosti dihal, oziroma preventivno pri astmatikih na protivnetni terapiji. Kadar se BPN pojavi kljub terapiji, oziroma je bolnik zdravila pozabil vzeti si lahko pomaga z dodatnimi vpihi kratko delujočih beta-2 agonistov med samim naporom. Pri otrocih je potrebna posebna pozornost, da se beta-2 agonisti ne uporabljajo prepogosto, saj lahko to rezultira v toleranci na njihov preventivni učinek.

Posebej moramo biti pozorni pri predpisovanju zdravil kategoriziranim športnikom. Zaradi zlorab kortikosteroidov in beta-2 agonistov za potrebe dopinga je mednarodna protidopinška komisija na listo

prepovedanih snovi vključila tudi omenjena zdravila. Dovoljuje se uporaba ob jasnih medicinskih indikacijah in ob predložitvi vnaprej izpolnjenega obrazca za terapevtske izjeme. Uporablja se tako imenovana skrajšana oblika obrazca, ki je namenjen prijavi uporabe beta-2 agonistov in topičnih kortikosteroidov. Izpolnjenemu obrazcu je potrebno predložiti medicinsko dokumentacijo, ki dokazuje potrebo po uporabi zdravil v terapevtske namene. Med potrebno dokumentacijo sodi dokaz bronhialne preodzivnosti (metaholinski test, test normokapnične hiperventilacije, spirometrije po obremenitvi), dokaz atopijskega statusa s pomočjo kožnega testiranja ali dokaz prisotnosti specifičnih protiteles in zgodovina bolnikove obravnave. Pred izdajo dovoljenja za uporabo zdravil lahko za to pristojna komisija preveri rezultate v svojem izbranem laboratoriju.

Literatura

1. Storms, WW. Asthma associated with exercise. Immunol Allergy Clin North Am 2005; 25:31.
2. Lucas SR, Platts-Mills TA. Physical activity and exercise in asthma: relevance to etiology and treatment. J Allergy Clin Immunol 2005; 115:928.

Zunajbolnišnična pljučnica: dve leti slovenskih smernic – diagnostika

Osolnik K
Bolnišnica Golnik – Klinični oddelek za pljučne bolezni in alergijo, Slovenija

Namen smernic za obravnavo zunajbolnišničnih pljučnic (ZBP) je standardiziranje in poenostavitev zdravniške obravnave v ambulantah in bolnišnicah. ZBP je eden najpogostejših vzrokov za hospitalizacijo in predstavlja največji delež akutnih pulmoloških hospitalizacij. Da bi lahko ocenili, kako zdravimo ta čas, to je po dopolnitvi in posodobitvi smernic, je potrebno, da svoje delo analiziramo, primerjamo s preteklim (pred posodobitvijo smernic) in na tak način ugotovimo, kje so možnosti za izboljšanje diagnostike in zdravljenja, racionalizacijo, izboljšanje sodelovanja med posameznimi nivoji obravnave bolnika in učinkovitejšo organizacijo dela. Z analizo lastnega dela lahko spremljamo kakovost obravnave bolnikov po priporočenih kazalcih. Namen prispevka je ugotoviti in pokazati spremembe v diagnostiki ZBP v ambulantni in bolnišnični obravnavi v zadnjih dveh letih in ugotoviti vpliv sprejetih prenovljenih smernic na diagnostiko in obravnavo bolnikov s pljučnicami domačega okolja v celoti.

Materiali in metode
Za retrogradno analizo sem uporabila 50 popisov bolnikov, ki so bili sprejeti v Bolnišnico Golnik - KOPA konec leta 2005 in v začetku leta 2006 (prva skupina) in bili zdravljeni zaradi ZBP in 50 popisov bolnikov, ki so bili sprejeti v KOPA Golnik konec leta 2006 in v začetku leta 2007 (druga skupina). V prvi skupini bolnikov je bilo 22 moških in 28 žensk, povprečna starost 71,1 let, 5 bolnikov je bilo oskrbovancev domov starejših občanov (10%). Povprečna ležalna doba je bila 9,4 dni (razpon 3 -28 dni). V drugi skupini bolnikov je bilo 35 moških in 15 žensk, povprečna starost 72,2 leti, 7 bolnikov je bilo oskrbovancev domov starejših občanov (14%). Povprečna ležalna doba je bila enaka - 9,4 dni (razpon 1 – 39 dni). Za tretjo skupino bolnikov sem izbrala 100 bolnikov hospitaliziranih v KOPA Golnik v letu 2007, ki so imeli etiološko pojasnjenega povzročitelja ZBP. V tej skupini je bilo 57 moških, 43 žensk, povprečna starost 70,8 let, delež bolnikov - oskrbovancev domov starejših občanov, je bil enak - 14%. Povprečna ležalna doba 10,6 dni (razpon 1 – 40 dni).

Rezultati
Bolnike so v KOPA Golnik napotili (po skupinah 1, 2 in 3):
- dežurni zdravniki 54%, 66%, 61%
- specialisti pulmologi 26%, 18%, 20%
- specialisti družinske medicine - izbrani zdravniki 20%, 16%, 19%.

Trend povečevanja napotitev iz dežurnih ambulant se nekoliko umirja, zajema pa več kot polovico napotitev bolnikov s pljučnico, deleža napotitev pulmologov in družinskih zdravnikov sta uravnotežena. Napotni zdravnik v dežurni ali splošni ambulanti postavi diagnozo pljučnice na podlagi anam-

neze in kliničnega pregleda. Nujno potrebno je, da izmeri frekvenco dihanja, pulza, telesno temperaturo in krvni tlak. Potrebno je, da oceni stanje hidriranosti, zavesti in orientiranosti. Pri bolnikih z dejavniki tveganja za težji potek bolezni in starejših od 65 let naj določi še KKS (kompletno krvno sliko) in dušične retente. Meritev nasičenosti hemoglobina s kisikom ob upoštevanju kliničnih ugotovitev omogoča oceno potrebe po dodatni aplikaciji kisika. Za oceno teže pljučnice je uporaben sistem CRB (Confusion, Respiratory rate, Blood pressure). Po pregledu sledi odločitev o napotitvi v bolnišnico ali začetku zdravljenja pljučnice ambulantno. V tem primeru se bolniku predpiše antibiotik v skladu s smernicami. Pred predpisom terapije in postavitvi diagnoze pljučnice je potrebno določiti CRP. Pred sprejemom v bolnišnico je prejemalo antibiotik:

- skupina 1: 22% bolnikov: (8% amoksicilin s klavulansko kislino, 6% makrolide, 4% respiratorni kinolon, 4% cefalosporin),
- skupina 2: 26% bolnikov: (10% amoksicilin s klavulansko kislino, 8% kinolone, 6% makrolide, po 2% cefalosporin in antimikotik),
- skupina 3: 27% bolnikov: (13% amoksicilin s klavulansko kislino, 11% kinolone, po 2% makrolide in peniciline, po 1% cefalosporin in rifampicin).

Rentgensko slikanje pljuč je zaželjeno že pred začetkom zdravljenja, če je le dosegljivo. Obvezno je, kadar predpisana terapija ni uspešna, kar lahko ugotovimo že ob neizogibnem drugem pregledu po dveh do treh dneh. Oceno teže pljučnice ob sprejemu v bolnišnico opravimo po PORT sistemu že v sprejemni ambulanti. Na tej oceni temelji odločitev o sprejemu ali odklonu bolnika in potrebnosti zdravljenja bolnika na intenzivnem oddelku. Pri vseh bolnikih s sumom na pljučnico je na začetku obravnave opravimo rentgensko slikanje pljuč, če za to ni kontraindikacije (npr. nosečnost), o kateri pa se glede njene relativnosti odločamo od primera do primera, plinsko analizo arterijske krvi, osnovne biokemijske preiskave, krvno sliko in kontroliramo saturacijo s kisikom. Takoj po sprejemu na oddelek pri vseh bolnikih izvajamo splošne ukrepe:

- zagotavljanje ustrezne oksigenacije in merjenje frekvence dihanja in zasičenosti arterijske krvi s kisikom,
- zagotavljanje zadovoljive hidracije in spremljanje diureze,
- zagotavljanje zadovoljivega krvnega obtoka in merjenje frekvence pulza ter krvnega tlaka.

Pri bolnikih s težjo klinično sliko odvzamemo kri za hemokulturo, vedno pred prvo aplikacijo antibiotika. Če je bolnik antibiotik že prejel pa neposredno pred naslednjim odmerkom.

Če bolniki izkašljujejo pregledamo izmeček, saj je razmaz obarvan po Gramu lahko v pomoč pri prvem predpisu antibiotika. Ob sumu na atipično pljučnico odvzamemo izmeček ali bris žrela za molekularno diagnostiko, v urinu lahko dokazujemo antigen bakterije *Legionella pneumophila sg.*1. Povzročitelj pljučnice iz izmečka je bil v prvih dveh skupinah izoliran pri približno četrtini bolnikov (*Streptococcus pneumoniae* 3x, *Haemophilus influenzae* 3x, *Staphylococcus spp.* 2x, *Pseudomonas aeruginosa*, *Proteus spp.*, *Klebsiella spp.* in enterobakterije po 1x, *Mycoplasma pneumoniae* 1x v prvi in *H. influenzae* 3x, *P. aeruginosa*, *K. pneumoniae* in *Enterobacter spp.* po 2x, *S. pneumoniae* 1x v drugi skupini). Taki podatki so skladni s podatki v literaturi. Tretja skupina (iz leta 2007) se od prvih dveh razlikuje prav v tem, da jo sestavljajo samo tisti bolniki, pri katerih smo v času hospitalizacije izolirali povzročitelja pljučnice. Med njimi smo v 25% izolirali *S. pneumoniae*, v 15% *H. influenzae*, v 10% *Staphylococcus spp.*,v 12% *P. aeruginosa*, v 9% enterobakterije (v 5% klebsielo in sporadično proteus, seracijo). Smrtnost zaradi pljučnice se je med skupinami razlikovala: 6% bolnikov je zaradi pljučnice umrlo v prvi skupini, v drugi skupini 14% in v tretji 9%. Če je na rentgenogramu viden plevralni izliv le-tega punktiramo za določitev pH, mikrobiološki, biokemični in citološki pregled. Če je plevralni izliv obsežen in ovira mehaniko dihanja ga je potrebno punktirati, če ima izliv značilnosti empiema ga je potrebno drenirati. Pred drenažo je zaradi natančne lokalizacije empiema potrebno opraviti CT. Če zdravljenje pljučnice ni uspešno - neregredirajoča pljučnica, nepoznan povzročitelj, se odločamo za invazivno diagnostiko. Pri bronho-skopiji lahko odvzamemo izpirek z zaščitenim katetrom za mikrobiološke preiskave ter vzorce za citološko in histološko analizo ob misli na nevnetno etiologijo neregredirajoče pljučnice.

Razprava

V bolnišnico zaradi ZBP sprejemamo predvsem starejše bolnike. ZBP je akutna bolezen, kar se odraža tudi v napotitvah bolnikov v bolnišnico. Več kot polovica bolnikov je napotenih iz urgentnih

ambulant. Ta podatek je potrebno upoštevati predvsem pri seznanjanju zdravnikov na terenu s smernicami in pri oblikovanju povezav, potrebnih za dobro sodelovanje (specialisti družinske medicine, pulmologi v ambulantah in bolnišnicah, pulmologi na kliniki). Ocena teže ZBP ob sprejemu v bolnišnico kaže, da sprejemamo bolnike z zmerno in hudo intenziteto pljučnice (70%), ki so srednje do visoko ogroženi. Naši podatki o umrljivosti zaradi ZBP so primerljivi s podatki v literaturi. Glede na naše ugotovitve imajo bolniki z etiološko pojasnjeno pljučnico, glede na oceno po PORT sistemu, pridruženih več spremljajočih bolezni. V primeru sprejetih bolnikov v KOPA Golnik opažamo pomemben porast napotenih bolnikov s pridruženimi drugimi pljučnimi boleznimi: KOPB, astma, post-TB spremembe. Takih bolnikov je več kot polovica. S tem podatkom si lahko v precejšnji meri razložimo seznam izoliranih povzročiteljev pljučnice v zadnji skupini, upoštevati pa ga je potrebno tudi ob presoji ob sprejemu predpisane empirične antibiotične terapije in trajanja intravenoznega zdravljenja. Na izbor antibiotika ob sprejemu ima tudi podatek o predhodnem prejemanju antibiotikov, ki so bili "neučinkoviti", največkrat brez spremljajočih podatkov o zanesljivosti in trajanju prejemanja, primernosti peroralne aplikacije (npr. ob bruhanju, ipd.) in argumentov za odločitev za določen antibiotik, še posebej, če izbor antibiotika ni v skladu s smernicami. Ob primerjavi skupin glede predhodno predpisanega antibiotika je opazen pomemben porast predpisa kinolonov, amoskicilina s klavulansko kislino in upad makrolidov. Še vedno ostaja praktično popolna odsotnost predpisovanja samih penicilinskih antibiotikov bolnikom, ki so sprejeti v bolnišnico.

Zaključek

Potrebno je redno in primerjalno spremljanje kakovosti obravnave bolnikov z ZBP po priporočenih kazalcih kakovosti na vseh nivojih, od primarnega do terciarnega.

Literatura

1. Mušič E, et al. Usmeritve za obravnavo zunajbolnišnične pljučnice (ZBP) pri odraslih, Golnik: Bolnišnica, Klinični oddelek za pljučne bolezni in alergijo, 2006.
2. Mušič E, Košnik M, eds. ZBP: Analiza slovenskih smernic, Ljubljana: Bolnišnica Golnik- Klinični oddelek za pljučne bolezni in alergijo, Katedra za družinsko medicino, Klinika za infekcijske bolezni in vročinska stanja, Združenje zdravnikov družinske medicine, 2007.

Zunajbolnišnična pljučnica: dve leti slovenskih smernic – zdravljenje

Mušič E, Eržen R, Osolnik K
Bolnišnica Golnik – Klinični oddelek za pljučne bolezni in alergijo, Slovenija

Po sprejetju slovenskih smernic o obravnavi zunajbolnišnične pljučnice (ZBP) smo dokument objavili v Zdravniškem vestniku, vsebino še isto leto predstavili na 48. Tavčarjevih dnevih s poudarkom na ZBP v ambulantni praksi in jih izdali tudi v samostojni publikaciji, katere izdajatelji so bili Bolnišnica Golnik - KOPA, Klinika za infekcijske bolezni in vročinska stanja, Katedra za družinsko medicino MF v Ljubljani in Združenje pnevmologov Slovenije (1, 2). Po letu dni smo se analitično ozrli na naše delo v zvezi z ZBP in na strokovnem srečanju ocenili naše pristope k ambulantni in bolnišnični obravnavi ZBP, še posebej smo razčlenili številnejše ambulantno obravnavane bolnike z ZBP. Ugotovili smo, da so smernice prinesle v roke ambulantnega in hospitalnega zdravnika nova, enostavna orodja, ki zboljšujejo kakovost obravnave ZBP. Med metodami v zagotavljanju kakovosti so se v bolnišnici pozitivno izkazale klinične poti, za standarde kakovosti v ambulantni obravnavi pa smo si zastavili nujne naloge. Podobno so bili predstavljeni tudi načini za vzpostavitev sistema, s katerim je možno primerjati kakovostno obravnavo ZBP (3). Simpozij nas je zavezoval, da našo obravnavo ZBP znova ocenimo po 2 letih, tako da smo se tokrat podrobneje posvetili pogojem ambulantnega dela pri ZBP. V to prakso želimo po 2-letni analizi stanja v svetu in pri nas vnesti enostavne kriterije kazalcev kakovosti v diagnostiki in terapiji. Ti naj bodo enostavni, kolikor je le mogoče, vendar ne toliko enostavni, da bi trpela kakovost (cit. po Einsteinu).

Namen – uporabnost slovenskih smernic v praksi
S smernicami smo v slovensko ambulantno prakso vgradili enostaven britanski sistem za ocenjevane teže ZBP, ki ga ponavljamo tukaj: to je sistem CRB-65, ki je enako učinkovit kot CURB-65 in tudi kot ameriški sistem PORT, ki je prikladnejši za bolnišnično obravnavo. Tako so povzeli tudi na strokovni prireditvi Pneumo update 2007 (4). Sistem CRB-65 je dostopen, brez stroškov in vključuje klinično oceno teže ZBP, ki jo napravi zdravnik.

Tabela 1. Simptomi in znaki pri bolniku za **CRB-65**

Confusion - novo nastala zmedenost
Respiratoty rate – frekvenca dihanja >30/min.
Blood pressure – sistolni KT <90 mmHg ali diastolni <60mmHg
Starost **>65 let**

Samo malo je potrebno še dodati, pa imamo v rokah za ambulantno prakso že poglavitne kazalce kakovosti obravnave, ki jih bomo oblikovali izkustveno. Po kriterijih CRB-65 obravnavamo doma le stopnjo 1 in stopnjo 2 ZBP, za vsako teh dveh stopenj smernice priporočajo izkustveno terapijo.

Stopnja 1 po CRB-65:
- s frekvenco dihanja <30/min
- z normalnim krvnim pritiskom
- starost <65 let.

Stopnja 2 po CRB-65:
- 1 ali 2 izmed naštetih kriterijev.

Že ta enotavnost pove, da bolnika z več kot 2 znakoma CRB-65 napotimo v bolnišnico. Izkustveno je ocenjeno, da je tak pristop k oceni ZBP enako uspešen kot CURB in celo PORT. V ambulantni praksi je torej pri ZBP potrebno oceniti psihično stanje, izmeriti frekvenco dihanja, krvni pritisk in upoštevati starost, da se odločimo o zdravljenju doma ali napotitvi v bolnišnico. Za seznam kazalcev kakovosti ne bomo veliko dodali: potrebna je RTG pc slika, kar naj bo cilj kakovostnega dela pri vseh ZBP, podobno tudi ocena oksigenacije in hidracije. V tem sestavku bo podana analiza in nasvet ambulantnega zdravljenja ZBP .

Ambulantno zdravljenje ZBP
Zdravljenje v ambulanti in v bolnišnici je določeno s stopnjo teže ZBP. V osnovi ločimo pljučnice stopnje 1 brez rizične ogroženosti bolnika in stopnjo 2 z že možno rizičnostjo. Vselej pa moramo presoditi, ali ni prisotna možnost okužbe z bakterijo *Pseudomonas aeruginosa*, ki zahteva poseben izbor antibiotikov, vendar je ta etiologija v ambulantni obravnavi redka. Ambulantno moramo biti vedno pozorni tudi na možnost legionelne ZBP, ki zahteva določeno terapijo. V splošnem velja, da je legionelnih ZBP več, kot jih dokažemo, zanje je značilen intenzivnejši in daljši potek. Po CRB-65 oceni, izmeri in korekciji arterijske oksigenacije ter hidracije izberemo antibiotik po smernicah:

Tabela 2. Izbira antibiotika za zdravljenje ZBP doma

• Stopnja 1	ZBP (brez rizičnosti) –
	Penicilin V 1,000.000-1,500.000 IE/6 ur per os 7-10 dni
	ali
	Amoksicilin 500-1000mg/8 ur
	ali
	Makrolid per os ob domnevi atipične ali legionelne ZBP
• Stopnja 2	ZBP (rizičen bolnik) –
	Amoksicilin+klavulanska kislina 625-1000mg/8 ur p.os
	ali
	Cefuroksim 750mg/12 ur p.os
	ali
	Moksifloksacin 400mg/24ur
• Domneva pseudomonasne ZBP –	
	Ciprofloksacin 500-750mg/12 ur p.os

Bolnik z ZBP mora biti tudi doma klinično znova ocenjen 3. do 5. dan zdravljenja, ponovno ocenimo CRB-65. Do te ocene je potrebno spremljati tudi diurezo na nek prirejeni način. Zanesljivo moramo oceniti vsaj centralno cianozo ali pa digitalno O_2 saturacijo arterijske krvi.
Ob neugodnih ugotovkih 3.dan je nujna hospitalizacija. Menjava antibiotika brez drugih preverjanj, je tvegana.

Klinična pot v obravnavi ZBP
V Bolnišnici Golnik - KOPA jo uporabljamo od leta 2002 dalje. Eržen R. je poročal o analizi kakovosti obravnave ZBP pred uporabo klinične poti in pet let kasneje (5). Klinično pot je prvo leto uporabljalo 45% zdravnikov, po 5 letih pa že 78% zaradi pozitivnih izkušenj. Preko klinične poti je bilo analiziranih 866 ZBP, samo 2 bolnika sta imela komaj blago obliko bolezni, kar je kompliment napotnim zdravnikom, da napotujejo primerno. V bolnišnici smo antibiotike aplicirali parenteralno povprečno 4,5 dni: amoksicilin s klavulansko kislino v 62%, moksifloksacin v 20%, druge antibiotike v 18%. Povprečna hospitalizacija je bila 11 dni, smrtnost pa 8,5%. S klinično potjo smo skrajšali ležalno dobo za 2 dni, parenteralno antibiotično terapijo tudi za 2 dni. S klinično potjo nadaljujemo, saj zdravnika vodi in vsak dan opominja.

Anketa o uporabnosti smernic v zdravljenju ZBP 2006-2007
V juniju 2008 smo poslali vprašalnik 70 zdravnikom družinske medicine in 140 članom Združenja pnevmologov Slovenije o uporabnosti naših smernic za ZBP z izpostavitvijo ocene ZBP po CRB-65, ki je ključ do ustreznega pristopa, o praksi RTG slikanja, o izbiri antibiotika, o beleženju smrtnosti zaradi ZBP. Ti parametri so tudi ključni za postavitev indeksov kakovosti dela, ki jih želimo vpeljati v prakso. Rezultate ankete bomo predstavili na kongresu v septembru. Prav tako bomo predstavili analizo zdravljenja hospitaliziranih ZBP zadnji 2 leti ob upoštevanju domačih smernic. Povzeti pa smemo že sedaj, da so smernice pozitivno vplivale na kakovost obravnave ZBP, na boljše rezultate zdravljenja in na farmakoekonomiko. Zavezani smo k obnovi tega dokumenta, ki naj se še bolj prime zdravnikov in jim olajša delo.

Pneumo update 2007 in ZBP
V primerjavi med ameriškimi smernicami o ZBP iz leta 2007 in evropskimi iz leta 2005 ugotavljajo na 400.000 primerih ZBP, da je sistem ocene po CRB-65 soliden in uporaben za evropske razmere (5). Pri težjih kliničnih slikah moramo biti pozorni še na krvno sliko, ev. levkocitozo in –penijo ter trombocitopenijo, hiper- in hipotermijo kot parametrov sepse. Opozarjajo na relativno nizek delež dokazanih atipičnih povzročiteljev in legionel, tako da v Evropi makrolidi ne morejo biti prvi izbor pri zdravljenju lažjih ZBP. Pri nas za ambulantno prakso ostaja amoksicilin na prvem mestu izbora. Po razmisleku gre morda za potrebo po kombinaciji amoksicilina in makrolida ali pa za sam moksifloksacin, ki lahko nadomestiti kombinacijo dveh antibiotikov in je učinkovit pri okužbi z atipičnimi povzročitelji (mikoplazma, klamidofila) in legionelami. Pseudomonasne ZBP, ki bi bile po klinični sliki dopustne za zdravljenje doma, so pri nas skrajno redke. Opozarjajo na možen vpliv inhaliranih glukokortikoidov (GK) na izid ZBP, saj bi lahko modulirali imunski odziv dihal, dokazov za o tem pa še ni. Raziskujejo pa pozitiven učinek dodatne sistemske terapije z GK v prvih dneh pnevmokokne pljučnice, ko je citokinska produkcija v vnetju zelo obsežna, seveda ob visokih dozah penicilina. Dodatek statinov v terapijo je znižal umrljivost za 46%, ACE-zaviralcev pa za 20%. Oboji imajo tudi aditivni imunomodulatorni učinek na makrofagno funkcijo pri različnih kroničnih boleznih. Nova kategorija ZBP je pljučnica oskrbovancev negovalnih ustanov in bolnikov na kronični dializi. Pri teh je povzročitelj večkrat tudi *P. aeruginosa* in celo *Staphylococcus aureus* odporen proti meticilinu (MRSA). V visoki starosti teh bolnikov in tudi starostnikov nasploh opozarjamo na vse komorbidnosti, ki zahtevajo poleg obravnave same ZBP poseben nadzor in dodatno terapijo. Smrt lahko nastopi zaradi poslabšanja kronične bolezni ob ZBP ali zaradi same ZBP. Intenzivne so aktivnosti za promocijo preventivnega cepljenja proti gripi in okužbi s pnevmokokom, zlasti v starosti nad 65 let in pri drugače ogroženih.

Indeksi kakovosti v ambulantni obravnavi (Deutsche Gesellschaft für Pneumologie, Lübeck 2008)
Po 6 letih analize ZBP v nemškem nacionalnem projektu CAPNETZ predlagajo spremljanje parametrov v ambulantni obravnavi ZBP v začetku, nekaterih znova po 3, 4, 5 dneh obravnave in ob zaključku obravnave:
- ocena CRB–65
- oksigenacija arterijske krvi
- aplikacija antibiotika po smernicah v vsaj 4 - 8 urah od diagnoze

• zgodnja mobilizacija, posedanje, vstajanje 1. dan
• kontrola CRP 4 - 5.dan
• kriteriji stabilnosti, izboljšanja
• smrtnost zaradi pljučnice.

Dogovorjene indekse kakovosti bomo beležili v zdravstveni karton, da bodo dostopni preverjanju in analizam.

Registracija ZBP, umrljivost

Želimo doseči dogovor, da doma obravnavane ZBP pravilno šifriramo po MKB-10 in da evidentiramo indekse kakovosti dela in smrtnost zaradi ZBP. Podrobnejše poteze prevzema Komisija za okužbe v dihalih pri ZPS.

Pobudniki smernic, pota k obnovi

Slovenske smernice, objavljene v januarju 2006, so nastale kot plod sodelovanja pulmologov, infektologov in specialistov družinske medicine. V letih zatem opažamo premike k bolj kakovostni obravnavi ZBP. Precej pa je treba še postoriti in se dogovoriti, pri čemer bodo ključna vodstva sodelujočih ustanov in strokovnih združenj.

Literatura

1. Kakovost v zdravstvu: Usmeritve za obravnavo zunajbolnišnične pljučnice odraslih. Zdrav Vestn 2005; 74:745-52.
2. Mušič E. Pljučnica v ambulanti družinske medicine. 48. Tavčarjevi dnevi, MF v Ljubljani 2006: 197-205.
3. Mušič E, Košnik M., eds. Zbornik simpozija Zunajbolnišnične pljučnice: Analiza slovenskih smernic, Ljubljana, februar 2007.
4. Eržen R, Mušič E, Košnik M. Clinical pathway as a tool of improving quality of care in patients with CAP. Eur Respir J 2007;30(Suppl 51): P 3932.
5. Magnussen H., ed. Pneumo update 2007. 4. Pneumologie-Seminar, Wiesbaden, November 2007.

KOPB – kako zmanjšati invalidnost

Fležar M
Bolnišnica Golnik – Klinični oddelek za pljučne bolezni in alergijo, Slovenija

Kronična obstruktivna pljučna bolezen (KOPB) je bolezen, ki povzroči trajne spremembe na pljučih. Prizadete so dihalne poti (kronični bronhitis), pljučni parenhim (emfizem), pljučne žile (pljučna hipertenzija) in srce (pljučno srce). Okvaro teh organov lahko zaustavimo oz. upočasnimo (prenehanje kajenja), delovanje pa malenkostno izboljšamo z zdravili (bronhodilatatorji, protivnetna zdravila). Moteno delovanje organa je tisto, ki povzroča bolniku težave in ne spremenjena sestava (morfologija). Delovanje organov merimo s funkcijskimi preiskavami in ravno stopnja okvarjene funkcije organa je tista, ki določa stopnjo telesne okvare, ki zaradi okvare tega organa nastane. Celotna telesna okvara pa je pogoj za nastanek invalidnosti, ki se izračuna po posebni formuli, ki sešteva okvare posameznih organov.

Definicije pojmov telesne okvare in invalidnosti
Telesna okvara je prisotna, če nastane pri zavarovancu izguba, bistvenejša poškodovanost ali znatnejša onesposobljenost posameznih organov ali delov telesa, kar otežuje aktivnost organizma in zahteva večje napore pri zadovoljevanju življenjskih potreb, ne glede na to, ali ta okvara povzroča invalidnost ali ne.
Vrste telesnih okvar, na podlagi katerih se pridobi pravica do invalidnine, in odstotke teh okvar določi minister, pristojen za delo, po predhodnem mnenju ministra, pristojnega za zdravstvo. Dokler navedeni podzakonski akt ne bo sprejet, se v ta namen še naprej uporablja Samoupravni sporazum o seznamu telesnih okvar (Uradni list SFRJ, št. 38/83 in 66/89).
Invalidnost je posledica sprememb v zdravstvenem stanju, ki jih ni mogoče odpraviti z zdravljenjem oziroma medicinsko rehabilitacijo.
Definicija invalidnosti je utemeljena v 1. čl. Konvencije Mednarodne organizacije dela št. 159, v katerem je določeno, da je "invalid" oseba, katere možnosti, da si zagotovi in obdrži ustrezno zaposlitev in da napreduje v njej, so bistveno zmanjšane zaradi telesne ali duševne okvare. Enako je opredeljen pojem "invalida" tudi v Priporočilu MOD št. 168. http://www.zpiz.si/src/invalidsko_zavarovanje/
Invalidnost po ZPIZ-1 razvrščamo v tri kategorije:
I. kategorija - če zavarovanec ni več zmožen opravljati organiziranega pridobitnega dela ali če je pri njem podana poklicna invalidnost, nima pa več preostale delovne zmožnosti;
II. kategorija - če je zavarovančeva delovna zmožnost za svoj poklic zmanjšana za 50 % ali več;
III. kategorija - če zavarovanec z ali brez poklicne rehabilitacije ni več zmožen za delo s polnim delovnim časom, lahko pa opravlja določeno delo vsaj s polovico polnega delovnega časa oz. če je za-

varovančeva delovna zmožnost za svoj poklic zmanjšana za manj kot 50 % ali če zavarovanec še lahko dela v svojem poklicu s polnim delovnim časom, vendar pa ni zmožen za delo na delovnem mestu na katerega je razporejen.
Pri odmeri invalidnin, ki so posledica poškodbe pri delu ali poklicne bolezni, se upoštevajo naslednje vrednosti:

Vrsta telesne okvare	Odstotek telesne okvare	Višina odstotka za odmero invalidnine
1. stopnja	100	24
2. stopnja	90	22
3. stopnja	80	20
4. stopnja	70	18
5. stopnja	60	16
6. stopnja	50	14
7. stopnaj	40	12
8. stopnja	30	10

Invalidnine za telesne okvare, ki so posledica bolezni ali poškodbe izven dela, znašajo 70% zneska telesne okvare, določenega za isto stopnjo telesne okvare, ki je posledica poškodbe pri delu ali poklicne bolezni, pri čemer pa 7. oziroma 8. stopnja telesne okvare še ne zagotavlja pravice do invalidnine. Če je telesna okvara posledica različnih vzrokov, se invalidnina odmeri v skupnem znesku glede na ugotovljeno skupno stopnjo telesne okvare. Znesek invalidnine pa se določi sorazmerno vplivu posameznega vzroka na skupen odstotek telesne okvare! Morebitno poznejše poslabšanje telesne okvare lahko vpliva na spremembo ugotovljene stopnje in višino invalidnine!

Kaj vpliva na invalidnost bolnika s KOPB?
Glavni simptom bolnika s KOPB je težka sapa oziroma dispneja. To je tudi simptom, ki je najbolj neposredno povezan s telesno aktivnostjo oz. se med njo močneje izrazi. Bolj ko bolnik zaznava ta simptom, bolj verjetno bo stopnja njegove invalidnosti večja.
S funkcijskimi preiskavami – preiskavo pljučne funkcije – ne uspemo jasno ločevati med bolniki z manj in bolj težko sapo. FEV_1 ali indeks Tiffeneau v 40% pojasnjujeta razlog za težko sapo. Hiperinflacija in ujetje zraka v pljučih (zmanjšanje IC – inspiratorne kapacitete, oziroma povečanje FRC – funkcionalne rezidualne kapacitete ter povečanje RV/TLC indeksa) pojasnjujeta težko sapo v 60%. Desaturacija med obremenitvijo je odgovorna za težko sapo pri manj kot 10% bolnikov. Torej, preiskava pljučne funkcije ni vedno merilo za stopnjo dispneje in s tem invalidnosti.
Poleg pljuč so pri KOPB bolni tudi drugi organi. Zaradi težke sape se bolniki gibljejo manj, prihaja do atrofije mišičja, upada aerobne zmogljivosti in težke sape, ki med telesnim naporom nastane zaradi laktacidoze kot posledice slabosti mišičja. Bolniki z napredovalo hudo in zelo hudo boleznijo imajo velikokrat razvito pljučno srce – dispneja nastaja zaradi kardiocirkulatorne omejenosti med obremenitvijo.
Kako lahko vplivamo na zmanjševanje simptomov – predvsem težke sape, ki določa stopnjo invalidnosti?
Z bronhodilatatorji in drugimi zdravili izboljšujemo delovanje pljuč. Dodajanje kisika bolniku v respiracijski insuficienci v mirovanju močno izboljša počutje in zmanjša dispnejo.
Rehabilitacijski postopki, med katerimi so med najpomembnejšimi fizoterapevtski postopki, ki preko telesne vadbe odpravljajo izvenpljučne razloge za težko sapo, pa so ključ uspeha pri zmanjševanju invalidnosti in izboljšanju kakovosti življenja. Ti postopki niso namenjeni zdravljenju pljuč, pač pa ostalih organskih sistemov, ki so pri KOPB neposredno ali posredno prizadeti.
Uspeh rehabilitacijskih postopkov je izmerljiv, vendar ne s parametri pljučne funkcije, pač pa z vprašalniki, ki ocenjujejo bolnikovo zdravstveno stanje. Za KOPB pridejo v poštev naslednji:
TDI (Transition Dyspnea Index) – ocenjuje zmanjšanje (spremninjanje) težke sape pri telesnih aktivnostih
SF-36 (Short Form 36) – ocenjuje splošno stopnjo zdravja oziroma bolezni

SGRQ (Saint George's Respiratory Questionaire) in CRQ (Chronic Disease Respiratory Questionaire)– ocenjujeta prizadetost oziroma spremenjeno kakovost življenja zaradi respiratorni vzrokov. SGRQ je na voljo tudi v slovenskem jeziku.

Zaključek

Boljšo kakovost življenja, manj simptomov in boljše počutje bolnika s KOPB bomo redko dosegli le z zdravljenjem z zdravili. Zavedati se moramo, da okvare pljuč kot posledice kajenja ne bomo mogli odpraviti, da pa je stopnjo invalidnosti ob tej okvari možno močno zmanjšati z ustreznimi rehabilitacijskimi postopki. Ćal dandanašnja ocena telesne okvare še vedno temelji na meritvah pljučne funkcije, ki pa ne pojasnjuje zadostno razlik v počutju in teži simptomatike bolnikov s KOPB. Uporaba validiranih vprašalnikov, ki so namenjeni spremljanju kakovosti življenja, bi v tem pogledu pomembno izboljšala oceno invalidnosti naših bolnikov.

Literatura

1. Nicholas S. Hill Pulmonary Rehabilitation. Proc Am Thorac Soc 2006; 3:66–74.
2. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, et al. on behalf of theATS/ERS Pulmonary Rehabilitation Writing Committee. American Thoracic Society/European Respiratory Society Statement on Pulmonary Rehabilitation. Am J Respir Crit Care Med 2006; 173:1390–1413.
3. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988; 93:580–6.
4. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992; 145:1321–7.
5. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987; 42:773–8.
6. Singh SJ, Sodergren SC,Hyland ME, Williams J, Morgan MD. A comparison of three disease-specific and two generic health-status measures to evaluate the outcome of pulmonary rehabilitation in COPD. Respir Med 2001; 95: 71–7.
7. Cote CG, Celli BR. Pulmonary rehabilitation and the BODE index in COPD. Eur Respir J 2005; 26:630–6.
8. Goldstein RS, Gort EH, Stubbing D, Avendado MA, Guyatt GH. Randomised controlled trial of respiratory rehabilitation. Lancet 1994; 344:1394–7.
9. Reardon J, Awad E, Normandin E, Vale F, Clark B, ZuWallack RL. The effect of comprehensive outpatient pulmonary rehabilitation on dyspnea. Chest 1994; 105:1046–52.
10. Bendstrup K, Ingemann E, Jensen J, Holm S, Bengtsson B. Out-patient rehabilitation improves activities of daily living, quality of life and exercise tolerance in chronic obstructive pulmonary disease. Eur Respir J 1997; 10:2801–6.

Medikamentozno zdravljenje bolnika z napredovalo obliko KOPB

Škrgat Kristan S
Bolnišnica Golnik - Klinični oddelek za pljučne bolezni in alergijo, Slovenija

Kronično obstruktivno pljučno bolezen (KOPB) označuje ireverzibilna in napredujoča obstruktivna motnja ventilacije. Bolezen je pogosta in najpogosteje prizadene kadilce. Vsak kadilec, ki kašlja, še nima KOPB. Zboli okoli 20 % kadilcev.
Pri KOPB gre za prizadetost velikih in malih dihalnih poti, emfizem in prizadetost pljučnega žilja. Pri posameznih bolnikih so naštete patološke komponente zastopane v različni meri. Kljub dejstvu, da torej dejansko obstajajo različni fenotipi bolezni, pa za sedaj veljavne smernice težo bolezni opredeljujejo z vrednostjo FEV1.

Huda oblika KOPB: 30 % <FEV1>50%, IT<70%
Zelo huda oblika KOPB: FEV1 pod 30%,IT<70%
ali
FEV1 pod 50% s pridruženo respiracijsko insuficienco.

Povzeto po GOLD-u; IT - Index Tiffenau

ZDRAVLJENJE STABILNE OBLIKE KOPB

Bronhodilatatorji
Bronhodilatatorji so temelj zdravljenja KOPB. Mednje prištevamo beta$_2$-agoniste in antiholinergike. Zmanjšujejo dinamično hiperinflacijo pljuč in posledično izboljšajo toleranco za napor. Dolgodelujoča beta-agonista (LABA) salmeterol in formoterol delujeta 12 ur in ju predpisujemo v rednih razmakih. Dolgodelujoči antiholinergik tiotropij ima 24 urno delovanje in ga prav tako predpisujemo v rednih razmakih. Pri napredovali obliki bolezni lahko uporabljamo kombinacijo dolgo delujočih bronhodilatatorjev (npr. beta-agoniste in antiholinergike). Kratkodelujoče bronho-dilatatorje zraven predpišemo po potrebi. Njihov učinek izzveni v 4 - 6 urah.
Bolnike je potrebno že v ambulanti poučiti o pravilni tehniki prejemanja inhalacijskih zdravil. Ob kontrolah vedno obnavljamo znanje in zavzetost bolnika.

Dolgodelujoči bronhodilatatorji	**Kratkodelujoči bronhodilatarorji**
- formoterol	- salbutamol (1 vdih = 100 mcg)
- salmeterol	- fenoterol (1 vdih = 100 mcg)
- tiotropij	- fenoterol/ipratropijev bromid (1 vdih = *50 mcg fenoterolijevega bromida, 20 mcg ipratropijevega bromida)*

Inhalacijski glukokortikoidi

Uporaba inhalacijskih glukokortikoidov pri KOPB je omejena, ne predpisujemo jih v monoterapiji. Inhalacijske glukokortikoide predpisujemo v kombinaciji z dolgodelu- jočimi bronhodilatatorji takrat, ko ima bolnik FEV1 pod 50 % in dve poslabšanji KOPB na leto ali več. V kolikor so bolnikova poslabšanja bolezni redkejša, inhalacijskega glukokortikoida ne predpišemo.

Teofilini

Teofilini so zdravila drugega izbora zaradi svoje toksičnosti in ozkega terapevtskega okna.

Kisik

O indiciranosti za uvedbo trajnega zdravljenja s kisikom na domu (TZKD) sklepamo v stabilnem obdobju bolnikove bolezni.

Kriteriji za uvedbo TZKD so:

- parcialni tlak kisika v arterijski krvi (PaO_2) 7.3 kPa ali manj, z ali brez hiperkapnije
- PaO_2 med 7.3-8.0 kPa ob pridruženi pljučni hipertenziji ali pridruženi policitemiji (hematokrit nad 55%).

Bolniki naj prejemajo kisik vsaj 17 ur na dan. Kisik prejmajo preko koncentratorja, z letošnjim letom pa bolniki namesto koncentratorja lahko prejmejo tekoči kisik. Do slednjega so upravičeni v primeru, da bolniki v času ocene na shuttle testu s kisikom prehodijo 300 m. Preden bolnik prejme vir kisika je nujna plinska analiza arterijske krvi (na ustreznem pretoku O_2) zaradi kontrole celotnega acidobaznega statusa. Nekontroliranega povečevanja pretoka O_2 na bolnikovem viru kisika ne smemo izvajati. V primeru poslabšanja bolezni bolnika napotimo v ustanovo/ambulanto, ki ima možnost izvajanja plinske analize arterijske krvi.

Literatura

1. Global Initiative for Chronic Obstructive Lung Disease. NIH: www.goldcopd.com 2006.
2. Carpenter G, Bernabei R, Hirdes J. Building evidence on chronic disease in old age. BMJ 2003; 32: 528-9.
3. Freeman D, Nordyke RJ, Isonaka S, Nonikov DV, Maroni JM, Price D, et al. Question for COPD diagnostic screeningin a primary care setting. Respir Med 2005; 1311-8.
4. Škrgat Kristan S, Šifrer F, Kopčavar Guček N, Osolnik K, Eržen R, Fležar M, et al. Slovenske usmeritve za zdravljenje akutnega poslabšanja kronične obstruktivne pljučne bolezni (ap-KOPB) - v tisku.

Ambulantna obravnava akutnega poslabšanja KOPB

Šuškovič S
Bolnišnica Golnik – Klinični oddelek za pljučne bolezni in alergijo, Slovenija

Poslabšanje kronične obstruktivne pljučne bolezni (KOPB) je življenje ogrožajoč dogodek. Zgodnje zdravljenje poslabšanja KOPB to poslabšanje skrajša in omili. Poslabšanja KOPB povzročajo dodaten upad pljučne funkcije ter podaljšano okrnijo kakovost življenja bolnikov. Poslabšanja zdravimo z bronhodilatatorji, glukokortikoidi, antibiotiki ter kisikom.

Definicija poslabšanja KOPB
Poslabšanje kronične obstruktivne pljučne bolezni (pKOPB) razkrijemo ob - v primerjavi s stabilno fazo KOPB - pomembnem ojačanju **dispneje, kašlja in/ali izkašljevanja**. Bolniki lahko tudi navajajo piskanje nad prsmi, stiskanje v prsih ali so utrujeni in splošnega slabega počutja. Bolnikom se lahko poveča zapora dihal, poglobi respiracijska insuficienca in pojavijo se motnje srčnega ritma ali znaki popuščanja srca. Akutni rinitis je zelo pogosto prvi znak poslabšanja KOPB. To ne sme presenečati, saj je virusna okužba dihal daleč najpogostejši vzrok za pKOPB.
Pomembno: za diagnozo pKOPB ni potreben ali celo zadosten pogoj poslabšanje zapore dihal ali pojav (poglobitev) respiracijske insuficience. Diagnoza pKOPB je izključno klinična – na podlagi posebnih simptomov. Je pa obseg poslabšanja respiracijske insuficience eno od meril težavnosti pKOPB.

Potek poslabšanja
Bolniki mnoga poslabšanja – morda kar dve tretjini od njih - prebijejo brez zdravniške pomoči. pKOPB nastopi počasi (»neakutno« - ne v minutah ali urah), simptomi ali pljučna funkcija pa se povrnejo na izhodiščne vrednosti šele nekaj tednov po poslabšanju. Kakovost bolnikovega življenja je pomembno okrnjena še nekaj mesecev po eni sami epizodi pKOPB. Pogosta poslabšanja pospešijo naraven potek izgube pljučne funkcije ter povzročijo trajno okrnjenost kakovosti življenja. V pKOPB umre vsaj desetina bolnikov.

Ocena težavnosti poslabšanja
Anamneza: trajanje poslabšanja, število prejšnjih poslabšanj, komorbidnosti.
Telesni pregled: ocena vitalnih znakov, raba pomožne dihalne muskulature, poslabšanje ali nastanek centralne cianoze, nastanek perifernih edemov, hemodinamska nestabilnost, znaki srčnega popuščanja, zaspanost, otopelost (pomemben predznak dihalne odpovedi!).

Spirometrija. Načeloma je ne opravimo, ker so bolniki utrujeni in je zanesljivost meritev majhna. Ugotovki spirometrije v času pKOPB - za razliko od poslabšanja astme - ne vplivajo na odločitev o zdravljenju poslabšanja.
Pulzna oksimetrija in plini v arterijski krvi. PaO_2<8,0 kPa in /ali SaO_2<90% brez ali s $PaCO_2$>6,7 kPa je ob dihanju sobnega zraka znak za respiracijsko odpoved ter indikacija za zdravljenje s kisikom. Ob dodatni acidozi s pH<7.36 in hiperkapniji je bolnik akutno ogrožen, saj je možen kandidat za mehansko ventilacijo. Radiogram prsnega koša prikaže komorbidnosti kot so levostransko srčno popuščanje, pljučnico ali pnevmotoraks. EKG pripomore k diagnozi hipertrofije desnega prekata ali koronarne bolezni predvsem pa omogoči opredelitev ob telesnem pregledu zaznanih motenj srčnega ritma.

Etiologija poslabšanja
Domnevajo, da virusi povzročajo v 40%, po nekaterih ocenah celo v 65% pKOPB. Poglavitni so rinovirusi – zato se velik delež pKOPB prične z akutnim »prehladnim« rinitisom, ki naj bo svarilni znak počasi nastajajočega pKOPB. Nedvomno se pomemben delež pKOPB odvija s kombinirano virusno in bakterijsko okužbo. Po nekaterih ugoditvah je bakterijska okužba bronhijev morda vzrok za 40% - 50% pKOPB. Najpogostejši bakterijski povzročitelji pKOPB so *Streptococcus pneumoniae*, *Haemophilus influenzae* in *Moraxella catarrhalis*. Atipične bakterije (*Mycoplasma pneumoniae, Chlamydophila pneumoniae* ali *Legionella spp.* so le redko (verjetno <5%) vpletene v pKOPB. Prisotnost bakterij v izmečku je lahko le nasledek kolonizacije bronhijev, ki jo imajo mnogi bolniki s KOPB. Pri čemer so za pKOPB (ali vsaj za hujše oblike pKOPB) najverjetneje odgovorni le novi sevi teh bakterij. Vloga bakterij pri pKOPB ali pomen antibiotičnega zdravljenja pKOPB niso docela spoznani. Zato velja pri odločitvi za ali proti predpisu antibiotika še toliko bolj premisliti! Akutno onesnaženja zraka (smog) je sprožilec (lahko množičnih) poslabšanj KOPB. Simptomi GERD pogosto spremljajo pKOPB. Ni še znano v kolikšni meri GERD sodeluje v patogenezi pKOPB. Pljučnica, srčno popuščanje ali akutni pljučni embolizmi ne povzročajo pKOPB, zato pa poslabšujejo klinično sliko pKOPB.
Vnetje bronhijev v poslabšanju pKOPB je vselej nasledek povečanega vnetja bronhijev. Vnetje bronhijev v pKOPB ima elemente eozinofilnega vnetja. To morda razloži, zakaj so sistemski glukokortikodi za zdravljenje pKOPB uspešni, povsem brez učinka pa so pri stabilni KOPB.

Zdravljenje poslabšanja
Zgodnje zdravljenje pomeni bistveno izboljšan potek in prognozo pKOPB. Bolnike je treba poučiti o zgodnjih simptomih pKOPB. Pomen samoopazovanja in samo-zdravljenja pKOPB je sicer manj jasen kot je pri akutnem poslabšanju astme. Bolniki poučeni za samozdravljenje pKOPB lažje razkrijejo poslabšanje svoje bolezni in se pričnejo ustrezno in hitreje zdraviti z glukokortikoidom ali antibiotikom ali se (kar je priporočljivo) posvetujejo z zdravnikom, česar pogost, morda v kar dveh tretjinah pKOPB, ne naredijo.

Kisik
Dodajanje kisika vdihanemu zraku je potrebno ob respiracijski insuficienci. Pri tem je potrebno bolnika skrbno nadzorovati na 30 - 60 minut, kajti dejavnikov, po katerih bi lahko napovedali nastanek ali povečevanje hiperkapnije, ne poznamo. Če je bolnik trajno zdravljen s kisikom na domu, si ob poslabšanju KOPB ne sme sam povečati pretoka kisika na koncentratorju.

Bronhodilatatorji
Kratkodelujoča simpatikomimetika beta$_2$ (salbutamol ali fenoterol) sta osnovni in primerljivi zdravili pri pKOPB. Koristno ju je (enega od njiju, ne obeh hkrati) kombinirati s kratkodelujočim antiholinergikom ipratropijem. Kratkodelujoče bronho-dilatatorje predpišemo redno 2 - 4 vdihe na 4 - 6 ur. Ambulantno se le redkeje odločimo za večje odmerke bronhodilatatorjev.
Kratko delujoče bronhodilatatorje predpišemo le preko velikega nastavka. Zdravljenje z nebulizatorji je v primerjavi z aplikacijo bronhodilatorjev preko velikega nastavka kvečjemu enako učinkovito, je pa bolj zapleteno, nenatančno in povezano z mnogimi zapleti. Zato uporabe nebulizatorjev v ambulantnem zdravljenju pKOPB ne priporočamo.

Glede na predhodno terapijo ter stopnjo težavnosti KOPB (klasifikacija GOLD) dodamo morda že v času pKOPB, vsekakor pa v izzvenjevanju pKOPB enega od dolgodelujočih simpatikomimetikov beta$_2$ salmeterol ali formoterol in dolgo delujoči antiholinergik tiotropij.
Dolgodelujoči simpatikomimetiki beta$_2$ formoterol deluje v pKOPB sinergistično bronhodilatatorno z dolgodelujočim antiholinergikom tiotropijem .
Teofilin je nevarno in le malo koristno zdravilo ter je za ambulantno zdravljenje pKOPB nezaželjen. Številni dejavniki kot so respiracijska odpoved, srčno ali jetrno odpovedovanje, zdravljenje s kinolonskimi ali makrolidnimi antibiotiki utegnejo pomembno upočasniti metabolizem in povzročiti hude, tudi smrtne intoksikacije s teofilinom.

Antibiotiki
Za odločitev o zdravljenju z antibiotki je verjetno še vedno primerna klasifikacija pKOPB po Anthonisnu, ki je po prisotnosti »kardinalnih« simptomov pojačanja dispneje, povečanja količine izmečka in povečanja gnojnosti izmečka razdelil pKOPB v tri skupine: tip III - prisoten je le eden od treh simptomov, tip II - prisotna je katerakoli kombinacija dveh od naštetih treh simptomov in tip I - prisotni so vsi trije simptomi.
Za antibiotično zdravljenje se načeloma odločimo le ob tipu I pKOPB po Anthonisnu. pKOPB zdravimo ambulantno le z enostavnimi antibiotiki prvega reda: penicilinom, ampicilinom, amoksicilinom, tetraciklini ali kombinacijo sulfametoksazola s trimetoprimom. Ni dokazil o prednosti kakega izmed naštetih antibiotikov prvega reda niti o prednostih novejših široko spektralnih antibiotikov pred starejšimi, enostavnimi antibiotiki prvega reda. **Pomembno**: z neumestno rabo antibiotikov sprožamo nastanek odpornih sevov bakterij. Ob neuspehu zdravljenja (ob tem prvič opravimo antibiogram izmečka) ali ob poznavanju bakterijske odpornosti pri posameznem bolniku, posežemo po novejših antibiotikih. Novejše antibiotike (amoksicilin s klavulansko kislino, fluorokinolone ali cefalosporine II. ali III. generacije) primarno uporabimo le pri hospitaliziranih bolnikih z dejavniki tveganja za neugoden potek poslabšanja. Ambulantno predpisujemo antibiotike načeloma le per os. Trajanje antibiotičnega zdravljenja naj bo 3 - 7 dni (verjetno je za večino pKOPB 3 dni dovolj).

Glukokortikoidi
Glukokortikoidi skrajšajo in omilijo potek pKOPB ter morda potencirajo učinkovitost antibiotikov. Običajni odmerek glukokortikoida je 16 - 32 mg metilprednizolona 7 - 10 dni. Glukokortikoide predpišemo per os. Ambulantno predpišemo glukokortikoid le pri bolnikih s predhodnim bazičnim FEV1<50% norme (težka ali zelo težka KOPB po klasifikaciji GOLD). Ob kontraindikacijah za glukokortikoide (nestabilni diabetes, itd) od njih bistveno hitreje odstopimo, kot pri akutnem poslabšanje astme.

Napotitev v bolnišnico
Za bolnišnično zdravljenje pKOPB se odločimo ob nenadni zelo hudi dispneji (posebej ob dispneji v mirovanju), novi respiracijski insuficienci ali poslabšanju le-te, znakih popuščanja desnega srca, pomembnih komorbidnostih, novih motnjah srčnega ritma ali ob neuspehu začetnega, ambulantnega zdavljenja pKOPB.

Literatura

1. Global Initiative for Chronic Obstructive Lung Disease. NIH: www.goldcopd.com 2008.
2. O'Donnell DE, Shawn A, Bourbeau J, Hernandez P, Marciniuk D, Balter M, et al. State of the art compendium: Canadian Thoracic Society recommendations for the management of chronic obstructive pulmonary disease. Can Respir J 2004: 11(Suppl B):39-43B.
3. Currie GP, Wedzicha JA. Acute exacerbation. BMJ 2006; 333:87-89.
4. Vestbo J. Clinical assessment, staging, and epidemiology of chronic obstructive pulmonary disease exacerbations. Proc Am Thorac Soc. 2006; 3:252-6.

Zdravljenje s kisikom

Šifrer F
Bolnišnica Golnik – klinični oddelek za pljučne bolezni in alergijo, Slovenija

Izvleček. Pri akutni dispneji ni razloga za aplikacijo kisika, če je zasičenost hemoglobina s kisikom nad 92%. Visoki pretoki kisika imajo škodljive fiziološke učinke in povzročajo zakasnitev prepoznavanja slabšanja kliničnega stanja. Kisik je diferentno zdravilo. Predpisan mora biti v opredeljeni količini ali koncentraciji. Potrebno je nadzorovati odgovor na zdravljenje s kisikom

Abstract. In acutely breathless patient oxygen saturation is measured by oxymetry. If the oxygen saturation is above 92%, oxygen therapy need not be routinely administered. High flow oxygen has adverse physiological effects and potential for delay in the recognition of a deteriorating clinical condition. Oxygen is a drug that should be prescribed for defined indications in which the benefits outweigh the risks, and prescriptions should specify the dose, method and duration of oxygen delivery. The patient's response to oxygen therapy should be monitored.

Ob predpisovanju kisika moramo pretehtati koristi pred škodljivimi učinki. Visoki pretoki kisika namreč poslabšajo ujemanje ventilacije s perfuzijo, povzročajo absorbcijske atelektaze, povečujejo intrapulmonalni šant in zavirajo refleksno pljučno hipoksično vazokonstrikcijo. Visoki pretoki kisika povečujejo sistemski žilni upor in s tem krvni tlak, znižujejo koronarni pretok, pretok krvi skozi možgansko žilje in ledvice (1).

Če oksimetrija pokaže zasičenost hemoglobina s kisikom pod 92% je potrebno napraviti plinsko analizo arterijske krvi. Z njo ugotovimo stopnjo hipoksemije, prisotnost hiperkapnije in opredelimo acidobazno stanje. Z izračunom alveolo - arterijskega gradienta za kisik ugotovimo, če je v prisotnosti hiperkapnije hipoksemija posledica izvenpljučnih razlogov (normalen gradient) ali pljučne bolezni (povečan gradient). Dispnoičen bolnik ni nujno tudi hipoksemičen. Pri bolnikih z boleznimi dihalnih poti ni hipoksemija razlog dispneje pač pa povečano dihalno delo zaradi ujetja zraka v pljučih. Tudi pri boleznih pljučnega parenhima (pljučnica) in levostranskem srčnem popuščanju je etiološko pravilneje popravljati hipoksemijo in dispnejo z dihanjem s stalnim pozitivnim tlakom v dihalnih poteh (CPAP). Če je vzrok hipoksemije hiperkapnija, je hipoksemijo potrebno odpravljati z izboljšanjem ventilacije z zdravili (npr. z bronhodilatatorji pri obstruktivnih boleznih pljuč) ali z mehanično ventilacijo .

Dodajanje kisika je smiselno, varno, potrebno in uspešno le ob znižanem delnem tlaku kisika pod 8 kPa oziroma kadar je zasičenost hemoglobina s kisikom pod 90%. Če kisik dodajamo nenadzorovano (visoki pretoki ali velike inspiratorne koncentracije) povzročamo hiperoksijo (izmerimo 100 % za-

sičenost hemoglobina s kisikom), ki pomeni številne neželene fiziološke učinke. Paradoksno, dodajanje kisika, ki presega količino, ki je potrebna za odpravo hipoksemije, zmanjša porabo kisika v tkivih. Zaradi vseh teh neželenih učinkov ni varno predpisovati dodajanja kisika dispnoičnim bolnikom brez hipoksemije. Kisik dodajamo, kadar je zasičenost hemoglobina s kisikom pod 92%. Če je zasičenost hemoglobina s kisikom med 85 in 92% pričnemo z dodajanjem kisika po katetru 2 – 3 litre na minuto, kar bo verjetno dvignilo zasičenost hemoglobina s kisikom nad 92%. Izhodiščna zasičenost hemoglobina s kisikom pod 85% bo verjetno zahtevala večje pretoke kisika. Najvarneje je uporabiti maske z znano inspiratorno koncentracijo (2).

Bolniki z napredovalo kronično obstruktivno boleznijo pljuč (KOPB) imajo pogosto znižano vsebnost kisika v krvi. Sprva se hipoksemija pojavlja le v obdobjih akutnih poslabšanj, sčasoma pa je prisotna stalno že v mirovanju ali pa le ponoči in ob telesni aktivnosti.

Dolgotrajno zdravljenje s kisikom je opredeljeno kot dodajanje kisika vdihanemu zraku več kot mesec dni. Če to zdravljenje poteka izven bolnišnice, ga imenujemo trajno zdravljenje s kisikom na domu (TZKD). Sicer je značilnost KOPB, da postajajo poslabšanja bolezni s časom vse težja, dolgotrajnejša in s slabšim funkcionalnim stanjem po stabilizaciji bolezni, tako da je večkrat potrebno celo več tednov, da hipoksemija, ki je nastala zaradi poslabšanja in še ni odraz napredovalosti bolezni, izzveni.

TZKD je edini terapevtski ukrep, ki podaljša preživetje in izboljša kakovost življenja bolnikom s KOPB. To velja le za tiste bolnike, ki imajo že v mirovanju in budnem stanju stalno delni tlak kisika v arterijski krvi pod 7,3 kPa. Študija NOTT iz leta 1981 je dokazala, da kontinuirano vdihavanje dodatnega kisika v primerjavi z nočnim dodajanjem značilno izboljša 24 mesečno preživetje. Študija MRC (1981) je dokazala, da TZKD pomembno izboljša 5 letno preživetje v primerjavi s skupino bolnikov z napredovalo KOPB, ki kisika ni prejemala (3).

Druge študije so dokazale, da nočno dodajanje kisika bolnikom, ki so hipoksemični samo ponoči, ne vpliva na njihovo preživetje. Prav tako ni zaznati izboljšanja triletnega preživetja pri bolnikih z zmerno KOPB, ko delni tlak kisika ni pod 7,8 kPa in ni znakov kronične hipoksemije (policitemije, pljučne hipertenzije). Nekatere sicer kratko potekajoče študije dokazujejo, da prenosni viri kisika z izboljšanjem oksigenacije med aktivnostjo zmanjšajo dispnejo med naporom in izboljšajo telesno zmogljivost. Bolniki poročajo o izboljšanju počutja, razpoloženja in olajšanju dihanja. Mnoge moti navezanost na vir kisika, s tem dodatno zmanjšana mobilnost in socialna izolacija (4).

Bolniki s KOPB naj prejemajo toliko kisika, da bo delni tlak kisika v krvi med 8 in 8,5 kPa oziroma, da bo zasičenost hemoglobina s kisikom okrog 90%. Odziv na kisik je potrebno preveriti z analizo dihalnih plinov v arterijski krvi, saj nas poleg tlaka kisika zanima tudi sprememba tlaka ogljikovega dioksida po dodatku kisika in acidobazno ravnovesje. Za zadostno oksigenacijo običajno zadoščajo nizki pretoki dodanega kisika po nosnih katetrih (1 do 3 litre na minuto). Za uspešnost TZKD je pomembno, da bolniki vdihujejo dodatni kisik večino ur dneva. Potrebno je preveriti, ali ponoči in ob aktivnostih potrebujejo povečanje pretoka kisika. Bolnikom in svojcem moramo dopovedati, da v poslabšanju bolezni ne smejo nenadzorovano spreminjati pretoka kisika. Tudi zdravstveno osebje naj razume, da v poslabšanju KOPB bolnika ogroža hiperkapnija s posledično respiracijsko acidozo, ki sta nastala zaradi odpovedovanja ventilacije zaradi povečanega dihalnega dela ob hiperinflaciji pljuč. Seveda vsaka hiperkapnija povzroči tudi poslabšanje hipoksemije. V taki situaciji se izognemo nenadzorovanosti oksigenoterapije z uporabo mask, ki omogočajo dodajanje kisika v vnaprej določeni stalni inspiratorni koncentraciji. Začnemo z masko, ki daje 28% kisik in nato na nekaj minut menjavamo nastavke, ki večajo inspiratorno koncentracijo kisika, dokler ne dosežemo zasičenosti hemoglobina s kisikom med 85 in 90% (5, 6).

Literatura

1. Beasley R, Aldington S, Robinson G. Is it time to change the approach to oxygen therapy in the breathless patient? Thorax 2007; 62:840 -1.

2. Bateman NT, Leach RM. ABC of oxygen: acute oxygen therapy. BMJ 1998; 317: 798 – 801.
3. Fox BD. Oxygen therapy in the breathless patient. Thorax 2008; 63:476.
4. Albert P, Calverley PMA. Drugs (including oxygen) in severe COPD. Eur Respir J 2008; 31:1114 – 24.
5. Cranston JM, Crocket AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive disease. Cochrane Database Syst Rev 2005; (4):CD001744.
6. Nonoyama ML, et al. Oxygen therapy during exercise training in chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2007; (2):CD005372.

Links between rhinitis and asthma

Škrgat Kristan S
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

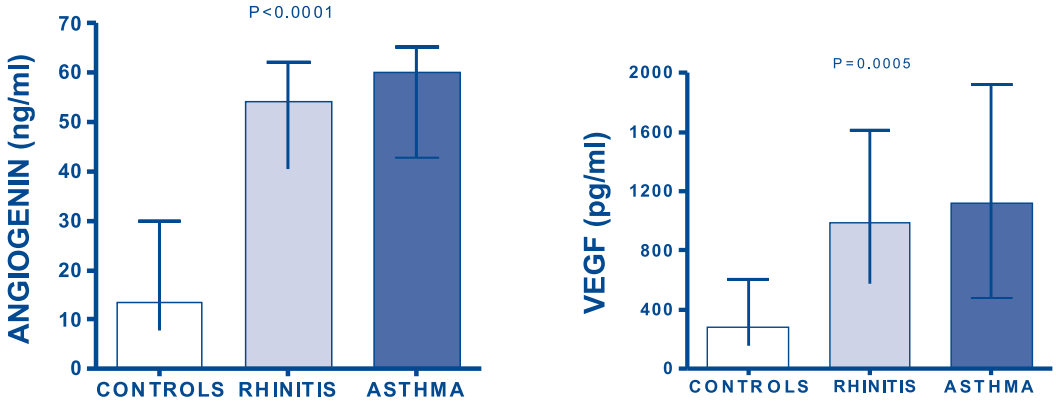
Background. Allergic rhinitis is characterized by an inflammatory infiltrate and the release of mediators responsible for the symptoms. The nasal airways and their closely-associated paranasal sinuses are an integral part of the respiratory tract The nasal and bronchial mucosa present similarities and one of the most important concepts regarding nose–lung interactions is the functional complementarity. Most patients with asthma have rhinitis suggesting the concept of one airway one disease. The presence of allergic rhinitis commonly exacerbates asthma, increasing the risk of asthma attacks, emergency visits and hospitalizations for asthma. However, not all patients with rhinitis have asthma and there are differences between rhinitis and asthma. Rhinitis is also a significant risk factor for adult-onset asthma in both atopic and non atopic subjects. It is not clear whether allergic rhinitis represents an earlier clinical manifestation of allergic disease in atopic subjects who will later go on to develop asthma or whether the nasal disease itself is causative for asthma. In allergic rhinitis, remodelling is still poorly understood. The stereological estimation of blood vessel surface (as a part of remodelling process) and volume densities was studied in human normal and rhinitic nasal mucosa. The volume and surface densities of the cavernous blood vessels in rhinitis were unaltered and there was no evidence of vascular remodelling. On the other hand, the hypervascularity and overexpression of the platelet-derived endothelial cell growth factor and Vascular Endothelial Growth Factor (VEGF), an angiogenic factor, were found in allergic nasal mucosa. Studies have therefore identified a temporal relationship between the onset of rhinitis and asthma, with rhinitis frequently preceding the development of asthma. In light of known temporal relationships between the onset of rhinitis and asthma, there is a lack of data about possible imbalance of major angiogenic factors in the airways of patients with rhinitis without concomitant asthma. Therefore we sought to determine whether the levels of angiogenin, VEGF, IL-8 (interleukin 8), bFGF (fibroblast growth factor), and TNF?-α (tumor necrosis factor-alfa), all known as angiogenic factors, are elevated in the induced sputum of patients with rhinitis without symptoms of asthma. The same angiogenic profile was determined in induced sputum of asthmatic patients who were well-controlled on their inhaled corticosteroid treatment.

Materials and Methods. We analyzed the induced sputum of 18 rhinitis patients, 16 asthmatic patients and 15 healthy controls. The concentrations of angiogenin, VEGF, IL-8, bFGF, and TNF-α were measured by cytometric bead array.

Results. We found significantly increased angiogenin and VEGF concentrations in the induced sputum supernatants of both rhinitis and asthma patients compared to the healthy control group

(P<0.0005). There was no difference in other angiogenic factors, except for TNF-α, which was higher in the rhinitis group in comparison to controls (P=0.02).

Figure 1A-B. Angiogenin A and VEGF B concentrations were significantly higher (P<0.0005; Kruskal-Wallis test) in the induced sputum of subjects with rhinitis (n=18) and controlled asthma (n=16) than in healthy controls (n=15).



Conclusions. The results showed that angiogenin and VEGF concentrations were significantly higher in rhinitis patents in comparison to healthy controls. Our data suggest that angiogenesis might be active in the lungs of patients with rhinitis without concomitant asthma. Furthermore, we also demonstrated significantly elevated VEGF and angiogenin concentrations in corticosteroid treated and well-controlled asthmatic patients. Our study supports the importance of airway angiogenesis in pathogenesis of rhinitis. It also supports continued investigation in VEGF and angiogenin for development of new treatments, which might affect airway remodelling.

References

1. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician–diagnosed allergic rhinitis in childhood. Paediatrics 1994; 94:895-901.
2. Bousquet J, Cauvenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001; 108 (Supp):148-334.
3. Togias A. Rhinitis and asthma: evidence for respiratory system integration. J Allergy Clin Immunol. 2003; 111:1171–83; quiz 84.
4. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. Allergy 2003; 58:691–706.
5. Bousquet J, Jacquot W, Vignola AM, Bachert C, Van Cauwenberge P. Allergic rhinitis: a disease remodeling the upper airways? J Allergy Clin Immunol 2004; 113:43–9.
6. Bachert C, Vignola AM, Gevaert P, Leynaert B, Van Cauwenberge P, Bousquet J. Allergic rhinitis, rhinosinusitis, and asthma: one airway disease. Immunol Allergy Clin North Am 2004; 24:19–43.
7. Salib R, Howarth P. Remodeling of the upper airways in allergic rhinitis: is it a feature of the disease? Clin Exp Allergy 2003; 33:1629–33.
8. Abrams DC, Toynton SC, Dore C, Emson MA, Taylor P, Springall DR, et al. Stereological estimation of blood vessel surface and volume densities in human normal and rhinitic nasal mucosa. Rhinology 1997; 35:22–7.
9. Watelet JB, Van Zele T, Gjomarkaj M, Canonica GW, Dahlen SE, Fokkens W, et al. Tissue remodeling in upper airways: where is the link with lower airway remodeling? Allergy 2006; 61:1249–58.
10. Mori S, Fujieda S, Kimura Y, Takahashi N, Saito H. Nasal challenge activates the mucociliary transport system on not only the ipsilateral but also the contralateral side of the nose in patients with perennial allergic rhinitis. ORL J Otorhinolaryngol Relat Spec 2000; 62:303–6.
11. Psarras S, Volonaki E, Skevaki CL, Xatzipsalti M, Bossios A, Pratsinis H, et al. Vascular endothelial growth factor-mediated induction of angiogenesis by human rhinoviruses. J Allergy Clin Immunol 2006; 117:291–7.

Organisation and emerging problems in antituberculosis activities in EU

Centis R, D'Ambrosio L, Migliori GB
WHO Collaborating Centre for TB and Lung Diseases, Fondazione Salvatore Maugeri, IRCCS, Tradate, Italy

Tuberculosis (TB) is a global problem and it is a continuing public health threat in Europe and worldwide.
The high incidence of TB and the high rate of multi-drug resistant TB (MDR-TB), mostly in the countries of the former Soviet Union, the appearance of extensive drug-resistant TB (XDR-TB), the rapid growth of the HIV epidemic in eastern Europe and, as a consequence the increase in HIV-related TB, the TB outbreaks in prisoners, the increasing mobility of people coupled with weak health systems represent the main challenges for TB control.

Epidemiology of TB in Europe
In 2006 there were 433,261 new cases of TB (5% of the new cases estimated at global level) and 62,197 TB-related deaths in Europe according to the World Health Organization (WHO) estimates, 75% of them located in eastern Europe (1). The estimated annual incidence rate of TB in the European Region was 49 cases per 100 000 population and the mortality rate was 7 per 100 000 population, with large variability between countries, increasing progressively when moving form West to East (from 5 new cases per 100 000 population per year in Norway to 198/100 000 in Tajikistan). Incidence in the Region's 18 high-priority countries for TB control (Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, the Republic of Moldova, Romania, the Russian Federation, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan) was comparable to rates in the developing world.
Three broad epidemiological patterns can be described in Europe:
1) **Low TB rates and mortality settings**. TB is increasingly prevalent in foreign-born populations and in groups affected by poverty and associated with low immunity status. Drug resistance is usually low, being higher in cases of foreign origin. HIV prevalence among TB patients vary from very low to medium-high level. These countries are mostly western European countries;
2) **High TB rates, high TB mortality settings**. The proportion of TB in patients of foreign origin is low with high levels of drug-resistance and increasing levels of HIV infection among TB patients. This pattern is mostly found in the Baltic States and in other previous Soviet Union (FSU) countries;
3) **Moderate to high TB rates settings**. TB incidence declined rapidly over the last 2 decades. TB cases among foreign origin, TB/HIV co-infection and drug resistance are uncommon.

These countries are central European states which joined the EU from 2004; several of them are bordering FSU countries.

Challenges to TB control

TB/HIV co-infection and MDR-TB are serious challenges to TB control. The estimated rates of MDR-TB in the 18 countries of eastern Europe are the highest in the world (2): MDR-TB was present in 15 to 20% of cases tested in 2005 in the Baltic States, but ranged from 0 to 6% in the rest of countries. With the expansion of the EU border eastward, the likelihood of imported MDR-TB to the EU is expected to increase. Moreover, XDR-TB has appeared in many countries particularly in eastern Europe, given the high incidence of MDR-TB and extensive use of second-line anti-TB drugs.

Strategy to control and eliminate TB in the Region

Reversing the TB epidemic in the Region requires higher political and financial commitment from governments: a) countries facing with the high burden of TB have to increase their national expenditure on rational strategies to address TB and its accompanying social conditions; b) countries of the Region and the European Union have to raise awareness to the TB emergency in the Region and to increase their financial contribution to TB control.

WHO is working to reduce the global burden of TB by 2015 in line with the Millennium Development Goals (MDGs) and the Stop TB Partnership targets in collaboration with the other partners. A comprehensive plan to control and eliminate TB in the Region was developed by the ECDC (3) and by the WHO European Region (4). The Europe Region of the UNION has collaborated with the European Respiratory Society (ERS) to revise and consults both plans. The Berlin High Level Ministerial Forum (December 2007) offered a unique opportunity to gather together donor and recipient countries to discuss the best strategy to finance and enhance coordination in the European response against the TB epidemic.

References

1. World Helath Organization. Global tuberculosis control: surveillance, planning, financing. WHO report 2008. WHO/HTM/TB/2008.393. Geneva, World Health Organization, 2008.
2. Zignol M, et al. Global incidence of multidrug-resistant tuberculosis. Journal of Infectious Diseases 2006; 194:479–85.
3. ECDC. Framework Action Plan to fight tuberculosis in the European Union. Available from http://www.ecdc.europa.eu/pdf/080317_TB_Action_plan.pdf
4. World Health Organization. Plan to stop TB in 18 high-priority countries in the WHO European Region 2007-2015. Copenhagen, WHO. Regional Office for Europe, 2007. Available from http://www.euro.who.int/document/e91049.pdf

Indication of new techniques in the diagnosis of tuberculosis

Rüsch-Gerdes S
Forschungszentrum Borstel, National Reference Center for Mycobacteria, Borstel, Germany

The increasing incidence of tuberculosis and other mycobacterial diseases has made it essential for laboratories to quickly detect and identify mycobacteria. The laboratory diagnosis of tuberculosis is currently based on acid-fast staining, culture, and direct nucleic-acid amplification techniques. All isolated mycobacteria should be differentiated immediately and drug susceptibility testing for all *M. tuberculosis* strains has to be performed.

All techniques used have to be performed in a well equipped laboratory and an internal and external quality control system has to be established.

Culture
Cultivation on solid media, such as Löwenstein-Jensen, is both, time-consuming (up to 4 weeks) and has low sensitivity. Introduction of liquid media has led to a considerable shortening of the time required for the detection of mycobacteria and has increased the sensitivity of isolation.

Nucleic-acid Amplification Techniques
Technologies involving Nucleic-acid Amplification Techniques (NAT) have provided an opportunity for more rapid diagnosis of tuberculosis. NAT have been studied extensively but there are concerns about lack of sensitivity for smear-negative specimens. Culture techniques are more sensitive and should be always performed additionally to NAT.

Differentiation
For identification of isolated mycobacteria, a lot of biochemical tests have been used, but these tests are time consuming and not all species can be differentiated by these methods. In the last years commercial molecular tests have been introduced for all species of the *M. tuberculosis* complex strains and for the most common non-tuberculous mycobacteria. All species can be identified within 1 day with hybridization by specific nucleotide probes bound on membrane strips.

Drug Susceptibility Testing
Drug resistant *M. tuberculosis* strains have been found in all countries surveyed worldwide. Based on this finding, drug susceptibility testing (DST) have to be performed for all isolated *M. tuberculosis* strains. Conventional DST can be performed on solid media, but at least 3 - 4 weeks of incuba-

tion are required to get the result. In liquid media results can be obtained in approx. 1 week. DST methods based on molecular tests have recently been developed for the detection of isoniazid and rifampicin, the two most important drugs in the treatment regimen.

Standards, methods and important circumstances influencing laboratory diagnostics of TB in Slovenia

Žolnir Dovč M, Eržen D
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

The preliminary diagnosis of tuberculosis (TB) is based on clinical and radiological findings, but the final diagnosis requires the isolation and identification of *Mycobacterium tuberculosis* complex from adequate specimens. In this regard, the fight against TB cannot be successful without a well functioning laboratory service. The WHO Laboratory Strengthening Task Force (LSTF) for TB control published recommended standards for modern TB laboratory services in Europe in 2006 (1).
The aim of our presentation is to show new LSTF standards for modern TB laboratory and to analyse the situation in Slovenian TB laboratories.

The most fundamental aspects of WHO LSTF recommendations are (1):
- each country should have an official national reference laboratory and TB laboratory network (recognised and financed by Ministry of Health) which is a part of a national TB program;
- all laboratories should be licensed to perform TB-related microbiological activity;
- adequate number of appropriately trained staff should work under appropriate biosafety conditions in laboratories;
- microscopy of appropriate specimens, bacteriological cultures (combination of liquid and solid media), drug susceptibility testing and identification of tubercle bacilli are still the cornerstones of TB diagnosis in modern laboratories;
- smear microscopy should be performed and reported within one working day from the arrival of specimens in the laboratory, culture and identification of *M. tuberculosis* from sputum and other specimens in 21 and 30 days, respectively ;
- drug susceptibility testing (DST) for first line drugs is recommended for all new TB cases by classical methods, DST using molecular methods is advisable (for rifampicin and isoniazid - sputum smear-positive cases only);
- clinicians should be informed of the results of all laboratory tests as soon as possible.

At the moment, there is no official National Reference Laboratory appointed by the Ministry of Health in Slovenia. Laboratory for Mycobacteria Golnik performs some tasks of the national reference laboratory, being an active link of Slovenian National TB Program. The most important tasks of Laboratory for Mycobacteria Golnik include control of laboratory work, training of staff from other TB laboratories and foreign countries, collection of laboratory data, education and advising to clinicians and laboratory staff. In Laboratory for Mycobacteria Golnik we perform more than 75% of smears

and TB cultures, all drug susceptibility tests, identification of mycobacteria and genotyping of all culture-positive patients in the country.
Three additional TB laboratories are performing microscopy and cultures only. All 4 laboratories are in the process of receiving a licence for performing laboratory activity. Only 2 of the 4 laboratories use fluorescent microscopy, liquid and solid media for all specimens, but they detected more than 94% of newly registered TB patients in our country in 2007. In all laboratories, microscopy is performed and reported within one working day and more than 90% of positive cultures were reported in 21 days (sputum) and 30 days (other specimens) in 2007. In the last years, Slovenia is one of the countries with the highest rate of culture-positive patients in the world (2). The biggest problems that the laboratories are faced with include lack and fluctuation of laboratory staff and work under inappropriate biosafety conditions.
DST for first line drugs was introduced in Slovenian routine work (for all new TB cases) on January 1st 1998. This might be one of the reasons for a very low proportion of drug resistant TB (1.5% in 2006) and only 1 case of MDR TB (registered in 2006) in the country (2). On the basis of these data and relatively low accuracy of molecular methods to determine isoniazid and rifampicin resistance, Slovenian TB team decided that there is no need to introduce molecular tests in routine DST at the moment.

In conclusion, the goal of WHO LSTF published recommendations is to harmonize TB laboratory services in Europe so that all laboratory procedures would be performed by appropriately trained staff, using standardised operating procedures in appropriately equipped and safe laboratories, against clear proficiency and quality standards. Slovenian TB laboratory services are performing well; however, there's still room for their improvement.

References

1. Drobniewski FA, Hoffner S, Ruesch-Gerdes S, Skender G, Thomsen V, WHO European Laboratory Strengthening Task Force. Recommended standards for modern laboratory services in Europe. Eur Respir J 2006; 28:903-9.
2. EuroTB (InVS/KNCV) and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2006. 2007:7-115.

Vpliv DOT na izid zdravljenja – kdo ga zasluži?

Zadnik B
Bolnišnica Golnik – Klinični oddelek za pljučne bolezni in alergijo, Slovenija

DOT (directly observed therapy) je strategija neposredno nadzorovanega zdravljenja, ki pomaga bolniku dokončati zdravljenje. Odkar se uporablja, se je standard zdravljenja močno izboljšal. Naloga DOT- a je zmanjšati število bolnikov, ki bi zdravljenje prekinili (tabela 1).

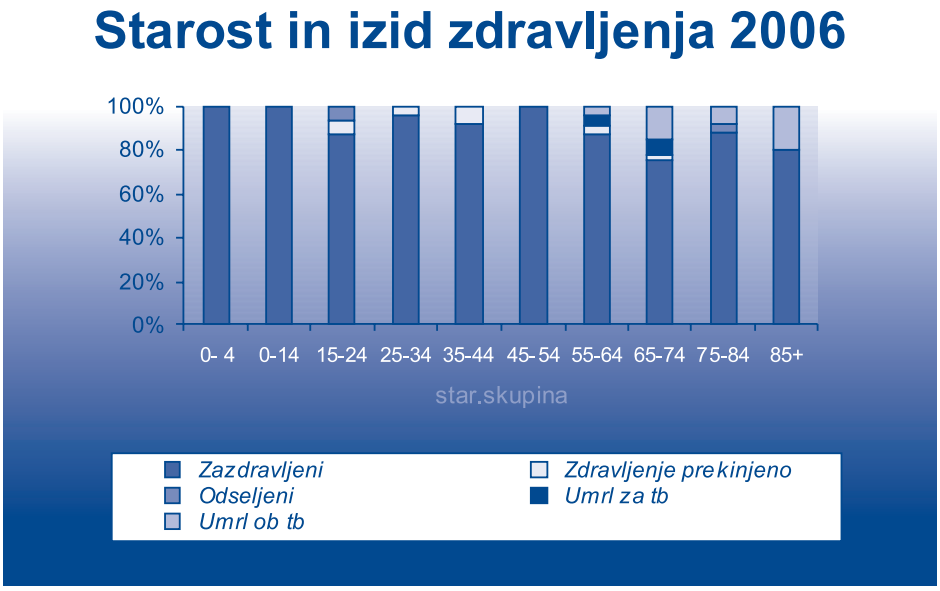


Tabela 1: Starost in izid zdravljenja bolnikov s TB v letu 2006

Prednosti nadzorovanega zdravljenja:
- ozdravitev in zaključek celotnega režima zdravljenja
- priložnost za opazovanje in odkrivanje težav
- pravočasno preprečevanje in reševanje zapletov
- zagotavlja prenehanje kužnosti

DOT je predviden in primeren za vse bolnike, ki se zdravijo z antituberkulotiki.
Posebej je priporočljiv za vse bolnike, ki pripadajo naslednjim rizičnim skupinam:

- bolniki z rezistetntimi oblikami TB
- bolniki, ki so zdravljenje prekinili
- bolniki, ki so zdravljeni z intermitentnim režimom
- alkoholiki
- brezdomci
- bolniki s psihiatričnimi obolenji
- starejši bolniki
- otroci in mladostniki

Naloge DOT- a
Poleg neposrednega nadzora jemanja zdravil je naloga samega DOT-a preskrba in priprava zdravil, preverjanje prisotnosti stranskih učinkov, dokumentiranje dogodka in izobraževanje bolnikov in njihovih svojcev.

Kdo in kje se DOT izvaja?
Nadzor lahko opravlja vsak zdravstveni delavec na oddelku za TB, osebje v ambulantah zdravstvenih domov ali druge odgovorne osebe v domovih za ostarele, metadonskih centrih, zavetiščih, šolah. Pomembno je, da se bolnik z nadzorom zdravstvenega osebja strinja. Družinski člani so za izvajanje nadzora manj primerni.

Pri izvajanju nadzorovanega zdravljenja zaznavamo naslednje težave:
- finančne omejitve
- čas
- obremenjenost osebja
- nesodelovanje bolnika in svojcev
- prisila

Leta 2005 se je z vsemi ukrepi porast TB, prvič v zgodovini ukrepov proti njej, zaustavil in pričenja se upad števila primerov. Pri tem lahko sodeluje vsak in v letu 2008 je bil dan TB posvečen prav posameznikom, ki s svojimi prizadevanji prispevajo k začetku zgodbe o uspehu ukrepov proti TB. Letošnji slogan partnerstva StopTB, ki združuje delovanje vseh organizacij proti TB v enotno svetovno kampanjo je »Zaustavljam tuberkulozo« (angl. I am stopping TB). To pomeni, da lahko vsak, ki je udeležen v ukrepih proti TB, bistveno prispeva k uspehu. Medicinske sestre lahko z zdravstveno vzgojo in izvajanjem DOT-a bistveno pripomoremo k preprečevanju širjenja in uspehu zdravljenja.

Literatura

1. Patient Adherence to Tuberculosis Treatment.V: CDC Self Study modules on Tuberculosis. Division of Tuberculosis Elimination, Atlanta Georgia. Oktober, 1999.
2. Weis SE, Slocum PC, Blais FX, e tal. The efect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. N Engl J Med 1994; 330(17);1179-1184.
3. 13. redni letni posvet o obravnavi in spremljanju bolnikov s tuberkulozo v Sloveniji, Zbornik predavanj, 2008
4. 12. redni letni posvet o obravnavi in spremljanju bolnikov s tuberkulozo v Sloveniji, Zbornik predavanj, 2007

How can health care workers protect themselves

Svetina Šorli P
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

TB is a contagious disease, which is transmitted via contagious airborne droplets. Hospital is a high-risk environment for a disease transmission from patient to patient or from patient to a hospital employee.
Risk of transmission in hospitals varies according to department orientation, prevalence of TB in local environment, referring patients, efficiecy of measures for transmission prevention and diagnostic procedures.
Main goal in transmission prevention is early diagnosis of active TB, which leads to effective isolation measures and proper pharmacological treatment. Proper decision-making should be in three steps. First and the most important is an administrative measure, which includes risk prediction and written protocols, implementation of good practice in everyday work, education, training and counseling to employees, screening among employees. Technological measures are the second step. Proper ventilation and HEPA filter directional flow are the measures to prevent spread of contagious aerosol particles and decrease their level in working environment. These measures should be done in rooms where patients with active TB are located.
Last step in line of TB spread prevention in health-care workers are personal preventive measures. Special facial masks (protective respirators) with 95% filtration of particles and less than 10% leak should be in use. Health-care workers must wear them always when they could be exposed to *M. tuberculosis* bacilli (patient's rooms, working process where contagious aerosols are produced – endoscopies, and other high-risk environment). Protective respirators should be used apropriately and during the whole time of possible exposure. They must be discarded at the end of the shift. Education must be provided throughout the year to ensure proper usage and alertness of health-care workers.
In search of circumstances leading to TB transmission besides medical documentation the use of novel methods of molecular genotyping is neccessary (RFLP). We use this method routinely since 2001 in all cases (prospective) and in cases of possible transmission in different circumstances (retrospective).

Obravnava in izobraževanje bolnika s tuberkulozo

Zadnik B
Bolnišnica Golnik – Klinični oddelek za pljučne bolezni in alergijo, Slovenija

Zdravstvena vzgoja je tisti pristop, ki osvešča, izobražuje in vzgaja ljudi za zdravo življenje. Pripravlja jih na pravočasno in pravilno ravnanje, ko se bolezen pojavi, da jo lahko sami ali s pomočjo strokovnjakov odpravijo in čim prej vzpostavijo prejšnje stanje ali se naučijo znova živeti v spremenjenih razmerah. Zdravstvena vzgoja je uspešna le tedaj, če ji sledi sprememba stališč in vedenja. Je potrebna in prisotna v celotnem življenju posameznika. Cilj zdravstvene vzgoje mora biti zdravstveno osveščen posameznik, saj le zdrav, produktiven in zadovoljen posameznik lahko veliko prispeva k svojemu in skupnemu razvoju.

Za zdravljenje tuberkujoze (TB) je zelo pomembno, da bolnik sodeluje pri zdravljenju, da spozna svojo bolezen in nevarnosti širjenja okužbe. Bolnik mora že na začetku zdravljenja spoznati vse zdravstveno vzgojne vsebine. Medicinska sestra te vsebine pri bolniku redno preverja in dopolnjuje.

Cilji zdravstvene zdravstvene vzgoje bolnikov s TB:
- bolnik bo poznal svojo bolezen
- poznal bo ukrepe za preprečevanje širjenja okužbe in jih tudi izvajal
- poznal bo zdravila in se zavedal pomena rednega jemanja zdravil
- pravilen način prehranjevanja
- ustrezen higienski režim
- ozdravitev

Zdravstvena vzgoja je:
- kontinuirana
- individualna
- skupinska
- prilagojena
- načrtovana
- dokumentirana
- ustna in pisna oblika

Vsebine:
- kaj je tuberkuloza - okužba, bolezen, bolezenski znaki, dokazovanje bolezni, izmeček

- ukrepi za preprečevanje prenosa okužbe: higiena izkašljevanja, prezračevanje, uporaba maske, baktericidna svetilka
- poznavanje zdravil, pomen rednega jemanja
- pomen zdrave prehrane
- vpliv kajenja in alkohola
- nadzorovano zdravljenje
- življenje v domačem okolju

Zdravstvena vzgoja je ena pomembnejših nalog medicinske sestre pri obravnavi bolnika s TB. Bolnik si z znanjem pridobi večjo samostojnost, krepi si samozavest in občutek varnosti.

Kakovostna zdravstvena vzgoja bolnika s TB pripomore k njegovi večji ozaveščenosti in samooskrbi. Izid zdravljenja in rehabilitacija ter povrnitev v domače okolje so boljši. S poznavanjem bolezni se pri bolniku zmanjša nevarnost nastanka rezistentne oblike TB in njenih posledic. Z dobro zdravstveno vzgojo bolnika in njegovih svojcev, pa se zmanjša možnost širjenja okužbe.

Literatura

1. Prestor L. 1. Šola za obravnavo bolnikov s tuberkulozo in pregledovanje kontaktov, Zbornik predavanj, Bolnišnica Golnik KOPA, 2006.
2. Bavdek R. in sod. Obravnava bolnika s TB: prijava, socialna obravnava, vzgoja, nadzor pri prejemanju zdravil, kontakti.V. zbornik prispevkov 11. rednega posveta o obravnavi in spremljanju bolnikov s TB v Sloveniji, Ljubljana Bolnišnica Golnik KOPA, 2006.
3. Bratkovič M. Uspešnost zdravstveno vzgojnega dela pri bolnikih s TB v Bolnišnici Golnik-KOPA, Diplomsko delo. Ljubljana: Visoka šola za zdravstvo 2005.
4. Hoyer S. Zdravstvena vzgoja in zdravstvena prosveta. Ljubljana. Tehnična založba Slovenije, 1995
5. The global plan to stop TB 2006-2015, Geneva, WHO 2006.

Relationship of the prevalence rate of allergic diseases and skin sensitivity to aeroallergens, with living conditions in two Croatian regions

Stipić Marković A
Department of Clinical Immunology, Pulmology and Rheumatology, General Hospital «Sveti Duh», Zagreb, Croatia

Background. Epidemiological investigations have shown differences of 20-fold, 30-fold, and 60-fold in the prevalence of symptoms of asthma, allergic rhinoconjuctivitis and atopic eczema dermatitis syndorme, respectively, between countries worldwide. We report prevalence of the allergy symptoms in children, living in the coastal and the continental regions of Croatia. Percentage of children in continental region with skin sensitivity to inhalant allergens is also shown. In adults, the trend in atopy markers (elevated total IgE, positive skin prick test to commom aeroallergens, clinical symptoms), during last fifteen years is reported. The differences in mite fauna between inland and coastal Croatia is discussed.

Materials and Methods. Seven epidemiological prevalence studies in children, from 1978 to 2001, were compared. Last two studies were done according to ISAAC methodology. Skin sensitivity was assesed by skin prick test with inhalant allergens (Allergopharma and Imunološki zavod Zagreb, Croatia). IgE was done by CAP RAST methodology (Pharmacia, Uppsala, Sweden).

Results. The studies comparing prevalences of allergic asthma in paediatric population showed continuous rise of 1,3%, 2,8%, 5,9%, 6,02%, 8,4% from 1978 to 2001, respectively. Allergic rhinitis is rising from 2,94% to 12,13% and 17,50 from year 1993 to 2002, respectively. Prevalence in continental region of the country is slightly lower than in coastal region. In continental region, higher prevalence is found in boys, in children attending kindergarten but not day care, children with *Bordetella pertussis* infection, children exposed to molds and tobacco during intrauterine life. Lower prevalence of allergy is found in children with parasitic infections and children with pertussis vaccination. The percentage of positive skin reactivity to aeroallergens, in children from continental region is higher than the prevalence of symptoms (52,34% positive SPT). High percentage (51.74%) of children with positive SPT were sensitized to three or more allergens, 29.35% of children with positive SPT were sensitized to only one allergen and 18.90% of children with positive SPT were positive to two allergens. Dermatophagoides pteronyssinus is the most common allergen (56.2%), followed by grass pollen (40.3%). In adults, investigation from year 1985 to 1999 showed the increasing trend in elevated IgE and allergy symptoms in male but not in female population. Analyzing floor house dust samples collected from coastal, inland rural and inland urban areas, regional differences in mite fauna were found. The highest Der p1 median levels were found in urban area. Der f1 is higher in households with central heating. Regarding the occupational environments, D. pteronyssinus should be consid-

ered as work-related allergen for fishermen. Cockroach allergen was positive in 9.6% of 187 adults from inland areas of Croatia, dominantly due to cross-ractivity to storage mites.

Conclusions. Allergic diseases in children in Croatia are rising in correlation with male sex, attending kindergarten without day care, and exposure to molds and tobacco in pregnancy. Dominant sensitizer is Der p allergen. In adults, positive trend is noticed only in male subjects.

Mechanisms of immunotherapy

Zidarn M
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Specific allergen immunotherapy has been shown to be effective for venom anaphylaxis and for rhinoconjunctivitis and asthma caused by inhalant allergens. Historically it was first thought that immunotherapy induces its effect by reducing IgE response and increasing allergen specific IgG concentrations. But it has later been shown that there is no association between clinical improvement and changes in antibody levels. In 1993 the role of shifting T cell response towards Th1 cytokine synthesis was first described by Varney et al. Role of effector cells especially mast cells and basophils has not been studied extensively.
Nowadays it is considered that allergen-specific immunotherapy induces its effects on at least three levels; changes in serum antibody response, altered T lymphocyte response and changes in the response of effector cells such as eosinophils, basophils and mast cells.

Immunotherapy is accompanied by increase in serum allergen-specific IgG1, IgG4 and IgA. IgG4 isotype blocks IgE mediated antigen presentation to T cells and IgE dependent histamin release from basophils. But there is weak correlation between IgG concentration and clinical response to treatment. Especially immunotherapy with rush protocol is also effective long before any changes in antibody synthesis are detected. But Michils et al. showed that there is a change in fine specifity of IgG antibodies that is apparent within the first few hours of ultrarush immunotherapy. Showing that activity of allergen-specific IgG is probably important. IgG4 also have antiinflamatory characteristics.

Immunotherapy acts on T cells to modify peripheral and mucosal Th2 response to allergen in favor of Th1 response. Especially local immune modulation is necessary for clinically successful immunothrapy. Regulatory Tcells produce IL-10 that suppresses mast cell, eosinophil and T cell response. It also acts on B cells to favor heavy chain class switching to IgG4. Expression of IL-10 is allergen driven and immunotherapy dependant. It is speculated that IL-10 restores a tolerant T cell response as seen in healthy individuals. Recently it has been shown that Foxp3-expressing $CD4^+CD25^+$ are induced in nasal mucosa of grass-pollen immunotherapy treated patients which further support the role of T reg cells in the induction of allergen-specific tolerance. Interesting is the role of dendritic cells in the induction of IL-10 secreting T regulatory cells. Another possible mechanism might be altered chemokine receptor expression on T cells as it was shown by Francis et al. They found CXCR1 expression on $CD4^+$ was low or absent in patients receiving immunotherapy, when compared with symptomatic patients.

Important changes are also observed on the level of effector cells. Allergen induced mast cell transepithelial migration is reduced following immunotherapy. Release of mast cell mediators is suppressed. Early effects of immunotherapy are related to mast cell and basophil desensitization. Most patients are protected against bee stings at an early stage of venom immunotherapy. An early decrease in mast cell and basophil activity for degranulation is observed. The mechanism of this desensitization effect is jet unknown. Mediators of anaphylaxis are released during immunotherpay without inducing systemic anaphylaxis. This piecemeal release may decrease the granule content of mediators and may affect the threshold of activation of mast cells and basophils.
Basophil activation test is a new method that allows flow cytometric quantification of the expression of the markers on basophil surface. CD 63 is a marker of basophil activation after allergen or non-specific stimulus. It can be used for predicting side effects of immunotherapy. Kosnik et al. showed that high sensitivity of basophils predicts side-effects in venom hypersensitivity. Sensitivity of basophils was defined as the ratio between CD 63 expression on the plateau of the dose response curve and a value on the steep part of the same curve. Recent study has shown that basophil response is higher in patients with venom immunotherapy failure. It was suggested that decreased basophil responsiveness is important for successful venom immunotherapy treatment.

References

1. Till SJ, Francis JN, Nouri-Aria K, Durham SR. Mechanisms of immunotherapy. J Allergy Clin Immunol 2004; 113:1025-34.
2. Akdis M, Akdis C. Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol 2007; 119:780-9.
3. Kosnik M, Silar M, Bajrovic N, Music E, Korosec P. High sensitivity of basophils predicts side-effects in venom immunotherapy. Allergy 2005; 60:140-6.
4. Peternelj A, Silar M, Erzen R, Kosnik M, Korosec P. Basophil sensitivity in patients not responding to venom immunotherapy. Int Arch Allergy Immunol 2008; 146:248-54.

Mechanism of basophil desensitization

Korošec P
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Our recent approach was directed to evaluate basophil sensitivity to allergen-specific *in vitro* stimulation (1). Therefore, we calculated the ratio of basophil CD63 expression between a value on the plateau and a value on the steep part of the curve. The ratio between those two selected log allergen concentrations (in our method 0.1 and 1 µg/ml, i.e. 0.1/1 sensitivity ratio) was representing the shift of the increasing dose-dependent basophil activation curve (median response at 0.1 was 50% of the response at 1). Of course, even more accurate approaches to measuring basophil sensitivity to the allergen exist, like concentrations giving 50% of maximum CD63 upregulation, as described in the article by Nopp et al. (2). Another possibility is to expand dose response curve with at least 4 log allergen concentrations and compare the responses between different sub-maximal concentrations (3). Nevertheless, MacGlashan showed that basophil sensitivity is an independent intrinsic property which does not correlate with maximal response (4). Therefore, sensitivity measured by a basophil activation test should be specifically evaluated for each clinical and/or research application and allergen (5).

Our group was the first one that evaluated basophil sensitivity in patients before receiving venom immunotherapy for possible predicting of the adverse reactions (1). The results showed that increased basophil sensitivity is associated with major side effects during venom immunotherapy (VIT) and that monitoring of CD63 concentration-dependent venom response could be a relevant tool for identification of patients at higher risk for side effects. Moreover, we also demonstrated a significant positive correlation between individual sensitivity ratio and clinical severity of side reactions. Second, we also evaluated basophile responsiveness in patients with completed venom immunotherapy and subsequent histories of field re-sting reactions (6). The results of this study suggest that higher basophil venom specific sensitivity is associated with the VIT treatment failure and that the dose response dependent basophil activation test might be a helpful tool for identification of patients at higher risk for systemic allergic reactions after completed VIT. Very recently we showed that specific basophil CD63 responsiveness is also changing markedly during birch pollen immunotherapy (3). Moreover in this study we also showed that functional IgG4 antibodies might be involved in basophil desensitization during birch pollen immunotherapy. All this results suggest two possible outputs. First, it seems that basophil and/or mast cell allergen specific sensitivity might be an important link between IgE sensitization and allergic diseases, as we know that around one third of individuals with allergen-specific IgE do not develop symptoms. Second, it seems that immunotherapy induces allergen specific cellular (basophils and/or mast cells) desensitization. We think that in pollen immunotherapy this desensitization might be largely connected with functional IgG4 antibodies, and in

venom immunotherapy desensitization is likely to be linked with remodelling of intracellular signalling pathways and/or regulatory T cells response.

References

1. Kosnik M, Silar M, Bajrovic N, Music E, Korosec P. High sensitivity of basophils predicts side-effects in venom immunotherapy. Allergy. 2005; 60:1401-6.
2. Nopp A, Johansson SGO, Ankerst J, Bylin G, Cardell LO, Grönneberg R,, et al. Basophil allergen threshold sensitivity: a useful approach to anti-IgE treatment efficacy evaluation. Allergy 2006; 61: 298–302.
3. Silar M, Lalek N, Erzen R, Kosnik M, Korosec P. Basophil responsiveness during birch pollen immunotherapy Allergy 2008; 63(Suppl 88):191.
4. MacGlashan D, Jr. Releasability of human basophils: cellular sensitivity and maximal histamine release are independent variables. J Allergy Clin Immunol. 1993; 91:605-15.
5. Peternelj A, Silar M, Erzen R, Kosnik M, Korosec P. Basophil sensitivity in patients not responding to venom immunotherapy. Int Arch Allergy Immunol. 2008; 146:248-54. Epub 2008 Feb 13.
6. Korosec P, Kosnik M. Predicting side-effects in venom immunotherapy by basophil activation: basophil sensitivity vs. maximal response. Allergy 2007; 62:81.

Double sensitization in venom allergy

Eržen R, Mušič E, Korošec P, Šilar M, Košnik M
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Double sensitivity (presence of sIgE to honey bee and wasp venoms) is a frequently encountered diagnostic and therapeutic problem in patients with stinging insect allergy. True double sensitization or cross-reactivity must be considered and diagnosed in this group of patients. Cross-reactivity through venom hyaluronidases or carbohydrate epitopes is possible. Identification of double sensitization or cross-reactivity is crucial for the choice of an appropriate allergen in order to perform specific immunotherapy. It should be emphasized that specific immunotherapy is efficient only when performed with the allergen which caused sensitization.

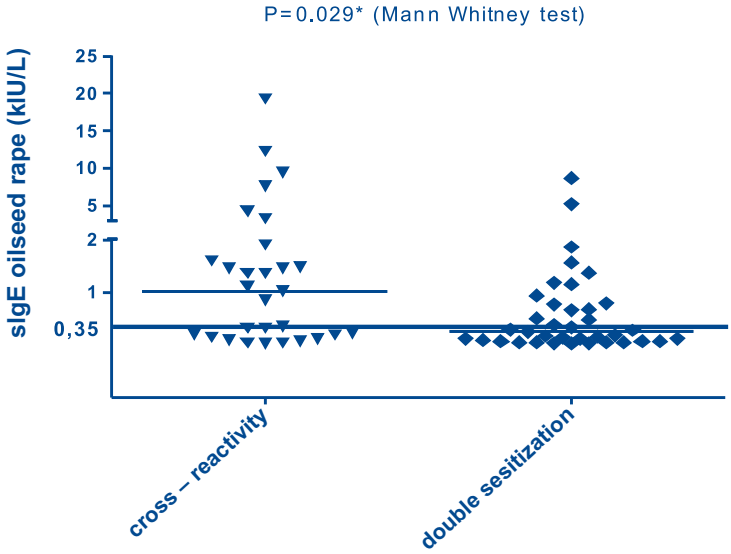
Materials and Methods. In our analysis, evaluation of the role of inhibition tests in the diagnostic procedure of Hymenoptera venom hypersensitivity was performed. In addition, the role and frequency of carbohydrate epitopes were observed. A group of double sensitized patients admitted to our hospital from 2001 to 2007 was analysed. The presence of sIgE to honey bee and wasp venoms was confirmed with the FEIA test. The FEIA inhibition test was performed to diagnose true double sensitivity or cross-reactivity. The concentration of oilseed rape (Brassica napus) sIgE and MUXF3 sIgE was measured in the vast majority of patients. The comparison of both methods for the measuring of carbohydrate epitopes sIgE was carried out.

Results. One hundred and seven double sensitized patients were included in the analysis. The culprit insect was not recognized in 41% of patients. Anaphylaxis stage 3 and 4 after the insect sting experienced 86,9% of patients. Inhibition tests revealed double primary sensitization in 65,4% of patients and cross-reactivity in 34,6%. Concentration of oilseed rape sIgE was measured in 68 patients. In this group of patients inhibition tests revealed 56,1% double primary sensitization and 43,9% cross-reactivity. Median value of sIgE in double-sensitive and cross-reactive patients was significantly different ($p < 0,02$, Kruskal-Wallis test). Correlation between the two tests for measuring oilseed rape sIgE and MUXF3 sIgE was excellent, Spearman's correlation coefficient was 0,92.

Conclusions. In the group of cross-reactive patients with the known culprit insect, inhibition tests have shown excellent correlation with the anamnestic data. It can be concluded that inhibition tests are a persuasive diagnostic tool. They are particularly useful in double positive patients who experienced anaphylaxis after the sting of an unknown insect. Inhibition tests can't be performed when the concentration of sIgE for honeybee/wasp venom is too low. The values of carbohydrate epitopes

sIgE in a group of double sensitized patients were significantly lower than in a cross-reactive group with either honey bee or wasp venom primary sensitization. These results confirm that carbohydrate epitopes are a frequent cause for double sensitivity. Concentration of carbohydrate epitopes sIgE can be of great help in double-sensitized patients when inhibition tests can't be performed.

Figure: Concentration of oilseed rape sIgE in double sensitive and cross-reactive patients



Legend: Concentration of oilseed rape sIgE in double sensitive and cross-reactive patients (together with mediana) are shown in the figure. Median value of sIgE in double-sensitive and cross-reactive patients is significantly different (p=0.029, Mann Whitney test).

References

1. Straumann F, Bucher C, Wütrich B: Double sensitization to honeybee and wasp venom: immunotherapy with one or with both venoms? Value of FEIA inhibition for the identification of the cross-reacting IgE antibodies in double-sensitized patients to honeybee and wasp venom. Int Arch Allergy Immunol 2000; 123:268-74.
2. Malandain H. IgE reactive carbohydrate epitopes-classification, cross-reactivity and clinical impact. Eur Ann Allergy Clin Immunol 2005; 37:122-8.

Slovenian study of sublingual immunotherapy

Košnik M, Štalc B, Mušič E, Bajrović N, Eržen R, Zidarn M, Mesić M, Mežnar B, Kafol Šušteršič A, Hudoklin I, Lopert A, Kecelj P, Devčič B, Zalokar P
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Sublingual immunotherapy (SLIT) is a well accepted mode of immunotherapy for carefully selected patients with respiratory allergy. Clinical studies showed comparable efficacy to subcutaneous immunotherapy when performed in mono/oligosensitized patients. In all clinical trials SLIT was performed with a single allergen or a combination of two allergens in full dose of each allergen. In Slovenia subcutaneous immunotherapy (SCIT) was performed in only few hospital-based centers, and most of outpatient bound allergologists had no experience with the selection of patients for immunotherapy and the evaluation of the efficacy of immunotherapy. For that reason we introduced the SLIT in Slovenia in a form of a open multi-centre nonintervention study.

Materials and Methods. National Health Insurance Company reimburses SLIT for patients, who fulfill the predefined conditions and are confirmed by allergy counsel. Members of Slovenian Association of Allergology were invited to participate in the study. A brochure with a clinical pathway for SLIT was used to follow the treatment. The study started in October 2007, majority of the patients started with SLIT (Staloral, Stallergen, France) in January - March 2008.

Results. Ninety adult patients were recruited by 12 allergologists. Forty-three patients were treated at Golnik hospital and 47 by other allergologists. Indications for SLIT were allergic rhinitis (seasonal 70, perennial 21) and asthma (31). In 2 patients SLIT was started after SCIT discontinuation because of side effects. Majority of patients (73) were treated with a single allergen, 16 with a full dose of two allergens and 1 with a mixture of allergens. The clinical outcome after the first pollen season will be analyzed when the pollen season finishes. However, it should be born in mind, that the pollination season 2008 was very mild.

ALLERGEN	house dust mite	grasses	birch	hazel	ambrosia	**SUM**
MONOTHERAPY	16	31	17	1	8	**73**
COMBINATION WITH						
house dust mite	-	-	-	-	-	
grasses	3	-	-	-	-	**3**
birch	1	4	-	-	-	**5**
hazel	0	1	7	-	-	**8**
ambrosia	0	0	0	0	-	**0**
SUM	**20**	**36**	**24**	**1**	**8**	**89**

* 1 patient was treated with a combination of grass, birch and hazel pollen

Conclusions. SLIT was effectively introduced in accordance with evidence based medicine and European guidelines for immunotherapy (Allergy 2006; 61: Suppl 82).

The study was sponsored by EwoPharma, a representative of STALLERGEN, Paris, France.

Efficacy and safety of SIT administered by alternative routes

Panzner P
Department of Immunology and Allergology, Medical Faculty Hospital, Plzeò, Czech Republic

Over the last 20 years, interest in non-injection routes for allergen-specific immunotherapy has increased, especially in Europe. These routes (oral, nasal, bronchial) have the overall aim of improving both, safety and compliance. During the past years, particularly the oral route has become a promising way for administration of specific immunotherapy (SIT), sublingual route being the most evidenced one. In spite of this, various manufacturers of vaccines still recommend slightly different ways of oral administration.
Forty-one patients suffering from grass pollen allergy underwent specific immunotherapy with standardized allergen extract consisting of six grass pollens (H-Al per os) administered either sublingually or supralingually for one year. In order to investigate clinical and immunological changes induced by the administration of allergens via the oral mucosa, the double-blind, placebo-controlled, randomized design of the trial with 30 other patients enrolled in placebo groups was applied.
Specific immunotherapy with oral drops administered sublingually or supralingually was performed in the same way, keeping the drops under or on the tongue, respectively, for 1 - 2 min. before swallowing them; at the end of the trial the cumulative dose of the allergen was almost 20 times higher than that of the subcutaneous therapy with corresponding allergen preparation. Data about symptoms scores and drugs intake during grass pollen season, as well as skin reactivity, levels of specific IgG and IgE antibodies, before the study and after the study's completion, were obtained.
It was found that both routes of administration are effective according to subjective clinical parameters and drug consumption, with a highly significant reduction of symptoms and drug intake favoring sublingual administration where a reduction of more than 60% was achieved. Only sublingual active group showed a significant increase in Dactylis glomerata-specific IgG serum levels. Adverse effects were limited to a small number of generally mild local and/or systemic reactions. The results suggest that the administration of allergens via the oral mucosa is safe and clinically effective, favoring the sublingual rather than supralingual route.

Omalizumab: 1 year experience

Škrgat Kristan S
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Asthma is a disease that causes debilitating daily symptoms and possible acute exacerbation of symptoms. Symptoms lead patients to limited activity, absences from work and school, hospitalizations, visits to emergency department and reduced quality of life. IgE plays a central role in the pathophysiology of asthma (Fig. 1). The two essential phases in this pathophysiology are sensitization to allergen and clinical
expression of symptoms on reexposure to the sensitizing allergen. During sensitization, inhaled antigen (i.e., aeroallergen) is taken up by antigen-presenting dendritic cells lining the airways. The allergen is then processed and presented to
antigen specific T cells. In some persons, these T cells respond by producing cytokines that stimulate the development of IgE-producing B cells. The Fc portion of
circulating IgE then binds to high-affinity receptors (Fc RIs) present on the surfaces
of mast cells and basophils (1,2). On reexposure, the sensitizing allergen cross-links IgE molecules present on mast-cell and basophil surfaces. This initiates degranulation and the release of inflammatory mediators, including histamine, prostaglandins, leukotrienes, chemokines, and cytokines. These mediators precipitate an immediate acute-phase reaction, resulting in acute bronchospasm, expressed clinically as an episode of acute asthma. Continued expression of mediators enlists an inflammatory response designated the late-phase reaction, which causes persistent symptoms, airway hyperresponsiveness and bronchospasm.

Effect of Therapy with Omalizumab
Omalizumab (Xolair, Genentech) is a recombinant humanized IgG1 monoclonal anti-IgE antibody that binds to the IgE molecule at the same epitope on the Fc region that binds to Fc RI. Reduced binding of IgE to Fc RIs on mast cells and basophils inhibits degranulation and the release of inflammatory mediators. There is also marked down-regulation of Fc RIs. Reduced IgE binding to Fc RI on dendritic cells may reduce the ability of these cells to process antigen efficiently. Reduced IgE binding to Fc RII on B cells is thought to alter B-cell differentiation and the regulation of IgE synthesis. All these effects may contribute to the prevention of acute exacerbations of asthma.

Clinical Use
The role of omalizumab in the management of asthma has not yet been precisely defined. This therapy should be considered in patients with uncontrolled or partialy controlled asthma with demonstrated characteristics of:

- environmental control (i.e., the elimination or minimization of exposure to aeroallergens)
- pharmacologic control (i.e., the use of inhaled corticosteroids, leukotriene modifiers or both)
- absence of smoking
- asthma in a patient with atopy (positive skin tests with perennial allergens)
- total serum IgE between 30 in 700 IU/ml
- good patient compliance with treatment

In addition, evaluation for coexisting conditions such as allergic rhinitis, sinusitis, and gastroesophageal reflux disease may prove beneficial. Patients who are particularly likely to benefit from the use of omalizumab include those with evidence of sensitization to perennial aeroallergens who require high doses of inhaled corticosteroids that have a potential for adverse side effects, those with frequent exacerbations of asthma associated with unstable disease. Analyses of pooled data from published clinical trials have indicated that patients who had a response to omalizumab had a ratio of observed to expected forced expiratory volume in one second (FEV1) of less than 65%, were taking doses of inhaled corticosteroids equivalent to more than 800 g of beclomethasone dipropionate per day, and had had at least one visit to the emergency department in the past year (30,31). Patients requiring daily oral corticosteroids to control their asthma may be less likely to have a response to omalizumab. A total serum IgE level should be measured in all patients who are being considered for treatment with omalizumab, because the dose of omalizumab is determined on the basis of the IgE level and body weight.

Our experience

We have started with omalizumab treatment in October 2007. Those patients who had normal lung function were able to achieve that only by taking systemic corticosteroids. At the time of writing this report, we have 9 patients included in the treatment with omalizumab. One of them has not yet started with the treatment. In other 6 patients we have achieved better asthma control with lower number of exacerbations and/or lower level of systemic corticosteroid use and better quality of life. In patient No.2 we achieved a level of controlled asthma without systemic corticosteroids. Two other patients have not yet been on therapy for 16 weeks (the usual time to make a clinical decision to continue with treatment or not). We continue the therapy in 6 patients after 16 weeks because of a good clinical response.

Table 1. Clinical characteristics of 5 patients (example), treated with omalizumab at the University Clinic of Respiratory and Allergic Diseases Golnik.

Sex/years	FEV1	Atopy	Total serum IgE IU/ml	Treatment before omalizumab	Side effects
1. M/37	55%	Dust mite, cat	333	IGK+LABA, montelukast, metilprednizolon 4-8-4 mg	Itching
2. F/53	N	Dust mite	122	IGK+LABA, montelukast, metilprednizolon 8-0-8 mg	Itching of the tongue
3. F/56	77%	Dust mite, pollen grass	497	IGK+LABA, montelukast, metilprednizolon 8-0-8 mg	Headache (mild)
4. F/50	N	Dust mite,	231	IGK+LABA, montelukast, metilprednizolon 16-8-16 mg	0
5. Ž/36	N	Dust mite, pollen grass, dog	120	IGK+LABA, montelukast, metilprednizolon – more times/year	Not yet started

Response to Treatment

Response to treatment can take several weeks to become apparent. These data suggest that patients should be treated for at least 16 weeks before efficacy is assessed. After 16 weeks the clinician has to evaluate the clinical response to therapy:

- frequency of exacerbations
- lung function
- level of asthma control according to guidelines

Dosing may need to be adjusted in the event of substantial changes in body weight.

Conclusions

The clinical trials of omalizumab enrolled patients with precisely defined characteristics of asthma, including sensitivity to specific perennial aeroallergens (i.e., dust mites, cockroaches, and dog or cat dander). The role of omalizumab in patients with asthma who have allergies to other aeroallergens, such as molds or pollens, or who have negative allergy skin tests, has not been defined. It is also not clear to what extent omalizumab might be effective in patients with total serum IgE levels outside the trial ranges (30 to 700 IU per milliliter for patients 12 to 75 years of age). The efficacy and safety of omalizumab have not been established for durations of treatment that exceeds one year, and it is not known how long clinical effects may persist after the therapy is discontinued.

References

1. Strunk RC, Bloomberg GR. Omalizumab for asthma. N Engl J Med 2006; 354:2689-95.
2. Nopp A et al. CD-sens and clinical changes during withdrawal of Xolair after 6 years of treatment. Allergy 2007; 62:1175-81.
3. Djukanovic R, Wilson SJ, Kraft M, Jarjour NN, Steel M, Chung KF, et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. Am J Respir Crit Care Med 2004; 170:583-93.
4. Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. Chest 2004; 125:1378-86.
5. Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell FcepsilonRI expression. J Allergy Clin Immunol 2003; 112:1147-54.
6. Finn A, Gross G, van Bavel J, Lee T, Windom H, Everhard F, et al. Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. J Allergy Clin Immunol 2003; 111:278-84.
7. Corren J, Casale T, Deniz Y, Ashby M. Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. J Allergy Clin Immunol 2003; 111:87-90.
8. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001; 108:184-90.
9. Geha RS, Jabara HH, Brodeur SR. The regulation of immunoglobulin E classswitch recombination. Nat Rev Immunol 2003; 3:721-32.
10. Infuhr D, Crameri R, Lamers R, Achatz G. Molecular and cellular targets of anti-IgE antibodies. Allergy 2005; 60:977-85.

Overview of some important studies of chronic obstructive pulmonary disease published in 2008

Šuškovič S
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Epidemiology
Chronic obstructive pulmonary disease (COPD) is - in spite of many efforts to stop its main cause i.e. smoking - increasing in prevalence and mortality and is consequently clinically and economically among most important diseases. Diagnosis of COPD is performed quite simply. Still, COPD seems to be very difficult to diagnose, especially in milder forms. Study of Bednarek et al. confirmed this unhappy situation (1). He and his colleagues investigated the prevalence of COPD in a primary care setting. From 4730 patients registered in a single primary care practice, 1960 patients aged 40 years or more were included. COPD was diagnosed in 9.3% participants. Only 18.6% of these patients had previously been diagnosed with COPD; almost all of these patients had severe or very severe forms of COPD. Substantial number of newly detected patients were symptomatic and subsequently had to be treated. Very interesting finding of the study was that limiting study only to smokers would have reduced the number of COPD diagnoses by 26%. Therefore investigators confirmed that COPD is not at all a rare disease among non-smokers. A reminder for further epidemiological studies! The study also clearly pointed out, that quite probably many of our own registered patients had »hidden« COPD.

Pathogenesis
Pathogenesis of COPD is still poorly understood. Dendritic cells (DCs) are known as antigen-presenting cells. Bronchial mucosal dendritic cells perhaps regulate immune response to inhaled antigens, viruses and bacteria also in COPD patients. Study performed by Rogers et al. partially clarified this intriguing question (2). Authors compared DC numbers in smokers and ex-smokers with COPD. Endobronchial biopsies were obtained from 15 patients with moderate to severe COPD and 11 non-smoker healthy controls. DC numbers were significantly lower in current smokers with COPD compared with ex-smokers with COPD. DC numbers in ex-smokers with COPD were similar to those in healthy controls. It is possible that cigarette smoking by inhibiting of DC function is (also) responsible for progression of COPD.
Emphysematous lung contain predominantly T helper type 1 (Th1) cells. It is not known how tobacco products induce this immunity. The study performed by Lee et al. explored the hypothesis that smoking induces an autoimmune response (3). Blood CD4+ T cells from patients with emphysema and controls were tested to a specific response to lung-derived elastin or collagen peptides in function as antigens. In response to elastin peptides, only peripheral blood CD4+ T cells from individuals with emphysema (n = 36) released interferon c (IFNc) and interleukin-10 (IL-10) and proliferated,

compared with controls (n = 27) and patients with asthma (n = 9). There was a significant association between the increase in T cell secretion of IFNc and IL-10 with disease severity (assessed by CT-based quantification and pulmonary function testing). The authors speculated that exposure to cigarette smoke induces secretion of proteolytic enzymes from cells of the innate immune system that liberate lung elastin fragments. In some individuals this may initiate T and B cell-mediated autoimmunity against elastin.
The study performed by Feghali et al. confirmed previously mentioned findings (4). The prevalence of anti–epithelial cell auto antibodies in 47 smokers/former smokers with COPD was greater than among 8 subjects with a smoking history but normal spirometry and 21 healthy control subjects who had never smoked. Antibodies against primary pulmonary epithelial cells were found in 12 of 12 patients with COPD versus only 3 of 12 never-smoked control subjects. Antibodies were (not surprisingly) associated with decreased body mass index. It seems that auto immune responses may be important part of the aetiology of COPD.
Latent viral infection has also been connected to the pathogenesis of COPD. To further confirm this hypothesis sputum samples were collected from patients during exacerbations of COPD and when stable (5). One hundred and thirty-six patients with COPD were recruited during an acute exacerbation and 68 when stable. Epstein Barr virus (EBV) was detected in 65 (48%) exacerbation cases and 31 (46%) stable patients. In the control group of 16 smokers with normal lung function (i.e. without COPD) EBV was demonstrated in only one (6%) case. EBV was present both at exacerbations as well as in stable phases, pointing that infection is clearly persistent. This study interestingly enlightened some parts of the pathogenesis of COPD.
Further studies are badly needed for translation of aforementioned intriguing findings into clinical practice.

Stable COPD
Long acting bronchodilators are used in almost all COPD patients. On the other hand studies comparing tiotropium with long-acting beta$_2$-agonists are still very few. Some recently performed studies helped to clarify this situation. In 6-week multicentre, randomised, double-blind study authors compared the bronchodilator effects of tiotropium 18 mg once daily vs. the combination of salmeterol 50 mg plus fluticasone 250 mg twice daily in patients with COPD (6). Treatment with tiotropium alone resulted in comparable bronchodilation compared with salmeterol plus fluticasone. In a six-week, multicentre, randomized, double-blind, parallel group study Rabe et al. compared spirometry improvements of tiotropium 18 g once daily *plus* formoterol 12 g b.i.d. to salmeterol 50 g b.i.d. *plus* fluticasone 500 g b.i.d in patients with COPD (7). Relatively large number of 592 patients were included in the study. After six weeks, the 12-hour lung function profiles in the group receiving tiotropium *plus* formoterol were superior to the salmeterol *plus* fluticasone group.
The combination of salmeterol and fluticasone propionate and tiotropium bromide is very common treatment in COPD but there were very few studies which addressed the usefulness of this triple therapy. Singh et al. compared the effects of salmeterol/flucasone 50/500mcg b.i.d. plus tiotropium 18mcg with the individual treatments alone (8). Forty-one COPD patients participated in a randomised, double-blind, double-dummy, 3-way cross-over study with 2-week wash-out periods between treatments. Lung function assessment included plethysmography and spirometry. Triple therapy led to greater improvements in bronchodilation compared with tiotropium and salmeterol/fluticasone alone. The advantages of triple therapy were also observed across a range of physiologically important parameters, including airway conductance and lung volumes. Triple therapy also led to patient-related benefits by improving dypnea (TDI) and lower use of rescue medications. This study included only a small number of patients it is fair to expect that larger studies will be soon performed on this interesting subject.
Exacerbations of COPD
Prevention of exacerbations is extremely important part of COPD management as exacerbations are very important cause of morbidity and mortality in COPD. Still the relative values of drugs used in this respect are not fully elucidated. Wedzicha et al. added knowledge to this subject as they compared the relative efficacy of the inhaled salmeterol/fluticasone propionate 50/500 mg twice daily and the

long-acting bronchodilator tiotropium 18 mg once daily in preventing exacerbations and related outcomes in severe and very severe COPD (9). A total of 1,323 patients were randomized in 2-year, double-blind, and double-dummy parallel study. Perhaps not unexpectedly more pneumonias were found in the salmeterol/fluticasone propionate group relative to tiotropium. Investigators found no difference in exacerbation rate between salmeterol/fluticasone propionate and tiotropium. A small (and very probably the only) statistically significant beneficial effect was found on health status, with an unexpected and difficult (if possible at all) to explain finding of lower deaths in salmeterol/fluticasone propionate–treated patients.

The clinical importance of bacterial colonisation of lower airways in COPD is rapidly emerging. To evaluate the colonisation in different groups of patients with chronic lung diseases, bronchial lavage fluid was investigated for bacteria (10). The potentially pathogenic bacteria colonisation rate varied from 10% in persons with no pathology to 43% in patients diagnosed with COPD and 63% in patients with bronchiectasis. The most frequent bacterium isolated was *Haemophilus influenzae*. Colonisation rates were associated with frequencies of respiratory infections.

The importance of measuring different inflammatory markers in stable or exacerbated COPD is also on the rise. Do the airway and systemic inflammatory markers in bacterial exacerbations of COPD differ from nonbacterial exacerbations? The relationship between severity of exacerbation and inflammation is also not fully understood. In a prospective longitudinal cohort study in COPD, sputum and serum samples obtained before, at, and following exacerbations during a 2-year period were studied by Sethi et al. (11). New strain exacerbations were associated with significantly greater increases from baseline in sputumTNF- and neutrophil elastase, and in serum C-reactive protein compared with the other types of exacerbation. Clinical resolution was accompanied by resolution of inflammation to preexacerbation levels, while persistent symptoms were correlated by persistently elevated inflammation. Neutrophilic airway inflammation and systemic inflammation were more intense with well-defined bacterial exacerbations than with nonbacterial exacerbations. In the context of this study it is worth to briefly mention a study performed by Pertunen et al. (12). They found that $beta_2$ agonists potentiate glucocorticoid induced neutrophil survival. As those two classes of drugs are very often used together it would be interesting to study the clinical consequences of the concomitant use of these two drugs on the course of bacterial exacerbation of COPD. Or indeed even on the course of stabile COPD in which effects of neutrophils are certainly not harmless.

In spite of many improvements, we are still waiting for firm evidence-based criteria, by which it would be possible without any doubts to differentiate between bacterial and viral aetiology of exacerbation. Or indeed – to elucidate if the bacteria found in sputum are really important for current exacerbation?

Comorbidities

COPD is a frequently missed and neglected co-morbidity in patients with heart failure (HF). In a recently performed study Rusinaru et al. helped to clarify some aspects of this problem (13). Consecutive patients (n = 799) admitted for a first episode of HF were prospectively included. COPD was diagnosed in an important segment of HF patients (156 patients - 19.5%). Compared with the no-COPD group, patients with COPD were predominantly men, more often smokers, and had lower discharge prescription rates of beta blockers (6% vs. 27%). Five-year survival rate in patients with COPD was significantly lower than that of the no-COPD group (31% vs. 42%). COPD was an independent predictor of mortality in patients with preserved left ventricular ejection fraction as well as in patients with reduced ejection fraction. So patients with HF and associated COPD have significantly poorer prognosis with an great excess mortality compared to HF patients without COPD and the general population. Beta-blocker prescription rates were also unacceptably low in this category of patients with HF. Finding, which is also in contrast with all positive knowledge of safety of these drugs in COPD patients, was, sadly, prevalent in similar previously performed studies.

References

1. Bednarek M, Maciejewski J, Wozniak M. Prevalence, severity and underdiagnosis of COPD in the primary care setting. Thorax 2008; 63:402-7.

2. Rogers AV, Adeltorth E, Hattotuwa K. Bronchial mucosal dendritic cells in smokers and ex-smokers with COPD. Thorax 2008; 63:108-14.
3. Lee SH, Goswami S, Grudo A, Song LZ, Bandi V, Goodnight-White S, et al. Antielastin autoimmunity in tobacco smoking-induced emphysema. Nat Med 2007; 13:567–9.
4. Feghali-Bostwick CA, Gadgil A, Otterbein LE, Pilewski JM, Stoner MW, Csizmadia E, et al. Autoantibodies in patients with COPD. Am J Respir Crit Care Med 2008; 177:156-63.
5. MacManus TE, Marley AM, Baxter N, Christie SN, Elborn JS, O'Neill JH, et al. High levels of Epstein-Barr virus in COPD. Eur Respir J 2008; 31:1221-6.
6. Bateman ED, van Dykb E, Sagriotisc A. Comparable spirometric efficacy of tiotropium compared with salmeterol plus fluticasone in patients with COPD: A pilot study. Pulmonary Pharmacology & Therapeutics 21 2008; 2: 20–5.
7. Rabe K, Timmer W, Sagkriotis A, Viel K. Comparison of a combination of tiotropium and formoterol to salmeterol and fluticasone in moderate COPD. Chest 2008; in press.
8. Singh D, Brooks J, Hagan G, Cahn A, O'Connor BJ, et al. Superiority of triple therapy with salmeterol/fluticasone proprionate and tiotropium bromide vs. individual components in moderate to severe COPD. Thorax 2008; 63:592-8.
9. Wedzicha JA, Calverley P, Seemungal T, Hagan G, Ansari Z, Stockley BA; INSPIRE Investigators. The prevention of COPD exacerbations by salmeterol/fluticasone proprionate or tiotropium bromide. Am J Respir Crit Care Med 2008; 177:19-26.
10. Weinreich UM and Korsgaard J. Bacterial colonisation of lower airways in health and chronic lung disease. The Clinical Respiratory Journal 2008; 2: 116–22.
11. Sethi S, Wrona C, Eschberger K, Lobbins P, Grove L, Cai X, et al. Inflammatory profile of new bacterial strain exacerbations of COPD. Am J Respir Crit Care Med 2008; 177:491-7.
12. Pertunnen H, Moilanen E, Zhang X, Barnes PJ, Kankaanranta H. Beta$_2$ agonists potentiate corticosteroid-induced neutrophil survival. COPD 2008; 5:163-9.
13. Rusinaru D, Saaidi I, Godard S, Mahjoub H, Battle G, Tribouilloy C. Impact of chronic obstructive pulmonary disease on long-term outcome of patients hospitalized for heart failure. Am J Cardiol 2008; 101:353–8.

Angiogenic factors in the lungs of patients with chronic obstructive pulmonary disease

Škrgat Kristan S
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Angiogenesis is a process of new vessel growth. Knowledge of angiogenesis processes in the human lung is limited. Among known inductors of angiogenesis are VEGF (vascular endothelial growth factor), angiogenin, interleukin 8 (IL-8), TNF-α (tumor necrosis factor alpha) and bFGF (fibroblast growth factor). The researches in the field of angiogenetic processes in COPD are at the beginning and furthermore, there are conflicting data on this topic. Studies on animal models signal that blocking of VEGF receptors results in small vessel loss and a consequent apoptosis at the level of alveolus and development of emphysema. In the remodelling process of the bronchial wall in patients with chronic bronchitis there is evidence of increased vascularity and increased levels of VEGF in the induced sputum. VEGF might therefore has a protective role at the level of alveolus and destructive one with the remodelling process at the level of bronchiolar/bronchial wall.
The aim of our study was to evaluate the airway levels of angiogenic factors VEGF, angiogenin, IL-8, TNF- α and bFGF in COPD patients in stable phase and in acute exacerbation of the disease. We were also interested in the relation between cigarette smoke and concentrations of angiogenic factors. For this purpose, the standardized protocol for sputum induction and flow cytometric analysis of angiogenic factors in COPD patients and in healthy smokers and non-smokers was used.

Materials and Methods. We included 28 COPD patients (9 female and 19 male) in the COPD group, according to the GOLD classification: 21 were of stage II and 9 of stage III, a median age was 62 years. Median lung diffusion capacity (DLCO) was 66% of predicted values. Their disease was stable for at least one month before the sample collection. In 13 of these patients we managed to get the proper samples during the acute exacerbation of the disease. According to Anthonisen classification the clinical severity of exacerbation was of stage II in majority of patients.
Eleven healthy smokers and 7 healthy non-smokers in the control group had normal lung function tests. The median burden of smoking with interquartille ranges in smokers was 11 (6-20) pack years. They didn't smoke for at least 24 hours before the examination. All subjects, except in the exacerbation group, were free of symptoms and signs of acute upper respiratory tract infection in the month preceding the study. They were free of all other systemic diseases or malignancies. The concentrations of angiogenin, VEGF, IL-8, bFGF, and TNF-α were measured by cytometric bead array.

Results. In the induced sputum of patients with stable COPD, compared with healthy control group and healthy smokers, we found significantly increased concentrations of VEGF (smokers, nonsmokers;P=0.007,P=0.02, respectively), angiogenin (smokers, nonsmokers; P<0.0001, P<0.0001, re-

spectively), IL-8 (smokers, nonsmokers; P<0.0003, P=0.0021, respectively), TNF-α (smokers, nonsmokers; P=0.02, P=0.03, respectively). During the exacerbation of COPD we didn't measure any additional increase of angiogenic factors in the induced sputum. We also didn't measure any significant difference in concentrations of angiogenetic factors between current stable COPD patients and exsmokers COPD patients. In the group of patients with COPD we didn't show any corellation between lung function parameters (FEV1 and DICO) and angiogenic factors.

Conclusions. Concentrations of angiogenic factors VEGF, angiogenina, IL-8, TNF-α are increased in the lungs of patients with stable COPD. There is no additional local increase of angiogenic factors during exacerbation of COPD. It seems that the cigarette smoke is not related to increase of angiogenic factors. Due to positive correlation between VEGF- angiogenin and VEGF- TNF-α, angiogenic factors might have sinergistic role in the etiopathogenesis of COPD.

References

1. Klagsburn M, D Amore PA. Regulators of angiogenesis. Annu Rev Physiol 1991; 53:217-58.
2. Folkman J, Klagsbrun M. Angiogenic factors. Science 1987; 235;442-7.
3. Tuder RM, Zhen L, Cho CY, Taraseviciene Stewart L, Kasahara Y, Salvemini D, et al. Oxidative stress and apoptosos interact and cause emphysema due to vascular endothelial growth factor receptor blocade. Am J Respir. Cell Mol Biol 2003; 29:88-97.
4. Kasahara Y, Tuder RM, Taraseviciene Stewart L, Le Cros TD, Abman S, Hirth PK, et al. Inhibition of VEGF receptors causes lung cell apoptosis and emphysema. J Clin Invest 2000; 106:1311-19.
5. Kanazawa H, Asai K, Hirata K, Yoshikawa J. Possible effects of vascular endothelial growth factor in the pathogenesis of chronic obstructive pulmonary disease. *Am J Med* 2003; 114:354-8.
6. Kanazawa H, Yoshikawa J. Elevated oxidative stress and reciprocal reduction of vascular endothelial growth factor levels with severity of COPD. Chest 2005; 128:3191-7.
7. Papaioannou AI, Kostikas K, Kollia P, Gourgoulianis KI. Clinical implications for vascular endothelial growth factor in the lung: a friend or foe? Respir Res 2006; 7:128.

Kolonizacija z MRSA pri bolnikih na TZKD

Novak M, Svetina Šorli P, Tomič V
Bolnišnica Golnik - Klinični oddelek za pljučne bolezni in alergijo, Slovenija

V Bolnišnici Golnik - KOPA že 6 let intenzivno spremljamo bolnike z MRSA in izvajamo aktivnosti, ki pripomorejo k preprečevanju širjenja le-te. Ena od teh aktivnosti je tudi spremljanje bolnikov z dejavniki tveganja za kolonizacijo z MRSA. V algoritmu so opredeljeni čas odvzema, odgovorne osebe za odvzem, vrsta nadzornih kužnin ter dejavniki tveganja.
Kot dejavniki tveganja so opredeljeni premestitve iz drugih bolnišnic, večkratna hospitalizacija v zadnjih 3 letih, operativni poseg v zadnjih 3 letih, hospitalizacija na oddelku za intenzivno terapijo katerekoli bolnišnice (tudi naše) v zadnjih 3 letih, premestitve iz doma starejših občanov, trajno zdravljenje s kisikom na domu (TZKD), znane MRSA kolonizacije v preteklosti ter s tem povezane neuspešne dekolonizacije, nepopolna potrditev uspešnosti dekolonizacije ali pa če ni informacij o izvedeni dekolonizaciji. Nadzor nad bolniki, za katere obstaja večja verjetnost, da so nosilci MRSA glede na navedene dejavnike tveganja, izvajamo na vseh bolniških oddelkih, na oddelku za intenzivno terapijo pa izvajamo nadzor nad vsemi sprejetimi pacienti, neodvisno od teh dejavnikov.
Bolnišnica Golnik - KOPA je v veliki meri usmerjena v obravnavo pljučnih bolnikov, ki so zaradi narave svoje bolezni pogosteje hospitalizirani. Prav to je razlog, da smo v odkrivanje MRSA ob sprejemu v bolnišnico vključili tudi populacijo, značilno za našo bolnišnico – to so bolniki na TZKD. Ti bolniki se zaradi narave svoje bolezni in morebitnih pridruženih drugih kroničnih bolezni pogosto vračajo v našo bolnišnico. Z retrospektivno študijo smo želeli ugotoviti, kolikšen delež bolnikov s TZKD je kolonizirano z MRSA in kakšne so razlike med bolniki s TZKD, ki so nosilci MRSA in bolniki s TZKD, ki niso kolonizirani z MRSA ter ali je TZKD ustrezna indikacija za odvzem nadzornih brisov za ugotavljanje kolonizacije MRSA ob sprejemu v bolnišnico.

Material in metode. V študijo smo vključili 30 bolnikov na TZKD. Petnajst bolnikov je bilo kolonoziranih z MRSA, ostalih 15 bolnikov, ki niso bili kolonizirani z MRSA, smo naključno izbrali med bolniki na TZKD, ki so bili hospitalizirani v naši ustanovi v letu 2007. Vseh 30 bolnikov je bilo v obdobju zadnjih 6 let ob sprejemu (v roku 72 ur) pregledanih na prisotnost MRSA (odvzete kužnine: bris nosu, žrela, ob prisotnosti urinskega katerta urin, ob prisotnosti rane bris rane ter na intenzivnem oddelku v primeru intubacije še aspirat tubusa; če je bil bolnik znan nosilec MRSA, smo kontrolirali predhodno pozitivna mesta). Skupini, kateri smo primerjali, sta bili primerljivi glede spola in starosti vključenih bolnikov. Pregledali smo podatke zadnjih 15 let. Primerjali smo število hospitalizacij v naši bolnišnici, pogostnost obravnav v ostalih zdravstvenih ustanovah, bivanje v domovih za starejše občane, antibiotično terapijo (in vrsto antibiotične terapije), trajanje zdravljenja s kisikom na domu, komorbidnost,

pogostost invazivnih posegov, kadilski status. Pri bolnikih z MRSA smo zabeležili obdobja, v katerih smo s pomočjo nadzornih kužnin ugotovili, da so nosilci te bakterije.

Rezultati. Vsi bolniki na TZKD so imeli pridruženih več bolezni. KOPB je bila prisotna pri 12 izmec 15 bolnikov na TZKD, koloniziranih z MRSA, in pri 8 od 15 bolnikov, ki niso bili kolonizirani z MRSA.
Bolniki na TZKD, kolonizirani z MRSA, so bili v zadnjih 15 letih v povprečju večkrat hospitalizirani v naši bolnišnici, prav tako so bili navedeni številnejši obiski ostalih zdravstvenih ustanov. Večkrat so bili zdravljeni z različnimi antibiotiki. Zdravljenje s kisikom na domu pri tej skupini bolnikov traja dalj časa, obenem so zdravljeni z večjim pretokom kisika (povprečje 2,3 litra).
Pri večini bolnikov na TZKD, koloniziranih z MRSA, smo MRSA z jemanjem nadzornih kužnin odkrili na začetku zadnje hospitalizacije (nadzorne kužnine smo jemali ob vsaki hospitalizaciji v zadnjih 6 letih). Ugotovili smo, da so bili bolniki med posameznimi hospitalizacijami v naši bolnišnici obravnavani tudi v drugih zdravstvenih ustanovah.

Zaključki. Bolniki naTZKD imajo že zaradi omenjenega zdravljenja s kisikom, komorbidnosti, različnih invazivnih posegov in pogostih hospitalizacij in zdravljenj z antibiotiki vse rizične dejavnike, ki povečujejo možnost kolonizacije z MRSA. Prisotnost TZKD je indikacija za odvzem nadzornih kužnin bolnikom ob sprejemu. Daljši čas trajajanja zdravljenja s kisikom na domu zvišuje verjetnost kolonizacije z MRSA.

Literatura

1. Navodila Bolnišnice Golnik – KOPA za izvajanje screeninga pri MRSA. http://www.klinika-golnik.si/dejavnost-bolnisnice/klinicna-dejavnost/datoteke/Navodila-za-preprecevanje-sirjenja-MRSA.pdf
2. Arhiv Bolnišnice Golnik - KOPA

Ocena kakovosti življenja bolnika s KOPB – vprašalnik St. George v povezavi s funkcijskimi testi

Bratkovič M, Kristan Škrgat S, Vegnuti M, Šorli J
Bolnišnica Golnik – Klinični oddelek za pljučne bolezni in alergijo, Slovenija

Kronično obstruktivno pljučno bolezen lahko opredelimo kot napredujočo obstruktivno motnjo ventilacije, ki ni povsem reverzibilna. Motena je mehanika dihanja zaradi hiperinflacije pljuč. KOPB zelo vpliva na obseg in intenzivnost dnevnih aktivnosti in tako na kakovost življenja, vezano na zdravje (angl. HRQoL – health related quality of life). V zadnjem času cilj zdravljenja ni samo lajšanje simptomov s simptomatsko terapijo, ampak vse bolj izboljšanje HRQoL. Razviti so bili različni instrumenti, ki ocenjujejo vpliv KOPB na bolnikovo življenje, zdravje in kakovost bivanja. V kliničnih raziskavah se uporabljajo za oceno spremembe HRQoL, pri čemer se merijo razlike med posameznimi bolniki.
Eden od instrumentov je vprašalnik »St. Georges Respiratory Questionnaire« (SGRQ), s katerim lahko merimo HRQoL.
Osnovni namen raziskave je primerjava HRQoL med bolniki, ki se trajno zdravijo s kisikom na domu, v primerjavi z bolniki s KOPB, ki tovrstnega zdravljenja še ne potrebujejo. Zanimalo nas je, kakšna je korelacija med rezultatom vprašalnika SGRQ-C in šestminutnim testom hoje ter parametri pljučne funkcije.

BOLNIKI IN METODE
Vsi pacienti, zajeti v raziskavi, so bili pregledani v isti ambulanti Bolnišnice Golnik — Klinični oddelek za pljučne bolezni in alergijo. Pregledani so bili v obdobju od januarja 2007 do aprila 2008. Vzorec zajema 13 bolnikov s povprečno starostjo 67,7 let, od tega 3 ženske in 10 moških, ki se zdravijo s kisikom na domu. Primerjalno skupino predstavlja 37 bolnikov s povprečno starostjo 58,4 leta, v razmerju 9 žensk in 28 moških, ki tovrstnega zdravljenja še ne potrebujejo.
Diagnoza KOPB je bila potrjena s spirometrijo (FEV1/FVC ≤ 70 %, FEV1 ≤ 80 %) in odsotnostjo odziva na bronhodilatator. Opravili so šestminutni test hoje, s katerim merimo bolnikovo telesno zmogljivost. Izpolnili so vprašalnik SGRQ-C o kakovosti življenja.

Instrumenti za meritev
Vprašalnik SGRQ je standardiziran vprašalnik o boleznih dihalnih poti, ki ga lahko sodelujoči sam izpolni in je razdeljen v tri kategorije: simptomi (1–8), dejavnost (11 in 15) in vplivi (9–10, 12–14, 16–17). Rezultati SGRQ so bili izračunani z uporabo algoritma za izračun rezultatov po priporočilu avtorja vprašalnika (P. W. Jones, St. George's Hospital Medical School, London, SW17 ORE UK).
Za vsako kategorijo in za celoten vprašalnik se rezultati gibljejo v odstotkih od nič (nobenih težav) do 100 (maksimalna prizadetost pri običajnem življenju) (2).

Vsak odgovor v vprašalniku ima empirično izpeljan koeficient ali ponder. Preračunani so rezultati vseh treh komponent vprašalnika – simptomi, aktivnosti in vpliv ter skupen rezultat vseh treh. Vsaka komponenta vprašalnika je preračunana ločeno v treh korakih:

- Koeficienti vseh pozitivnih odgovorov so sešteti.
- Koeficienti manjkajočih odgovorov so odbiti od maksimalnih možnih točk za vsako komponento. Manjkajoči koeficienti vseh komponent so odšteti od celotnega števila točk.
- Rezultat je izračunan z deljenjem seštevka pozitivnih odgovorov z maksimalnim številom točk in je izražen v odstotkih.

Vsota maksimalnih možnih točk za vsako komponento skupno znaša:

- simptomi 662.5,
- aktivnosti 1209.1,
- vpliv 2117.8,
- vsota 3989.4.

Narejene so bile različne modifikacije vprašalnika in proučeni učinki manjkajočih odgovorov. Tako sta v primeru simptomov dovoljena dva manjkajoča odgovora, pri aktivnostih štirje in pri vplivu šest manjkajočih odgovorov. V naši raziskavi je bilo tako maksimalno zbranih naslednje število točk:

- simptomi 573.3,
- aktivnosti 982.9,
- vpliv 1653.1,
- vsota 3209.3.

Preiskava pljučne funkcije je bila izvedena na spirometru Master Scope CT IOS. Izmerjena je bila počasna vitalna kapaciteta (SVC), forsiran ekspirij v eni sekundi (FEV1), forsirana vitalna kapaciteta (FVC), indeks Tiffneau in opravljen bronhodilatatorni test.

Šestminutni test hoje (6-MTH) je varen, enostaven za izvedbo in bolje odraža bolnikovo zmožnost opravljanja dnevnih aktivnosti kot drugi testi. Pri tem testu merimo prehojeno razdaljo, lahko pa tudi saturacijo hemoglobina s kisikom in bolnikovo zaznavanje dispneje med naporom. Bolnik mora hoditi sam, brez spremstva drugih bolnikov ali terapevta. Terapevt oziroma raziskovalec prav tako ne sme pomagati prenašati rezervoarja kisika, če ga bolnik uporablja. Najpogosteje se uporablja za oceno funkcionalnega statusa in uspešnosti farmakološke terapije in rehabilitacijskega programa pri bolnikih s KOPB. Pri šestminutnem testu hoje mora biti razlika v prehojeni razdalji vsaj 54 metrov, da se lahko prizna za klinično pomembno. Test je najbolj zanesljiv, če se izvaja po standardiziranem protokolu in se ponovi najmanj dvakrat (4).

Statistične metode

Za prikaz porazdelitev podatkov so uporabljene mere srednjih vrednosti in razpršenosti: aritmetična sredina, mediana, standardna deviacija in koeficient variabilnosti, ki predstavlja razmerje med standardno deviacijo in aritmetično sredino. Za testiranje razlik med skupinama je bil uporabljen Mann-Whitney U test; za korelacije med spremenljivkami pa Spearmanova korelacija rangov. Statistično značilnost smo preverjali v intervalu 95 % zaupanja oziroma z napako za zavrnitev ničelne hipoteze v velikosti $\alpha = 0{,}05$.

REZULTATI

1. Opis vzorca

Povprečna starost bolnikov v skupnem vzorcu je 60,8 let. Tretjino opazovanih bolnikov predstavljajo ženske, dve tretjini pa moški.

SGRQ-rezultate, ki jih dobimo z vprašalnikom, lahko razdelimo na tri področja: simptomi (kašelj, sputum), aktivnosti (fizična aktivnost, omejena z občutkom težke sape), vplivi (socialni in psihološki vplivi bolezni).

Največjo variabilnost med bolniki, ki jo izraža koeficient variacije kot relativno razmerje med standardno deviacijo in aritmetično sredino, smo opazili pri ocenjevanju lestvice BORG, zelo veliko variabilnost pa izražajo bolniki tudi pri ocenjevanju **vplivov** bolezni v sestavu rezultata SGRQ. Druge spremenljivke v vzorcu imajo koeficient variabilnosti pod 50 %, kar lahko kaže tudi na razmeroma večjo homogenost skupine (Tabela 1).

Tabela 1: Povprečne vrednosti in razpršenost podatkov za merjene spremenljivke na celotnem vzorcu (n = 50)

	Aritmetična sredina	SD	Minimum	Maksimum	Razlika Min/Maks	Koeficient variabilnosti
starost	60,8	8,1	48	77	29	13,3 %
borgD1	0,9	1,2	0	5	5	131,3 %
borgD2	3,8	2,9	0,5	10	9,5	77,8 %
hoja	360,4	129,0	80	630	550	35,8 %
SVC(L)	3,4	1,0	1,39	5,48	4,09	29,3 %
FEV1(L)	1,4	0,7	0,48	3,08	2,6	47,5 %
FCV(L)	3,4	1,0	1,37	5,55	4,18	28,1 %
IT	41,0	11,9	20	66	46	29,0 %
SVC(L)%	83,8	17,2	46	115	69	20,6 %
FEV(1)%	45,0	18,3	16	80	64	40,7 %
FCV(L)%	86,6	17,6	50	120	70	20,4 %
SGRQ_C	50,1	22,8	13,6	96,4	82,8	46,3 %
VPLIV	38,7	31,2	0	95,0	95,0	63,4 %
AKTIVNOST	63,9	68,4	14,9	100	85,1	42,4 %
SIMPTOMI	59,2	57,4	0	100	100	45,9 %

Legenda: SVC – počasna vitalna kapaciteta, FEV1 – forsiran ekspirij v sekundi, FVC – forsirana vitalna kapaciteta, IT – indeks Tiffneau

2. Razlike med skupinama bolnikov

Glede na različne instrumente merjenja, s katerimi smo ocenjevali klinično, fizično in psihosocialno stanje bolnika, pri čemer so nekatere ocene lahko tudi subjektivne (vprašalnik SGRQ), druge pa razmeroma bolj ali celo zelo objektivne (BORG, test hoje in meritve pljučne funkcije), lahko analiziramo, ali se med skupinama bolnikov s KOPB kažejo specifične razlike, in to morda pri kateri od uporabljenih metod bolj kot pri drugi.

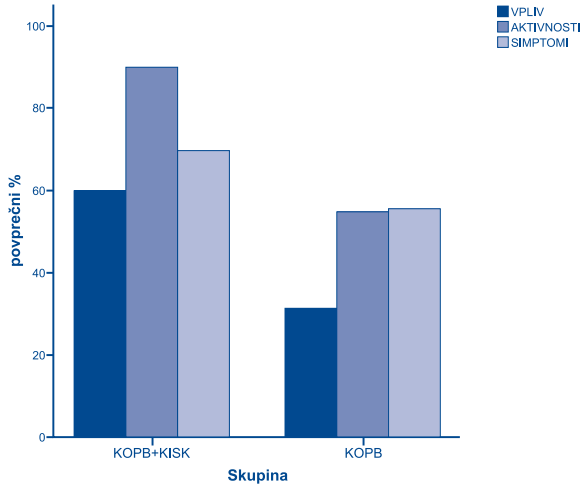
Tabela 2: Razlike skupin (skupina s kisikom, brez kisika) glede na položaj vrednosti opazovanih spremenljivk

	Povprečna vrednost		SD		Mann-Whitney U test	
	Skupina		Skupina			
	KOPB+KISIK	KOPB	KOPB+KISIK	KOPB	Z	p
starost	67,7	58,4	7,4	7,0	-3,436	0,001
borgD1	1,8	,8	1,6	1,2	-2,787	0,005
borgD2	7,1	2,8	2,3	2,3	-4,026	0,000
hoja	238,3	397,7	113,7	109,8	-3,469	0,001
SVC(L)	2,5	3,7	,8	,9	-3,473	0,001
FEV1(L)	,8	1,6	,3	,7	-3,993	0,000
FCV(L)	2,5	3,6	,9	,9	-3,55	0,000
IT	35,4	42,9	11,1	12,1	-1,937	0,053
SVC(L) %	66,0	89,2	13,4	14,2	-4,072	0,000
FEV1(L) %	29,3	49,4	8,0	17,8	-3,684	0,000
FCV(L) %	67,5	91,9	14,6	14,8	-3,994	0,000
VPLIV	59,9	31,2	19,0	20,6	-3,904	0,000
AKTIVNOSTI	90,1	54,7	8,8	24,5	-4,189	0,000
SIMPTOMI	69,7	55,6	23,9	26,9	-1,637	0,102
SGRQ_C	70,9	42,8	14,7	20,5	-3,727	0,000

Legenda: SVC – počasna vitalna kapaciteta, FEV1 – forsiran ekspirij v sekundi, FVC – forsirana vitalna kapaciteta, IT – indeks Tiffneau

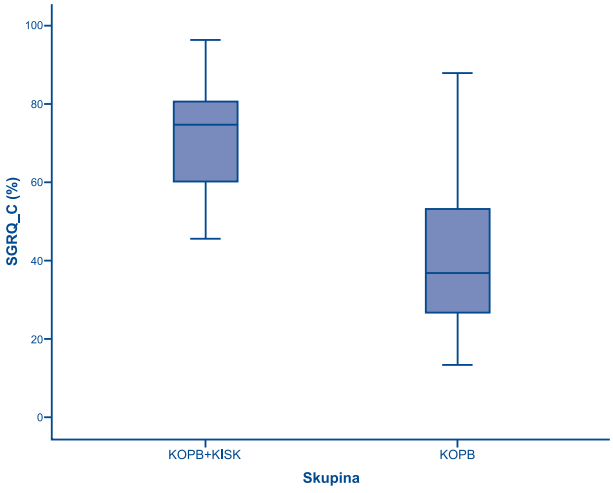
Skupini (KOPB s kisikom in KOPB) se statistično značilno razlikujeta v vseh opazovanih spremenljivkah, razen v oceni simptomov (podlestvica SGRQ). Statistično značilno različna je tudi starost skupin: v povprečju je skupina s kisikom 9,5 let starejša.
Kazalci pljučne funkcije so pri skupini bolnikov s KOPB, ki imajo terapijo s kisikom, približno od 30 do 50 % slabši.

Slika 1: Povprečni odstotek posameznih komponent lestvice SGRQ glede na primerjavo med skupinama



Odstotek celotnega zbira točk na vprašalniku SGRQ je pri bolnikih s KOPB samo 42,8 v primerjavi z bolniki KOPB s kisikom, ki imajo 70,9 %. Največjo razliko znotraj lestvice SGRQ predstavlja komponenta aktivnosti, ki je pri bolnikih s kisikom mnogo višja od primerjalne skupine. Višji odstotek SGRQ pomeni večjo prizadetost bolnika oziroma slabšo kakovost življenja.

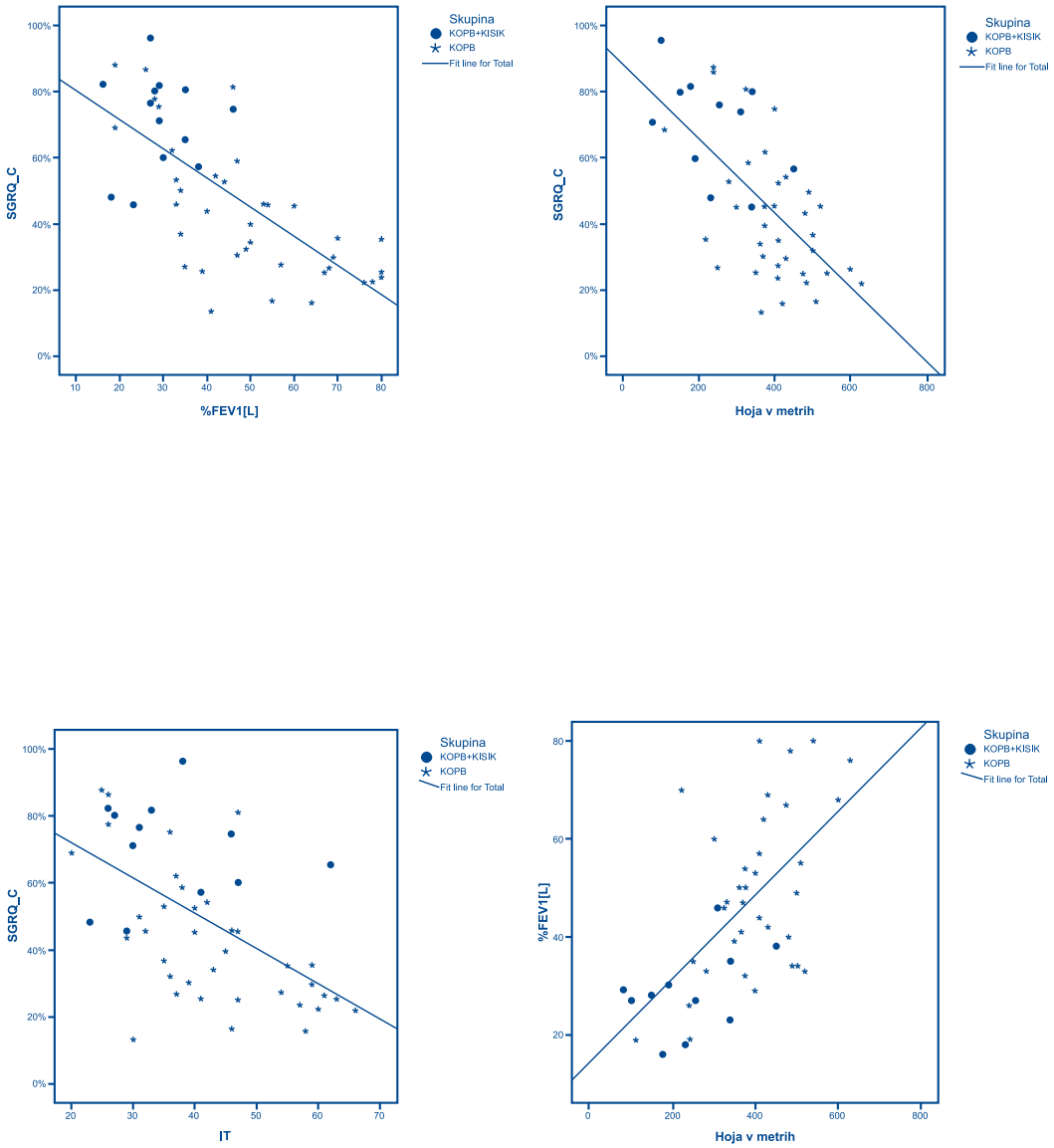
Slika 2: Porazdelitev lestvice SGRQ glede na skupini bolnikov KOPB



3. Vloga različnih testov pri opisu stanja bolnika

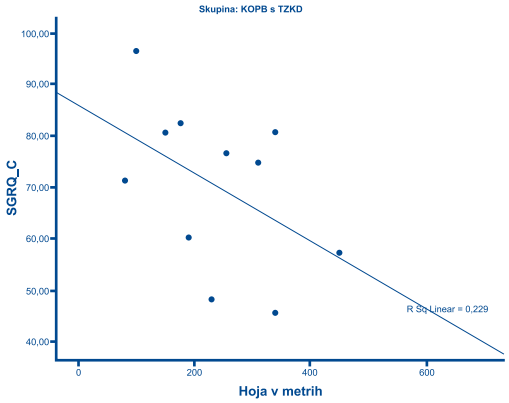
Vprašalnik SGRQ, ki ga izpolnjuje bolnik sam, predstavlja osebno zaznavanje bolezni in ima teoretično vse možnosti za pristransko oceno, ki se ne bi ujemala s klinično sliko in fizičnim stanjem na preizkusu zmožnosti. Po pregledu korelacij med rezultatom SGRQ in drugimi meritvami, vključno s starostjo, ugotovimo, da so na vzorcu naših bolnikov statistično značilne vse medsebojne korelacije. Bolniki z visokimi odstotki na lestvici SGRQ (večji upad aktivnosti, več simptomov in večji vpliv na bolnikovo socialno funkcioniranje) imajo značilno nižje kazalce pljučne funkcije in so zmožni prehoditi krajše razdalje.

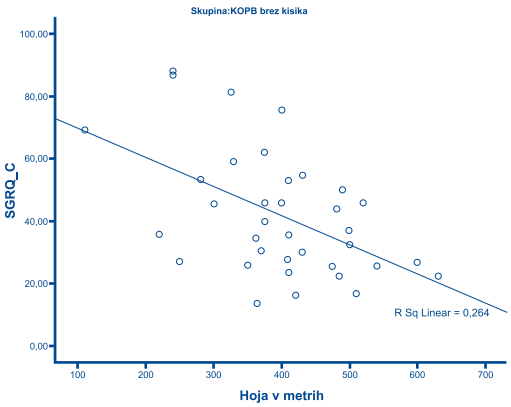
Slika 3: Korelacije med opazovanimi spremenljivkami na celotnem vzorcu

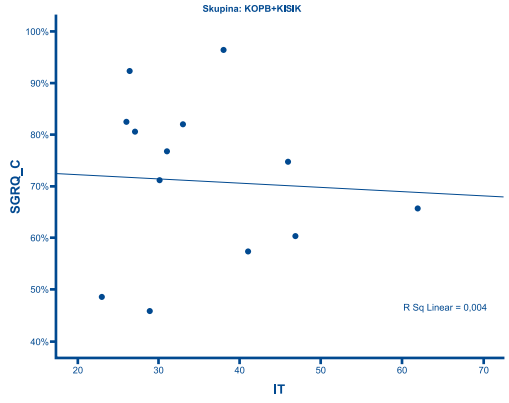


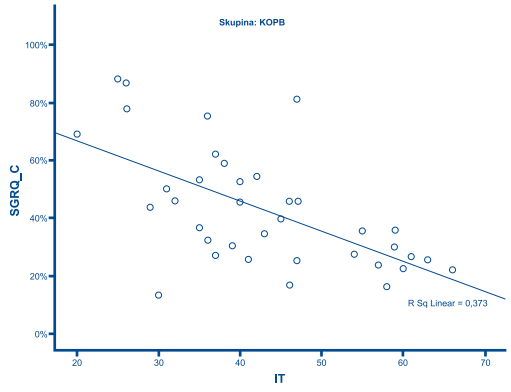
4. Skupina bolnikov na trajnem zdravljenju s kisikom in brez

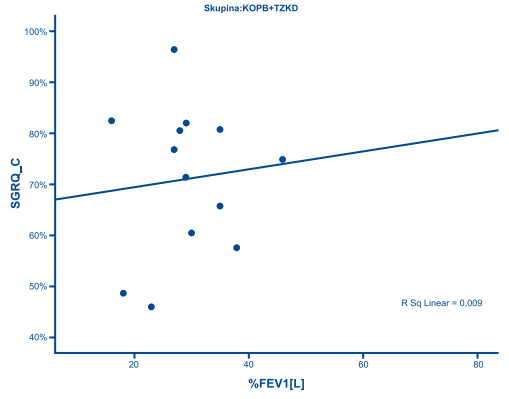
Slika 4: Primerjava šestminutnega testa hoje, IT in SGRQ med skupino opazovancev na trajnem zdravljenju s kisikom in brez

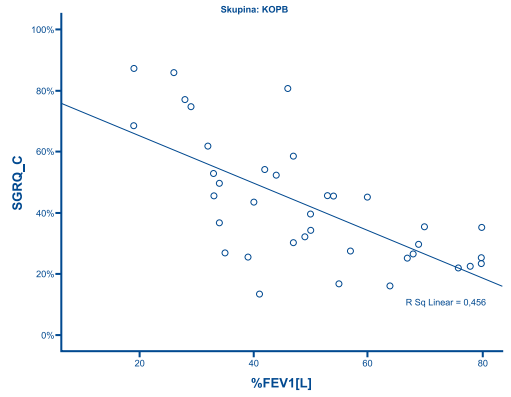












Pri bolnikih, ki so na TZKD, nam FEV1 le malo pove o njihovi kakovosti življenja. Medtem ko šestminutni test hoje tudi pri slabših bolnikih da dober vpogled v njihovo kakovost življenja. Iz tega sledi, da je za oceno kakovosti življenja ob vprašalniku povednejša bolnikova telesna zmogljivost kot preiskave pljučne funkcije (7).

RAZPRAVA

Z zdravjem povezana kakovost življenja (HRQL) je postala pomemben element za bolnike z boleznimi dihal, saj je bilo v zadnjih letih razvitih več vprašalnikov o kakovosti življenja, povezani z zdravjem, ki so bili oblikovani posebej za bolezni dihal.

Med njimi je vprašalnik o boleznih dihal St. George (SGRQ) postal najširše uporabljeni instrument za ocenjevanje z zdravjem povezane kakovosti življenja pri bolnikih z boleznimi dihal, poleg tega je bil preveden v več jezikov. Uporabili smo ga tudi v naši raziskavi.

Osnovni namen raziskave je primerjava HRQoL med bolniki, ki so na trajnem zdravljenju s kisikom na domu, v primerjavi z bolniki s KOPB, ki tovrstnega zdravljenja še ne potrebujejo. Zanimalo nas je, kakšna je korelacija med rezultatom vprašalnika SGRQ-C in šestminutnim testom hoje ter parametri pljučne funkcije.

Skupini (KOPB s kisikom in KOPB) se statistično značilno razlikujeta v vseh opazovanih spremenljivkah, razen v oceni simptomov (podlestvica SGRQ). Pomembno je poudariti, da se skupini razlikujeta tudi v starosti preiskovancev. Bolniki na TZKD so v povprečju 9,5 let starejši.

Vprašalnik SGRQ, ki ga izpolnjuje bolnik sam, predstavlja osebno zaznavanje bolezni. Odstotek celotnega zbira točk na vprašalniku SGRQ je pri bolnikih s KOPB samo 42,8 v primerjavi z bolniki KOPB s kisikom, kjer znaša 70,9 %. Največjo razliko znotraj lestvice SGRQ predstavlja komponenta **aktivnosti** (fizična aktivnost, omejena z občutkom težke sape), ki je pri bolnikih s kisikom 90,1 in je mnogo višja od primerjalne skupine, kjer znaša 54,7. Sledi ji podskupina **vplivi** (socialni in psihološki vplivi bolezni): 59,9 proti 31,2. Najmanj razlik med skupinama preiskovancev opazimo pri kategoriji **simptomi** (kašelj, izmeček): 69,7 proti 55,6. Višji odstotek SGRQ v skupnem seštevku in za posamezne komponente pomeni večjo prizadetost bolnika oziroma nižjo kakovost življenja (razpon od 0 do 100).

Po pregledu korelacij med rezultatom SGRQ in drugimi meritvami ugotovimo, da so bolniki z visokimi odstotki na lestvici SGRQ (večji upad aktivnosti, več simptomov in večji vpliv na bolnikovo socialno funkcioniranje) zmožni prehoditi krajše razdalje (238,3 proti 397,7) in imajo 30 do 50 % nižjo pljučno funkcijo.

Ocenjujemo, da je kakovost življenja bolnika s KOPB na TZKD v primerjavi z bolniki s KOPB, ki tovrstnega zdravljenja še ne potrebujejo, po izvedenih subjektivnih (SGRQ) in objektivnih meritvah (šestminutni test hoje, preiskava pljučne funkcije) bistveno slabša.

KOPB se v napredovani fazi bolezni kaže s prizadetostjo celega organizma. Napredujoča funkcijska okvara pljuč bolnika vse bolj omejuje v gibljivosti in vodi v socialno izolacijo in depresijo. Zaradi citokinov, ki se v obilici sproščajo v bolezensko vnetih pljučih in preplavijo organizem, periferno mišičje propada, bolniki tudi hujšajo. Zaradi slabe prehrane in pomanjkanja gibanja se pri bolnikih pogosto razvije pomembna osteoporoza (6). Vse našteto vpliva na kakovost življenja, povezano z zdravjem.

V našem preiskovalnem vzorcu je v skupini bolnikov na TZKD bolezen bolj napredovala, kar se kaže v slabši pljučni funkciji, telesni zmogljivosti in kakovosti življenja. Pri oceni korelacij med vprašalnikom SGRQ in šestminutnim testom hoje vidimo, da dobro prikaže kakovost življenja bolnika, medtem ko ima pljučna funkcija slabšo napovedno vrednost. Iz tega sledi, da je za oceno kakovosti življenja ob vprašalniku povednejša bolnikova telesna zmogljivost kot preiskave pljučne funkcije.

Vprašalnik SGRQ se pogosto uporablja pri raziskavah z deskriptivnim in terapevtskim vrednotenjem (bronhodilatorji, terapija s kisikom, psihoterapija in respiratorna rehabilitacija), vendar je ta obsežna uporaba omejena večinoma na raziskovalno okolje. Meritve z zdravjem povezane kakovosti življenja imajo številne slabe strani, zlasti kar zadeva njihovo uporabo v klinični praksi. Dejansko je bilo ugotovljeno, da je razlaga rezultatov vprašalnikov o z zdravjem povezani kakovosti življenja ena od glavnih ovir za njihovo širšo uporabo v kliničnem okolju (3).

Raziskava »COPE self-management« je velika kontrolna raziskava, ki naj bi ocenila učinkovitost programa izobraževanja za samostojno zdravljenje (self-management programme) in fitnes programa za KOPB.
Ta raziskava je potrdila najmanj 3 elemente HRQoL, ki jih vprašalnik SGRQ ni primerno predstavil: samozavest, občutek varnosti, socialna izolacija. Raziskava je tudi potrdila, da je za maksimalno HRQoL pri KOPB bolnikih potrebna dobra ocena fizioloških parametrov (1).
Naslednja raziskava, ki je bila predstavljena v članku (5), se je dotaknila ravno teh vprašanj glede ocene kakovosti življenja z vidika bolnika. Ugotovitve, predstavljene v tem članku, ponujajo nekaj vpogleda v to, kako pomembno je za bolnike sodelovanje v fizičnih in družbenih dejavnostih kljub njihovim fizičnim omejitvam.
Iz vsega povedanega lahko zaključimo, da nas mora pri obravnavi bolnikov s KOPB voditi misel o izboljšanju njegove kakovosti življenja. Če želimo doseči to, pa moramo v sklopu ocene njegovega stanja opraviti tudi meritve, ki so s kakovostjo življenja tesneje povezane kot preiskava pljučne funkcije (vprašalniki o HRQoL, ocena telesne zmogljivosti).

Literatura

1. Monninkhof E, van der Aa M, van der Valk P, van der Palen J, Zielhuis G, Koning K, Pieterse M. A qualitative evaluation of a comprehensive self-management programme for COPD patients: effectiveness from the patients' perspective. Patient Educ Couns. 2004 Nov; 55 (2): 177–84.
2. Jones PW,Spencer S, Adie S. The St Georges respiratory questionnaire manual. http://www.aamr.org.ar./cms/archivos/secciones/rehab/sgrq manual may03.doc
3. Ferrer M, Villasante C, Alonso J, Sobradillo V, Gabriel R, Vilagut G, Masa J F, Viejo JL, Jiménez-Ruiz CA, Miravitlles M. Interpretation of quality of life scores from the St George's RespiratoryQuestionnaire. Eur Respir J. 2002 Mar; 19 (3): 405–13.
4. Murnik M. Primerjava šestminutnega testa hoje in stopenjskega testa hoje pri bolnikih s KOPB, 2005.
5. Williams V, Bruton A, Ellis-Hill C, McPherson K. What really matters to patients living with chronic obstruktive pulmonary diseases? An exploratory study. Chron respir Dis. 2007; 4, 77.
6. Šuškovič S. Zgodnje odkrivanje kronične obstruktivne bolezni: ali se splača in kako to naredimo? Med Razgl 2003; 42: S 4: 5–9.
7. Šorli J ml. Nefarmakološka obravnava bolnika s KOPB – rehabilitacija. Med Razgl 2003; 42: S 4: 15–17.

Respiratory insufficiency in an overweight patient

Gabrijelčič J
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Due to increased prevalence of obesity, especially severe form (body mass index (BMI) > 40kg/m^2), more and more such patients present with hypercapnic respiratory failure. First, other lung/heart diseases are to be excluded, and then, new modalities of non-invasive ventilation are to be implemented (BIPAP, PACV, PSV) as home- ventilation. Still, the most prevalent breathing disorder, linked to obesity, is obstructive sleep apnea. Here, classical CPAP therapy with appropriate mask selection, leads to correction of apneas and desaturation. In obstructive sleep apnea syndrome (OSAS) only, we do not encounter daytime respiratory insuffciency; if so called overlap syndrome exist (COPD + OSAS), more prominent respiratory failure is detected.

Affluent and emerging societies alike are currently experiencing an alarming increase in the prevalence of obesity (defined by WHO as BMI > 30 kg/m^2). Importantly, the increase in obesity has been characterized by a marked increase in »severe« or »morbid« obesity (BMI >40 kg/m^2). Only from 2000 - 2005, the prevalence of self-reported obesity (BMI>30 kg/m^2) increased by 24% in USA. Over the same period, the prevalence of self-reported BMI >40 and >50 kg/m^2 increased two or three times faster, respectively. Significant social, economic, and health burdens are associated with these levels of obesity. WHO defines 4 categories of excess body weight (regarding body mass index-BMI more than 25 kg/m^2); and also uses waist circumference to estimate further disease risk. Obesity-BMI > 30kg/m^2, can compromise lung function, and can cause respiratory insufficiency by itself - without concomittant lung/heart diseases.

Accumulation of fat tissue impairs ventilatory function in a restrictive pattern, presumably due to diminished diaphragm excursions and reduced thoracic compliance. Moreover, obesity increases work of breathing through reduction of chest wall compliance and respiratory muscle strength.This generates the perception of increased breathing effort and of dyspnea, although maximal oxygen consumption is generally preserved.

As a consequence of breathing at low lung volumes, small airway closure is likely to occur, with the potential for air trapping.

Patients with obesity frequently report dyspnea and wheezing and are therefore often given therapy for asthma without objective diagnostic confirmation by pulmonary function testing.
Since OSAS and COPD are both prominent diseases, a substantial »overlap« occurs, affecting aprox. 0.5 % of whole population.

The diseases most clearly linked with obesity are obstructive sleep apnea syndrome and obesity hypoventilation syndrome (OHS).

OSAS is characterized by intermittent upper airway closure due to the inability of pharyngeal musculature to maintain upper airway patency in the presence of alterations in airway shape and diameter. This results in a fall in arterial oxygen content, a rise in carbon dioxide levels and increased inspiratory efforts that lead to abrupt awakenings as the person struggles to breathe. The result is profoundly disturbed sleep. It is estimated that 4% of male population develop OSAS, and half of that incidence (2%) occurs in female. Obesity is a well-recognized risk factor for obstructive sleep apnea. Increased fat tissue deposition in the pharyngeal region and reduced operating lung volumes in obesity act together to reduce upper airway caliber, modify airway configuration and increase their collapsibility; airways are thus predisposed to repetitive closures during sleep. Typically, no respiratory insufficieny is detected during wakefulness (if no concomittant lung/heart disease is present), but patients complain of progressive daytime fatigue and sleepiness. About 70% of people with obstructive sleep apnea are obese, and, conversely, the prevalence of the disorder among obese people is approximately 40%. Indeed, almost all men with class III obesity also have obstructive sleep apnea. Obstructive sleep apnea is associated with excess mortality from accidents related to daytime sleepiness and to the high incidence of cardiovascular disorders. Therefore, obstructive sleep apnea is one of the life-threatening sequelae of obesity.

Nocturnal polysomnography is the standard diagnostic test for sleep apnea. It allows identification of complete cessation of airflow and of reduction of airflow associated with a decrease in oxygen saturation and arousal or both. When more than 5 apneas per hour of sleep are detected, a diagnosis of OSA is made. OSA is then further graded as mild (5-15 apneas/hour), moderate (15-30/h) and severe (more than 30/h) form. OSA is defined as the presence of apneas during the night; and OSAS when somnolence and excessive daytime sleepiness is becoming noticeable.

Most efficient therapy for OSAS is continuous positive airway pressure therapy (CPAP); the pressure between 5-20 cm of water being delivered via nasal or oro-nasal mask. All attempts to succesfully reduce body weight, should be encouraged, too.

OHS is defined as daytime hypercapnia > 45 mm Hg, BMI > 30 kg/m^2, absence of any other causes of hypoventilation; and associated sleep-related breathing disorder. Hypercapnic respiratory failure, severe hypoxemia, and cor pulmonale with pulmonary hypertension are most common symptoms. The three main mechanisms that link obesity to the development of daytime hypoventilation can be grouped as follows: those related to abnormal respiratory mechanisms, those arising from abnormal central ventilatory control and those associated with sleep disordered breathing. 70-90% of patients will have predominantly obstructive events during sleep, and it seems today that sleep plays critical role in the development and progression of the OHS.

It is acknowledged lately that non-invasive ventilation (NIV) for OHS (BIPAP, PACV, PSV) is one of the most emerging indications for NIV; more so, because many of these patients come to medical attention with acute- or chronic respiratory failure due to superimposed conditions, such as respiratory tract infection, or even post-anesthetic for an unrelated surgical procedure.

Again, other possible reasons of respiratory insufficiency (COPD, asthma, heart failure) should be excluded before setting the diagnosis.

Traditionally, patients with OHS were put on domiciliary oxygen, but lately NIV techniques are tested to normalize hypercapnia, eliminate hypoventilation and improve oxygenation. Normally, only nocturnal ventilation is needed, and with successfull weight loss programme NIV may be switched to CPAP alone.

In near future, we can expect many more such patients.

References

1. Sanders MH, Givelber R. Obesity, in Encyclopedia of Respiratory Medicine.
2. Poulain M, Doucet M, Major GC, Drapeau V, Series F, Boulet LP, et al. The effect of obesity on chronic respiratory diseases: pathophysiology and therapeutic strategies. CMAJ 2006; 174:1293-9.
3. Kopelman PG, Caterson ID, Dietz WH. Clinical obesity in adults and children.
4. Curr Opin Pulm Med 2007;13(6).

Severe respiratory failure

Šifrer F
University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia

Respiratory failure is a syndrome in which the respiratory system fails in one or both of its gas exchange functions: oxygenation and carbon dioxide elimination. In practice, respiratory failure is defined as a PaO_2 value of less than 60 mm Hg while breathing air or a $PaCO_2$ of more than 50 mm Hg. Furthermore, respiratory failure may be acute or chronic. While acute respiratory failure is characterized by life-threatening derangements in arterial blood gases and acid-base status, the manifestations of chronic respiratory failure are less dramatic and may not be as readily apparent.
In respiratory failure, the level of oxygen in the blood becomes dangerously low, and/or the level of CO_2 becomes dangerously high. There are two ways in which this can happen. Either the process by which oxygen and CO_2 are exchanged between the blood and the air spaces of the lungs (a process called "gas exchange") breaks down, or the movement of air in and out of the lungs (ventilation) does not take place properly.
Hypoxemic respiratory failure (type I) is characterized by a PaO_2 of less than 60 mm Hg with a normal or low $PaCO_2$. This is the most common form of respiratory failure, and it can be associated with virtually all acute diseases of the lung, which generally involve fluid filling or collapse of alveolar units. Some examples of type I respiratory failure are cardiogenic or noncardiogenic pulmonary edema, pneumonia, and pulmonary hemorrhage (1).
Hypercapnic respiratory failure (type II) is characterized by a $PaCO_2$ of more than 50 mm Hg. Hypoxemia is common in patients with hypercapnic respiratory failure who are breathing room air. The pH depends on the level of bicarbonate, which, in turn, is dependent on the duration of hypercapnia. Common etiologies include drug overdose, neuromuscular disease, chest wall abnormalities, and severe airway disorders (eg, asthma, chronic obstructive pulmonary disease [COPD]).
Acute hypercapnic respiratory failure develops over minutes to hours; therefore, pH is less than 7.3. Chronic respiratory failure develops over several days or longer, allowing time for renal compensation and an increase in bicarbonate concentration. Therefore, the pH usually is only slightly decreased.
The distinction between acute and chronic hypoxemic respiratory failure cannot readily be made on the basis of arterial blood gases. The clinical markers of chronic hypoxemia, such as polycythemia or cor pulmonale, suggest a long-standing disorder (2).
Several different abnormalities of breathing function can cause respiratory failure. The major categories, with specific examples of each, are:

- Obstruction of the airways. Examples are chronic bronchitis with heavy secretions; emphysema; cystic fibrosis; asthma (a condition in which it is very hard to get air in and out through narrowed breathing tubes).

- Weak breathing. This can be caused by drugs or alcohol, which depress the respiratory center; extreme obesity; or sleep apnea, where patients stop breathing for long periods while sleeping.
- Muscle weakness. This can be caused by a muscle disease called myasthenia; muscular dystrophy; polio; a stroke that paralyzes the respiratory muscles; injury of the spinal cord; or Lou Gehrig's disease.
- Lung diseases, including severe pneumonia. Pulmonary edema, or fluid in the lungs, can be the source of respiratory failure. Also, it can often be a result of heart disease; respiratory distress syndrome; pulmonary fibrosis and other scarring diseases of the lung; radiation exposure; burn injury when smoke is inhaled; and widespread lung cancer.
- An abnormal chest wall (a condition that can be caused by scoliosis or severe injury of the chest wall).

Respiratory failure can arise from an abnormality in any of the components of the respiratory system, including the airways, alveoli, central nervous system (CNS), peripheral nervous system, respiratory muscles, and chest wall. Patients who have hypoperfusion secondary to cardiogenic, hypovolemic, or septic shock often present with respiratory failure.

Hypoxemic respiratory failure: The pathophysiologic mechanisms that account for the hypoxemia observed in a wide variety of diseases are ventilation-perfusion (V/Q) mismatch and shunt. These 2 mechanisms lead to widening of the alveolar-arterial oxygen difference, which normally is less than 15 mm Hg. With V/Q mismatch, the areas of low ventilation relative to perfusion (low V/Q units) contribute to hypoxemia. An intrapulmonary or intracardiac shunt causes mixed venous (deoxygenated) blood to bypass ventilated alveoli and results in venous mixture. The distinction between V/Q mismatch and shunt can be made by assessing the response to oxygen supplementation or calculating the shunt fraction following inhalation of 100% oxygen. In most patients with hypoxemic respiratory failure, these 2 mechanisms coexist (3).

Hypercapnic respiratory failure: At a constant rate of carbon dioxide production, $PaCO_2$ is determined by the level of alveolar ventilation (Va), where VCO_2 is ventilation of carbon dioxide and K is a constant value (0.863).

$$Va = (K \times VCO_2)/PaCO_2$$

A decrease in alveolar ventilation can result from a reduction in overall (minute) ventilation or an increase in the proportion of dead space ventilation. A reduction in minute ventilation is observed primarily in the setting of neuromuscular disorders and CNS depression. In pure hypercapnic respiratory failure, the hypoxemia is easily corrected with oxygen therapy.

Hypoventilation, V/Q mismatch, and shunt are the most common pathophysiologic causes of acute respiratory failure. Hypoventilation is an uncommon cause of respiratory failure and usually occurs from depression of the CNS from drugs or neuromuscular diseases affecting respiratory muscles. Hypoventilation is characterized by hypercapnia and hypoxemia. The relationship between $PaCO_2$ and alveolar ventilation is hyperbolic. As ventilation decreases below 4-6 L/min, $PaCO_2$ rises precipitously. Hypoventilation can be differentiated from other causes of hypoxemia by the presence of a normal alveolar-arterial PO_2 gradient.

V/Q mismatch is the most common cause of hypoxemia. V/Q units may vary from low to high ratios in the presence of a disease process. The low V/Q units contribute to hypoxemia and hypercapnia in contrast to high V/Q units, which waste ventilation but do not affect gas exchange unless quite severe. The low V/Q ratio may occur either from a decrease in ventilation secondary to airway or interstitial lung disease or from overperfusion in the presence of normal ventilation. The overperfusion may occur in case of pulmonary embolism, where the blood is diverted to normally ventilated units from regions of lungs that have blood flow obstruction secondary to embolism. Administration of 100% oxygen eliminates all of the low V/Q units, thus leading to correction of hypoxemia. As hypoxemia increases the minute ventilation by chemoreceptor stimulation, the $PaCO_2$ level generally is not affected.

Shunt is defined as the persistence of hypoxemia despite 100% oxygen inhalation. The deoxygenated blood (mixed venous blood) bypasses the ventilated alveoli and mixes with oxygenated blood that has flowed through the ventilated alveoli, consequently leading to a reduction in arterial blood content. The shunt is calculated by the following equation:

$QS/QT = (CCO_2 – CaO_2)/(CCO_2 – CVO_2)$

QS/QT is the shunt fraction, CCO_2 (capillary oxygen content) is calculated from ideal alveolar PO_2, CaO_2 (arterial oxygen content) is derived from PaO_2 using the oxygen dissociation curve, and CVO_2 (mixed venous oxygen content) can be assumed or measured by drawing mixed venous blood from pulmonary arterial catheter.

Anatomical shunt exists in normal lungs because of the bronchial and thebesian circulations, accounting for 2 - 3% of shunt. A normal right-to-left shunt may occur from atrial septal defect, ventricular septal defect, patent ductus arteriosus, or arteriovenous malformation in the lung. Shunt as a cause of hypoxemia is observed primarily in pneumonia, atelectasis, and severe pulmonary edema of either cardiac or non-cardiac origin. Hypercapnia generally does not develop unless the shunt is excessive (>60%). When compared to V/Q mismatch, hypoxemia produced by shunt is difficult to correct by oxygen administration.

A majority of patients with respiratory failure are short of breath. Both low oxygen and high carbon dioxide can impair mental functions. Patients may become confused and disoriented and find it impossible to carry out their normal activities or do their work. Marked CO_2 excess can cause headaches and, in time, a semi-conscious state, or even coma. Low blood oxygen causes the skin to take on a bluish tinge. It also can cause an abnormal heart rhythm (arrhythmia). Physical examination may show a patient who is breathing rapidly, is restless, and has a rapid pulse. Lung disease may cause abnormal sounds heard when listening to the chest with a stethoscope: wheezing in asthma, "crackles" in obstructive lung disease. A patient with ventilatory failure is prone to gasp for breath, and may use the neck muscles to help expand the chest.

The symptoms and signs of respiratory failure are not specific. Rather, they depend on what is causing the failure and on the patient's condition before it developed. Good general health and some degree of "reserve" lung function will help see a patient through an episode of respiratory failure. The key diagnostic determination is to measure the amount of oxygen, carbon dioxide, and acid in the blood at regular intervals. A sudden low oxygen level in the lung tissue may cause the arteries of the lungs to narrow. This, in turn, causes the resistance in these vessels to increase, which can be measured using a special catheter. A high blood level of CO_2 may cause increased pressure in the fluid surrounding the brain and spinal cord.

The outlook for patients with respiratory failure depends chiefly on its cause. If the underlying disease can be effectively treated, with the patient's breathing supported in the meantime, the outlook is usually good (4).

If the kidneys fail or the diseased lungs become infected, the prognosis is worse. In some cases, the primary disease causing the lungs to fail is irreversible. The patient, family, and physician together then must decide whether to prolong life by ventilator support.

Because respiratory failure is not a disease itself, but the end result of many lung disorders, the best prevention is to treat any lung disease promptly and effectively. It is also important to make sure that any patient who has had lung disease is promptly treated for any respiratory infection (even of the upper respiratory tract). Patients with lung problems should also avoid exposure to pollutants, as much as is possible. Once respiratory failure is present, it is best for a patient to receive treatment in an intensive care unit, where specialized personnel and all the needed equipment are available. Close supervision of treatment, especially mechanical ventilation, will help minimize complications that would compound the problem.

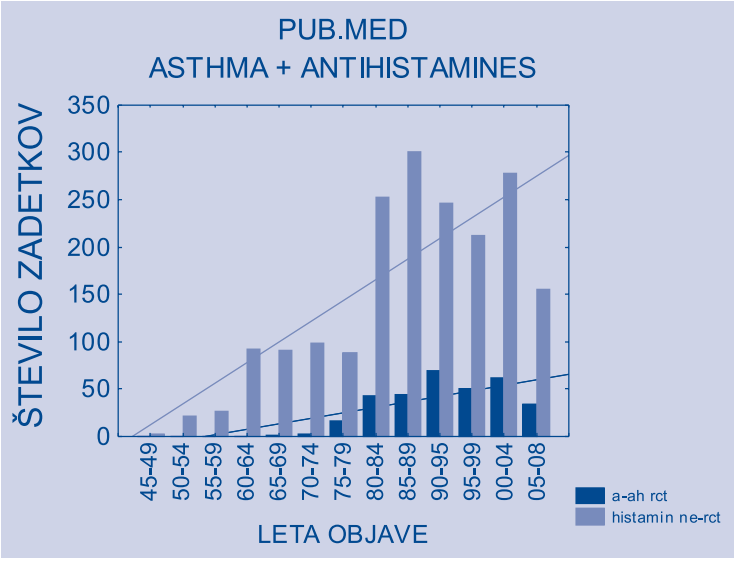
References

1. Kregenow DA, Rubenfeld GD, Hudson LD, Swenson ER. Hypercapnic acidosis and mortality in acute lung injury. Crit Care Med 2006; 34:1–7.
2. Andrews P, Azoulay E, Antonelli M, Brochard L, Brun-Buisson C, de Backer D, et al. Year in review in intensive care medicine 2005. Acute respiratory failure and acute lung injury, ventilation, hemodynamics, education, renal failure. Intensive Care Med 2006; 32:207– 16.
3. Broccard AF. Respiratory acidosis and acute respiratory distress syndrome: time to trade in a bull market? Crit Care Med 2006; 34:229–31.
4. Connors AF, Dawson NV, Thomas C, Harrell FE Jr, Desbiens N, Fulkerson WJ, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. Am J Respir Crit Care Med 1996; 154:959–67.

Statistična in znanstvena signifikanca: razvoj zdravljenja astme z antihistaminiki

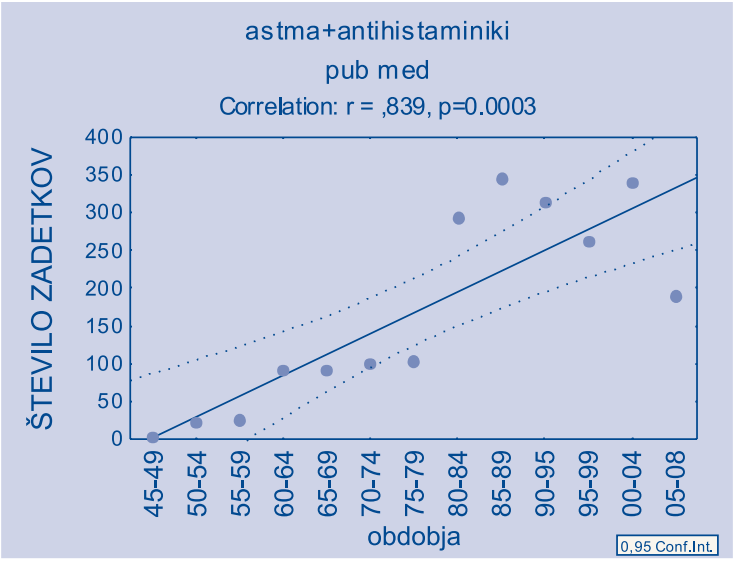
Šuškovič S
Bolnišnica Golnik - Klinični oddelek za pljučne bolezni in alergijo, Slovenija

Dael in Laindlow sta že pred dobrimi sto leti ugotovila, da injiciranje histamina poizkusnim živalim (še posebej pri budri) sproži astmatsko dušenje (1). Pomembnost histamina v astmatskem dušenju sta med drugimi 30 let kasneje potrdila Randolph in Rackeman (2) z razkritjem povečane koncentracije histamina v krvi bolnikov s poslabšanjem astme.
Herxheimer je 1949 leta prikazal, da antihistaminik phenergan občutno zavira bronhospazem sprožen z vdihavanjem acetil-metilholina ali pelodov (3). Zaključil je, da so antihistaminiki »of considerable value in the treatment of asthma«.
Učinek tega in še nekaj njemu podobnih sporočil iz tega časa je bil nepričakovano velik.
V PubMedu je najti za iskalni niz »asthma + antihistamines« 2185 zadetkov. Od tega 324 zadetkov za randomizirane kontrolirane raziskave (RCT) in 1861 zadetkov za ostala poročila (slika 1).



Slika 1. Objave v PubMedu o antihistaminikih pri astmi.(RCT-randomised controled trial).

Razviden je jasen in tudi statistično pomemben trend naraščanja tovrstnih poročil in raziskav (slika 2). Upravičeno?



Slika 2. Naraščanje poročil v PubMedu o vseh objavah o antihistaminikih pri astmi.

O tem se je že 1980 leta vprašal Chai (4). Zaključil je »The outlook for antihistamines becoming a prominent feature in the management of asthma is not very bright. Time will tell«.
Poglejmo, kaj je prinesel čas. Leta 1997 je bila objavljena meta-analiza o vlogi antihistaminikov pri astmi (5). Z zaključkom »Respiratory effects observed after use of antihistamines do not support the use of these medications in the treatment of asthma«.
Kljub temu je bilo po letu 1997 opravljenih preko 100 RCT na to temo.
Kar se odraža v jedrnatem mnenju letošnjih Britanskih smernic za astmo (6): »Antihistamines are ineffective«.
Vendar glede na jasen trend naraščanja preučevanj antihistaminikov pri astmi vseh raziskovalcev še ni prepričalo. Tudi etičnih komisij očitno ne.

Literatura

1. Dale HH, Laidlaw PP (1910). J. Physiol. 41, 318. (v: Epstein D. The action of histamine on the respiratory tract. J. Physiol. 1932; 76: 347–67.
2. Randolph TG., Rackemann FM. The blood histamine level in asthma and in eosinophilia. J.Allergy 1941; 12: 450.
3. Herxheimer H. Antihistamines in bronchial asthma BMJ 1949: 22: 901-5.
4. Chai H. Antihistamines and asthma;do they have a role in therapy? Chest 1980; 78:420-2.
5. Van Ganse E, Kaufman L, Derde M, Yernault JC, Delaunois L, Vincken W. Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. Eur Respir J 1997; 10:2216-24.
6. British Guidelines on the Management of Asthma. British Thoracic Society Scottish Intercollegiate Guidelines Network. Thorax 2008; 63;1-121.

Predicting efficacy of venom immunotherapy with basophil activation test

Peternelj A, Šilar M, Eržen R, Košnik M, Korošec P
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Treatment failure of venom immunotherapy (VIT) is not rare and the risk and pathogenic factors for those failures are so far poorly understood. For that reason we evaluated allergen-specific basophil sensitivity in patients, who did not tolerate field re-stings after completed VIT treatment.

Materials and Methods. Basophil responsiveness was evaluated by flow cytometry analyses of basophil CD63 surface expression induced by different concentrations of bee or wasp venom (1, 0.1 and 0.01 µg/ml) in 14 treated patients who had experienced systemic allergic reactions (Muller grades II-III) and 17 treated patients who had no reactions after the field re-stings. We also included a group of 28 Hymenoptera venom allergic patients who have not received VIT.

Results. In 14 patients who still reacted to bee or wasp sting, basophil response at a venom concentration of 0.1 µg/ml was significantly higher then in patients who tolerated field re-stings (P=0.03; t-test). Basophil response was also slightly higher at a concentration of 1 µg/ml, but not to statistical significance (P=0.12; t-test). There was no difference in the response to direct cross-linking of the IgE and in venom specific IgE and IgG4 serum concentrations between those two groups (P>0.8; Fischer exact test, t-test). Patients who tolerated field re-stings also had significantly lower basophil response in comparison to patients who have not received VIT, both at 0.1 and 1 µg/ml of venom concentrations (P<0.001; t-test).

Conclusions. The results suggest that basophil venom specific sensitivity is associated with the efficiency of venom immunotherapy.

The prevalence of autoimmune thyroiditis in chronic urticaria

Adamič K, Bajrović N, Košnik M
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Chronic urticaria (CU) has been defined as daily or almost daily symptoms of hives for more than 6 weeks. BSACI guidelines included also the patients with episodic acute intermittent urticaria lasting for hours or days and recurring over months or years. Urticaria may occur alone in about 50% of cases, urticaria with angio-oedema in 40%, and angio-oedema without urticaria in 10%. CU affects 0.5%-1% of individuals and significantly reduces quality of life. Women are affected 2 times more often than men. The aetiology of CU is unknown in up to 90% of cases. Autoimmune urticaria accounts for about 30-50% of CU. In the skin there are present IgG antibodies against the Fc^{o}-RI on mast cells or against the IgE bounded to mast cells. It may be associated with other autoimmune conditions such as thyroiditis. Autoimmune urticaria is more resistant to treatment and can follow a protracted course. In about one quarter of patients CU is associated with anti-thyroid antibodies. Many of them are euthyrotic or subclinically hypothyrotic. In some cases the symptoms of urticaria were improved after treatment with levothyroxine, even in euthyrotic patients. The papers estimate the prevalence of anti-thyroid antibodies in general population around 6-8%, but the extensive American survey NHANES III has found the presence of anti-thyroid antibodies in 18% of white population all ages, respectively in 29% of women aged 60 years or more.

Materials and Methods. In the retrospective survey we investigated adult patients with CU treated in our clinic from January 2005 until June 2008. The patients data were collected from the hospital information system Birpis. The values of thyroid antibodies were provided by the Head of Department for Nuclear Medicine (Prof. S. Hojker).

Results. From January 2005 until June 2008, 320 patients with CU were treated in our clinic. In 62 (19%) of them the anti-thyroid antibodies (anti-thyroid peroxidase and anti-thyroglobulin antibodies) were increased. 58 (94%) were female with a mean age of 46 (range 18-79 years), 4 (6%) male with a mean age of 58 (range 49-83 years). 36 (58%) were euthyroid, 17 (27%) hypothyroid, 3 (5%) hyperthyroid and there are no data on thyroid function for 6 patients. All of them were reffered to the specialist for thyroid diseases.

Conclusions. The prevalence of antithyroid antibodies in our group of patients with CU is comparable to the prevalence of antithyroid antibodies in general population in NHANES III study. These results suggest that CU and thyroiditis are probably two parallel autoimmune diseases. The treatment with levothyroxine has been associated with the remission of CU in some cases, but there is not

enough evidence. The randomized double-blind placebo-controlled study is required to evaluate the role of the treatment with levothyroxine in CU.

References

1. Košnik M., Zbornik sestanka: Kronična urtikarija in angioedem 2008; Ljubljana.
2. Powell RJ, Du Toit GL, Siddique N, Leech SC, Dixon TA, Clark AT, et al. BSACI guidelines for the management of chronic urticaria and angio-oedema. Clinical & Experimental Allergy 2007; 37:631-50.
3. Kaplan AP. Chronic urticaria: pathogenesis and treatment. JACI 2004; 114:465-74.

IgG induced basophil desensitisation during birch pollen immunotherapy

Lalek N , Šilar M , Eržen R , Košnik M , Korošec P
[1]Department of Pulmology, Hospital Topolšica, Topolšica, Slovenia
[2]University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Changes in specific responsiveness of effector cells in allergic inflammation might be an important mechanism of allergen specific immunotherapy (SIT).

Materials and Methods. Basophil surface CD63 expression induced by birch pollen allergen was measured by flow cytometry in 9 patients before and during treatment with subcutaneous birch pollen specific immunotherapy. Basophil sensitivity was evaluated by comparing the increasing dose dependent CD63 activation induced by 4 different log allergen concentrations. We also included 9 patients with birch pollen allergic rhinoconjunctivitis (5 for positive control group, 4 for inhibition experiments) and 8 negative control subjects.

Results. Basophil CD63 responsiveness was significantly decreased at submaximal concentrations 2, 3 and 5 months after starting the treatment with birch pollen immunotherapy ($P<0.03$; nonparametric Wilcoxon test). Serum of the patients on specific immunotherapy also showed inhibitory effect. This was observed by the induction of decreased allergen specific response in donor basophils, after mixing donor blood with serum of patient on SIT. Decreased CD63 responsiveness of donor basophils was not observed after removal of IgG from the serum.

Conclusions. Results showed that specific basophil CD63 responsiveness is changing markedly during birch pollen immunotherapy. One of the important mechanisms for desensitization appears to be the formation of birch pollen specific IgG during specific immunotherapy. Basophil responsiveness seems to be very useful for the determination of patient`s pollen allergen sensitivity and should be further evaluated for the possible measurement and monitoring of immunotherapy treatment efficacy.

Candida albicans antigen should not be part of allergen skin prick test screening panel

Kopač P, Bajrović N, Zidarn M
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Hypersensitivity to *Candida albicans* has a controversial role in pathogenesis of allergic diseases. It is commonly found in cultures from the nasopharynx and the faeces of healthy persons and thus considered mainly "saprophytic". *C. albicans* is proposed to play a role in asthma, allergic rhinitis, urticaria and atopic dermatitis, although so far studies have not clearly confirmed that. No correlation between the saprophytic growth and allergy symptoms was found (1). Positive skin response to *C.albicans* is common in normal population. In our environment *C. albicans* antigen is often part of allergen skin prick test screening panel, although a positive result is rarely of clinical significance.

Materials and Methods. We retrospectively analyzed 100 randomly chosen patients out of 482 patients who had positive results of skin prick test with *C. albicans* performed in our institution from 2002 until 2007.

Results. Forty-three patients had symptoms of rhinoconjunctivitis. 19 patients (44%) had explicitly seasonal problems and had confirmed sensitization to pollens. Sixteen patients (37%) had annual problems; 9 of them were sensitized also to house mite allergen while 7 patients were not sensitized to any other important annual allergen. Eight patients had other diagnoses: vasomotoric rhinitis (4 patients), nasal polyposis (3) and rhinitis due to occupational allergen (1). Sixteen patients had asthma; 4 of them (25%) achieved good asthma control using only inhaled corticosteroids, while 10 patients (62%) needed addition of long-acting $ß_2$-agonist or leukotriene modifier. Two patients suffered from occupational asthma (baker, tanner). Twenty-six patients had skin symptoms; 4 of them (15%) had atopic dermatitis and 15 (57%) chronic idiopathic urticaria. Other patients were treated because of food induced urticaria (2 patients), contact dermatitis (nickel or latex - 4) and other dermatological diseases (1). The diagnoses of the remaining 15 patients were as follows: dermographism (4 patients), insect venom allergy 84), gastroesophageal reflux disease (3), coeliac disease (1) and chronic cough (1).

Conclusions. Positive reactions of skin prick test with *C. albicans* were most common in patients with rhinoconjunctivitis, which is also the most common allergic disease in our environment (2). In most of these patients, according to patient's history, sensitization to another allergen was important. 15% of the patients had positive skin prick tests only with *C. albicans*, although none had any specific therapeutic consequences. Diagnosis of allergic fungal sinusitis is based on histological and radiographic

criteria (4). Most patients with asthma achieved good control with inhaled corticosteroids in combination with long-acting $ß_2$-agonist. None of them had severe asthma or steroid dependent asthma. Allergic bronchopulmonary mycosis is possible entity in patients with severe asthma. Diagnosis is based on the presence of a combination of immediate cutaneous reaction, clinical, biological and radiological criteria. Reefer et al. have shown that hypersensitivity to microbial allergens is an unlikely trigger for eczematous eruptions (5). We suggest the removal of skin prick test with *C. albicans* antigen from allergen skin prick test screening panel, as its role remains indistinct and a positive reaction to the test is not followed by any therapeutic measures. It should however be used in case of defined disease suspicion (e.g. allergic bronchopulmonary mycosis) (3).

References

1. Koivikko A, Kalimo K, Nieminen E, Viander M. Relationship of immediate and delayed hypersensitivity to nasopharyngeal and intestinal growth of Candida albicans in allergic subjects. Allergy 1988; 43:201-5.
2. Dahl R, Andersen PS, Chivato T, Valovirta E, de Monchy J. National prevalence of respiratory allergic disorders. 2004; 98:398-403.
3. Roig E, Malo JL, Montplaisir S. Anti-Candida albicans IgE and IgG subclasses in sera of patients with allergic bronchopulmonary aspergillosis (ABPA). Allergy 1997; 52:394-403.
4. Schubert MS. Medical treatment of allergic fungal sinusitis. Ann Allergy Asthma Immunol 2000; 85:90-101.
5. Reefer AJ, Satinover SM, Wilson BB, Woodfolk JA. The relevance of microbial allergens to the IgE antibody repertoire in atopic and nonatopic eczema. JACI; 120:156-63.

Shorter ultra rush immunotherapy protocol for Hymenoptera sting allergy is not associated with higher frequency of side effects

Kopač P, Adamič K, Zidarn M, Eržen R, Bajrović N, Košnik M, Mušič E
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Hymenoptera venom allergy is a significant epidemiological problem. Systemic allergic reactions after Hymenoptera sting occur in 0.15% – 3% of general population. Specific venom immunotherapy (VIT) is the only effective way to reduce severe systemic allergic reactions. Since the first use of VIT in 1974 several protocols of various duration have been in use. Time required to reach maintenance dose (MD) of 100 µg in dose increase phase varies from months to days (rush) and even hours (ultra rush). The precise mechanisms responsible for beneficial effects of VIT remain unclear. There is a shift from Th2 to Th1 type cytokine production. Production of specific IgG4 subclass, which may intercept the allergen and block the response, is stimulated and IgE are inhibited (1). There are also changes on the level of effector cells of allergic inflammation such as eosinophils, basophils and mast cells. Activity for degranulation and systemic anaphylaxis in mast cells and basophils is decreased. That is important for early effect of immunotherapy. The precise mechanism of this effect is still unknown and also least studied. Brechler et al. had shown that shorter dose increase phase reduces the incidence and severity of adverse reactions (3).
We performed an analysis of rush two-day protocol in which we analyzed 875 patients hospitalized from year 2000 to 2006 in our institution. Frequency of systemic side effects during dose increase phase was 18% with honeybee VIT and 8% with wasp VIT. Frequency of local side effects was 8% (4). With this study we wanted to compare safety of one-day ultrarush protocol VIT with our previous two days protocol. The whole MD (100 µg) in single injection was first administered on day 5 in one day protocol, in contrast to two days protocol, where it was first administered on day 25.

Materials and Methods. Thirty-four patients with Hymenoptera venom allergy (14 honeybee-, 20 wasp venom – allergic patients) underwent one day ultrarush protocol. They received 111 µg of venom in 3 hours. All patients received antihistamine premedication. Local and systemic side effects were recorded.

Results. During dose increase phase of one day ultrarush protocol with honeybee venom 2 patients (14%), experienced mild systemic side effect (grade I) with facial rash. One patient (5%) treated with wasp venom experienced large local reaction.

Conclusions. In comparison with the two days ultrarush protocol, the one day protocol had shown fewer systemic and local side effects. According to this analysis administration of increasing doses of venom within a very short period is not associated with the higher frequency of side effects. Ex-

perience with more patients is needed. MD in single injection was administered much earlier in one day protocol than in two days protocol.

Comparison of two different protocols of VIT: two days ultrarush protocol versus one day ultrarush protocol.

Two days protocol:

day	time (min)	dose (µg)
1	**0**	0,02
	15	0,03
	30	0,05
	45	0,2
	60	0,3
	75	0,5
	90	2
	105	3
	120	5
2	**0**	10
	15	20
	30	30
	45	40
4	**0**	20
	15	30
	30	50
11	**0**	50
	15	50
25	**0**	100

One day protocol:

day	time (min)	dose (µg)
1	**0**	0,03
	15	0,07
	30	0,3
	45	0,7
	60	2
	75	3
	90	5
	105	10
	120	20
	135	30
	150	40
2	**0**	50
	15	50
5	**0**	100

References

1. Bonifazi F, Jutel M, Bilo MB; Birnbaum J, Muller U; EAACI Interest Group on Insect Venom Hypersensitivity. Prevention and treatment of hymenoptera venom allergy. Allergy 2005; 1459-70.
2. Roll A, Hofbauer G, Ballmer-Weber BK, Schmid-Grendelmeier P. Safety of specific immunotherapy using a four-hour ultra-rush induction scheme in bee and wasp allergy. J Investig Allergol Clin Immunol 2006; 16:79-85.
3. Brechler R, WolfH, Kutting B, Schnitker J, Luger T. Safety of a two.day ultrarush insect venom immunotherapy protocol in comparison with protocols of longer duration and involving larger number of injections. JACI 2000; 105:1231-5.
4. Adamič K, Zidarn M, Bajrović N, Košnik M. Stranski učinki subkutane imunoterapije. Klinična imunologija, KOPB: zbornik predavanj. Golniški simpozij 2007.

Hypersensitivity occurring during anaesthesia – analysis of test results in hospitalized patients

Edelbaher N[1], Mušič E[2]
[1]University Clinical Centre, Maribor, Slovenia
[2]University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Drug hypersensitivity represents about 15% of all adverse drug reactions. During anaesthesia patient is exposed to many different substances. Neuromuscular blocking agents (NMBA) are most common cause of anaphilaxis during anaesthesia.

Materials and Methods. We performed retrospective analysis of test results of 301 patients (261 females and 40 males) tested in University Clinic of Respiratory and Allergic Diseases Golnik from January 1, 2005 to December 31, 2007 because of hypersensitivity reaction during local or general anaesthesia.

Results. 249 patients were tested with local anaesthetics (LA) and only 3 tested positive. 71 patients were tested for hypersensitivity during general anaesthesia and 55 tested positive for NMBAs.

Conclusions. LA are rarely the cause of anaphilaxis. We probably had some false positive results in group tested positive for NMBA. Patients are referred to allergologist with insufficient data.

Long-term follow-up of immunotherapy of grass pollen allergy by measurement of changes of serum IgE level

Prnjavorac B[1], Abduzaimovic K[1], Jevric Causevic A[2], Mujaric E[3]
[1]General Hospital, Tesanj, Bosnia and Herzegovina
[2]Department of Biochemistry, Faculty of Pharmacy, University of Sarajevo, Bosnia and Herzegovina
[3]Cantonal Hospital, Zenica, Bosnia and Herzegovina

Background. According to last GINA guidelines immunotherapy is one of the regular choices of treatment of allergic diseases. It is noted in the shortest issues of recommendations for treatment of allergic diseases, actually in the column of forth choice of methods. Surely, the first choice is treatment with inhaled steroids. In many cases first or second step of therapy according to GINA concept, failed to control symptoms of diseases. Current concept of therapy of allergic diseases considers immunotherapy as effective in patients with IgE-mediated reactions. New concept of immunotherapy takes in consideration new approach for allergen applications, mostly as sublingual immunotherapy.

Materials and Methods. Patients with grass pollen allergy, tested by subcutaneous methods have been analysed. In these patients measurement of IgE level was performed before immunotherapy, and after two years of regular subcutaneous treatment. IgE concentration was measured by ELISA method, using ABBOT analyzer. Immunotherapy was performed with standard four steps of allergen concentrations.

Results. During period of nine years we performed skin testing for 448 patients. 223 out of them were taken for long term subcutaneous immunotherapy. Among them 56 were treated for grass pollen allergy. At the start of the treatment mean IgE level was 518 IU/ml (SD 386), ranged from minimal 36,8 IU/ml to maximal 3697 IU/ml. After two years of immunotherapy mean level was 249 IU/ml (SD 278), minimal 33,5 IU/ml, maximal 2885 IU/ml. 5 patients withdrew from immunotherapy for different reasons, most of them in the first three months. Statistical analysis was performed by Kolmogorow-Smirnov nonparametric test, because of dispersed IgE results. Decreasing of IgE level was significant at level of $p<0,05$. Reduction of symptoms in patients was evident.

Conclusions. According to our results immunotherapy with standard grass pollen allergen is effective and safe. Results were performed by 9 years follow up of patients in whom allergy was diagnosed by skin testing and measurement of serum levels of IgE. No serious adverse reactions of immunotherapy were registered. Effectiveness of therapy was shown after three months of therapy. Reduction of symptoms in patients, as well as decreasing of IgE, was shown.

The role of native purified allergen components in diagnosis of bee/wasp double sensitized patients

Peternelj A, Šilar M, Korošec P, Košnik M
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Double-sensitized bee/wasp allergic patients have either distinct antibodies for each venom or cross-reacting antibodies that recognize similar or identical epitopes in both venoms. The aim of this study was to test phospholipase A2 nAPI m1 on a well defined group of patients and to show whether it could distinguish cross-reactors from non cross-reactors. Phospholipase A2 nApi m1 is an allergen component purified from the venom of Honey bee (Apis mellifera). Phospholipase A2 (PLA2) is a biochemically well-defined glycoprotein of 14-16 kDa, consisting of 134 amino acids with a single carbohydrate side chain at a position Asn13. It constitutes 12-14% of the dry weight and is the major protein component in honey bee venom. 90% of bee-venom allergic patients have elevated sIgE for PLA2. No cross-reactivity with vespidae phospholipase A1 has been reported.

Materials and Methods. PLA2 nAPI m1-specific IgE (k203; Phadia, Uppsala, Sweden) were measured in 30 well defined Hymenoptera venom allergic patients with CAP-FEIA (Phadia, Uppsala, Sweden). Twenty of these patients had positive sIgE for wasp venom and no detectable levels of sIgE for bee venom. Ten patients had positive sIgE for bee and wasp venom.

Results. nAPI m1-specific IgE were negative in all 20 patients with positive sIgE only for wasp venom. All 10 patients with positive sIgE for bee and wasp venom had positive sIgE for nAPI m1. In this group inhibition test revealed 5 double primary sensitization (all 5 negative sIgE for MUXF3; 4 negative and 1 positive sIgE for oilseed rape), 1 bee venom primary sensitization (positive sIgE for MUXF3 and oilseed rape) and 4 wasp venom primary sensitization (3 positive and 1 negative sIgE for MUXF3; 2 positive and 2 negative sIgE for oilseed rape).

Conclusions. We showed that nAPI m1 provides no false positive results. Our results also indicate that nAPI m1 confirms bee venom allergy in patients diagnosed as double sensitized. Therefore, our results suggest that purified and molecularly defined allergens could help to identify the precise allergen reactivity in sensitized individuals. However, further studies with more patients are needed to reveal whether nAPI m1 strictly distinguishes true double sensitized patients from cross-reactors.

Olopatadine in the treatment of allergic conjunctivitis

Zidarn M, Eržen D, Mušič E, Eržen R, Bajrović N, Košnik M
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Allergic rhinoconjunctivitis is the most frequent allergic disease. Estimated prevalence in European countries ranges from 11,7% to 33,5% (1, 2). 90% of patients with allergic rhinoconjunctivitis have ocular symptoms. Conjunctivitis is frequently the most troublesome part of the disease. Olopatadine (Opatanol®, Alcon) is new anti-allergic drug with dual mechanism for the treatment of allergic conjunctivitis. It inhibits H_1 receptor activation and stabilizes mast cell membranes. Onset of action is within 5 minutes after administration, while duration of action is over 8 hours. Several studies had confirmed good efficacy and comfort. In our study we wanted to determine the efficacy of olopatadine in the treatment of allergic conjunctivitis and its influence on the quality of life in our patients with allergic conjunctivitis.

Materials and Methods. Eighteen patients with current symptoms of seasonal or perennial allergic conjunctivitis and confirmed sensitization to seasonal or perennial allergen were enrolled in this two visit study. Patients received the drug at the first visit and filled out the questionnaire. They were asked to use two drops of medication per eye per day. Other antiallergic medications were allowed. The second visit was scheduled after 14 days of treatment. Ocular symptoms score and conjunctivitis health related quality of life questionnaire was assessed before and after 14 days of treatment.

Results. Average ocular score was 15,4 (±5,6) before treatment and was reduced to 8,2 (±5,8) after 14 days of treatment. Difference was statistically significant (t=3,81; p=0,0014). Average health related quality of life score before treatment was 107,1 (±43,2) and was reduced to 68,8 (±40,9) after treatment. Difference was statistically significant (t=3,15; p=0,0058). No serious adverse events were reported.

Conclusion. The results indicate that olopatadine is effective in the treatment of allergic conjunctivitis.

Acknowledgement
This study was supported by Alcon Slovenija.

References

1. Dahl R, Andersen PS, Chivato T, Valovirta E, de Monchy J. National prevalence of respiratory allergic disorders. 2004; 98:398-403.
2. Nathan H, Meltzer EO, Selner JC, Storm W. Prevalence of allergic rhinitis in the United States. J Allergy Clin Immunol 1989; 99:s808-14.

Relationship between basophil activation test results and clinical picture of acetylsalicylic acid intolerance

Mavsar N, Bajrović N, Šilar M, Košnik M, Korošec P
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. The mechanism of aspirin (ASA) intolerance (AI) is not fully understood yet. It is believed to be linked to the pharmacological effect of ASA. ASA inhibits the cyclooxygenase enzyme which catalyzes the transformation of arachidonic acid to prostaglandins. The diagnosis of ASA intolerance can be confirmed with provocation tests, which can be oral, nasal or bronchial. The testing is dangerous and time-consuming. Therefore, methods are being developed where a provocation test could be done in vitro. One of them is the basophil activation test (BAT). The principle of the test is basophil activation with ASA, followed by the measurement of CD63 - surface markers of basophil activation.

Materials and Methods. We performed a retrospective single-blind study to determine the relationship between the clinical diagnosis and the BAT results. Clinical data of patients with history of AI were analyzed and conclusions on ASA tolerance were formed. Afterwards, BAT results were obtained.

Results. We found no statistical difference between the baseline response of ASA tolerant and ASA intolerant participants. Furthermore, there was no statistical difference between the two groups after the addition of the two positive controls. A statistical difference was shown between the groups when comparing the BAT index. The BAT index is the ratio between the basophil response after the addition of 1 mg/ml concentration of ASA and the baseline basophil response. The basophils of ASA intolerant participants were more responsive and the BAT index for this group was larger. The participants were further divided into subgroups. There were larger BAT index changes in the subgroups of participants without chronic urticaria but who had asthma, rhinitis, nasal polyposis or other chronic condition, or were otherwise healthy. The BAT index median was 1,5 for the ASA tolerant subgroup and 3,6 for the ASA intolerant subgroup. The limit is set to current BAT index value of 3.

Conclusions. Despite the difference shown between BAT indexes of ASA tolerant and ASA intolerant participants, BAT was not proven to be a clinically useful method. Specificity and sensitivity were 82,9% in 52,4%, respectively. Due to such low values, too many false positive and false negative results would be obtained during ASA intolerance testing. Therefore, BAT was shown to be primarily useful for the research of disease mechanism.

The increase of allergic respiratory diseases

Edoba P
Central Hospital Benin, Benin

Background. The increasing prevalence of allergic respiratory diseases, asthma and allergic rhinoconjunctivitis has been attributed in part to the lack of microbial burden in 1st and 2nd world countries.

The inverse relationship between the number of infection early in life and atopy has been interpreted as the "Hygienic hypothesis".

We evaluated here the role of coding variation, ser 249 pro, in the TLR 6 gene in the pathogenesis of asthma, atopic dermatis (AD) and chronic obstructive pulmonary disease (COPD).

Methods. Genotype of the ser 249 pro polymorphism in 63 unrelated adult patients and 127 unrelated children with asthma, 180 unrelated patients with COPD, 290 unrelated individuals with AD.

Results: We analysed a weak association of the 249 ser allele with childhood ashma (P 0.03). No association was evident to AD or COPD.

Conclusion. Omalizumab provides an integrated approach for the treatment and management of allergic respiratory diseases.

High sensitivity of basophils predicts side effects in bee venom immunotherapy in children

Žitnik S[1], Glavnik V[1], Avčin T[1], Accetto M[1], Toplak N[1], Šilar M[2], Košnik M[2], Korošec P[2]
[1]Childrens Hospital Ljubljana, Department of Allergy, Rheumatology and Clinical Immunology, Ljubljana, Slovenia
[2]University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Systemic side effects of venom immunotherapy (VIT) represent a considerable problem in the treatment of children allergic to bee venom.
Materials and Methods. Basophil surface expression of activation marker CD63 induced by different concentrations of honey bee and wasp venom (0.1 µg/mL and 1 µg/mL) was measured by flow cytometry in 12 children with history of systemic anaphylactic reactions to bee sting just before starting VIT, 5 days after VIT and 6 months after VIT.

Figure 1

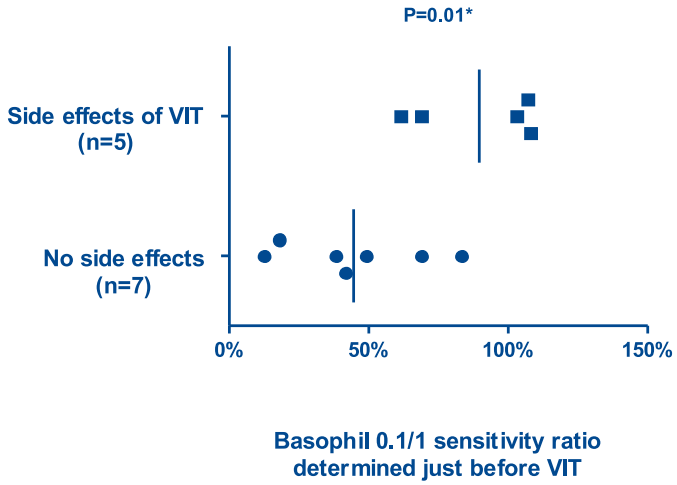
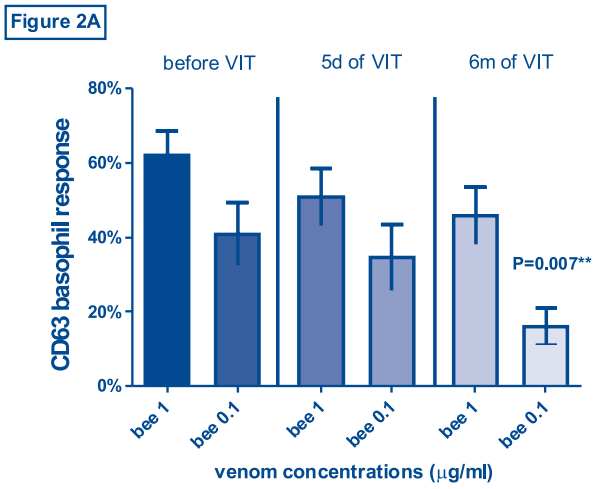


Figure 1. Basophil sensitivity determined just before bee VIT as a percentage ratio between CD63 in vitro response at 0.1 µg/ml and 1 ug/ml of bee venom dilutions in children with (n=5) and without (n=7) side-effects to bee venom immunotherapy. The vertical solid bars indicate the mean value for each group.

Results. Four of 12 children had systemic anaphylactic reaction (Mueller grades I-II) and 1 patient a large local reaction to bee venom immunotherapy. In these 5 children, mean percentage of activated basophils after stimulation with VIT specific venom in concentration of 0.1 µg/mL was 90% (range 61–108%) of value reached with stimulation with 1 µg/mL. In contrast, in 7 children with no side effects the mean 0.1/1 ratio was 45% (range 13–84%). These concentration-dependent activation ratios were significantly different between the groups with and without side reactions (P=0.01, t-test). We also show that 0.1/1 ratios fall significantly after 6 months of immunotherapy in majority of our study children population (mean 0.1/1 ratios: 64% vs.34%; P=0.003, t-test). There was no significant difference only after 5 days of treatment.

Conclusions. The results suggest that increased basophil sensitivity to allergen specific in vitro stimulation is significantly associated with side effects of bee venom immunotherapy in children. Furthermore, we also showed that in children already 6 months of immunotherapy induce decreased basophile specific sensitivity. These results support the importance of continued investigation of basophil specific sensitivity in venom immunotherapy.



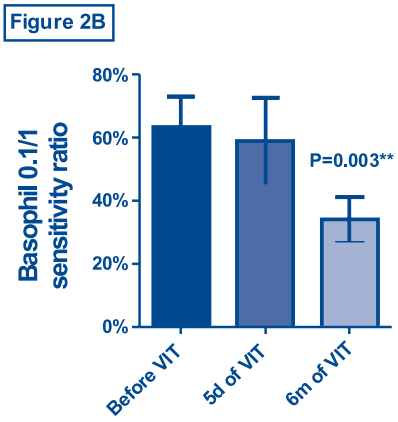


Figure 2. Basophil *in vitro* responsiveness at 1 and 0.1 ug/ml of bee venom **(2A)**, and basophil 0.1/1 sensitivity ratio **(2B)** in patients before bee venom immunotherapy (VIT), after 5 days of VIT and after 6 months of VIT. Data are presented as mean (SEM).

Drugcheck

Toni J
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

DrugCheck is an on-line, pan-European service, which gathers, organizes, stores, makes available and presents information and data covering pharmaceuticals and their interactions. The service provides a user-friendly, reliable, intelligent and fast mechanism to assist healthcare professionals in making the appropriate decisions on medication prescriptions and pharmaceutical treatments both in and out of the hospital without interrupting healthcare delivery.

The validation of the DrugCheck service is funded by the European Community program eTEN. Greece, The Netherlands, France and Slovenia (The University Clinic Golnik and Alianta) are co-operating on the project. Data covering pharmaceuticals and their interactions was prepared by Faculty of Medicine, University of Ioannina (Greece).
DrugCheck service can be a valuable tool to all healthcare professionals who want fast access to trusted and verified information about potential interactions between pharmaceuticals. The service is not limited to the information offered from the drug's documentation provided from the companies but offers information on mechanisms and results of interactions between pharmaceuticals based on latest bibliography and publications.

Drugcheck service offers the following functionality:
- Drug Interactions: The service describes the various types of interactions between pharmaceuticals (and also nutritional elements).
- Detailed description of the interaction mechanism and the mechanism in case of special patients groups, location of interaction, pharmacokinetic properties etc.
- Reference to the necessity of the measurement of the levels of some of the medicines already administered or scheduled to be administered to the patient, in order to decide the right dose of the medicine to minimize the risk of potential interactions
- Effect of interactions and management of effects

It is envisaged that the service, after its deployment, will be an invaluable companion to a wide range of healthcare professionals, by enhancing their skills and empowering their decision-making processes, thus reducing unwanted effects and improving cost-effectiveness of patients' treatment and therefore contributing to better healthcare services for all citizens.

http://www.drug-check.org/

Influence of multi-drug resistance proteins on the outcome of chemotherapy in patients with small cell lung cancer

Cof B[1], Triller N[1], Knez L[1], Mrhar A[2], Košnik M[1]
[1]University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia
[2]University Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia

Background. The phenomenon of drug resistance to anticancer drugs is one of the major causes of treatment failure in cancer. There are several mechanisms that contribute to drug resistance. Multi-drug resistance (MDR) is cross-resistance to some structurally and functionally unrelated drugs and is related to transport mediated resistance for which transmembrane proteins P-glycoprotein (P-gp), multi-drug resistance protein 1 (MRP1) and cytoplasmic lung resistance protein (LRP) are responsible. These transport proteins are present in normal cells, where they protect cells from toxic substances, as also in tumour cells, where they extrude chemotherapeutic drugs out of the cells, away from the site of action, leading to reduced drug action.
The aim of our study was to investigate the influence of multi-drug resistance proteins, P-gp, MRP1 and LRP, on the outcome of chemotherapy in patients with small cell lung cancer (SCLC). The outcome was defined as the response to chemotherapy and survival of patients.

Materials and Methods. Fifteen patients diagnosed with SCLC and treated with chemotherapy, were retrospectively enrolled in the study. Enrolled patients had to be chemo- and radiotherapy naive, and had to have an ECOG performance status between 0 and 2. The response to chemotherapy was evaluated by chest X-ray films according to RECIST criteria after the completion of the second and fourth cycle of chemotherapy. Survival of patients was estimated by Kaplan-Meier method. Specimens were obtained by biopsy of lung tumor or by puncture of metastatic enlarged mediastinal lymph nodes. Expression of P-gp, MRP1 and LRP was determined in fifteen immunocytochemically stained tumor specimens of SCLC, which were methanol-fixed. Enzyme-coupled avidin-biotin indirect method was used. ICC was performed in apparatus Ventana BenchMark™ (Ventana Medical Systems, Inc., Tuscon, USA). For P-gp mouse monoclonal antibody (Ab) to P-gp (Abcam Ltd., Cambridge, UK) at 1:40 concentration was used. For MRP1 mouse anti-MRP1 (Kamiya biomedical company, Seattle, USA) at 1:50 was used. For LRP mouse monoclonal Ab to MVP (Abcam) at concentration 1:50 was used. Primary antibodies were detected by *ultra*View™ Universal DAB Detection Kit (Ventana Medical Systems). Specimen evaluations were performed on an Olympus BH-2 microscope with an ocular magnification of 20x and 40x by two independent observers. If there were more than 10% of stained tumor cells, the expression was interpreted as positive.

Results. The study included 15 patients (12 men, 3 women), with a median age of 65 years (range 53 - 80). All patients received SCLC chemotherapy of two different schemes: eight patients received

cisplatin/etoposid scheme, three patients received cyclophospamide/epirubicin/vincristine and four patients received a combination of both schemes. Five patients received also chest radiotherapy. The expression of MDR proteins was determined to be P-gp positive in six out of 14 patients, MRP1 positive in five out of 15 patients, and LRP positive in ten out of 13 patients (Table 1). The association between the expression of P-gp, MRP1 or LRP and chemotherapy response was not statistically significant (Likelihood ratios, p>0,05), however, patients had to be negative for P-gp or MRP1 and positive for LRP to have a complete response. Survival of patients in the study (median survival: 285 days) was comparable to the expected survival of patients with SCLC. The association between MDR proteins and survival was not proven as statistically significant (LogRank, p>0,05), however, patients positive for P-gp, negative for MRP1 and negative for LRP had shorter median survival.

Table: P-gp, MRP1 and LRP expression in chemo-naive patients in comparison to chemotherapy response after the completion of the second and fourth cycle and median survival of patients regarding to expression of MDR proteins.

		ICC	The completion of the **second** cycle				The completion of the **fourth** cycle				Median survival in **days**
	Expression	**N**	**n**	**CR**	**PR**	**SD**	**n**	**CR**	**PR**	**SD**	
P-gp	negative	14	8	2	3	3	8	3	2	3	272
	positive		6	0	4	2	4	0	2	2	253
MRP1	negative	15	10	2	3	5	8	2	1	5	265
	positive		5	0	4	1	5	1	3	1	642
LRP	negative	13	3	0	1	2	3	0	1	2	182
	positive		10	2	6	2	8	3	3	2	272

Legend: CR-complete response, PR-partial response, SD-stable disease; N-number of ICC samples, n-number of patients

Conclusions. The described study found no correlation between expression of MDR proteins and patient response to chemotherapy and survival. However, the results of this study suggest an influence of the expression of MDR proteins on both outcomes, which correlate with the data from previous studies (1,2,3). While interpreting the results of the study we have to take into account the limitations of the study: the small number of patients, the collection of specimens from different sites in tumor tissue, differences in the chemotherapy regimens. Thus, further studies on a larger group of patients are necessary to investigate more in detail the influence of MDR proteins in patients with SCLC.

References

1. Yeh JJ, Hsu NY, Hsu WH, Tsai CH, Lin CC, Liang JA. Comparison of chemotherapy response with P-glycoprotein, multidrug resistance-related protein-1, and lung resistance-related protein expression in untreated small cell lung cancer. Lung 2005; 183:177-83.
2. Triller N, Korosec P, Kern I, Kosnik M, Debeljak A. Multidrug resistance in small cell lung cancer: Expression of P-glycoprotein, multidrug resistance protein 1 and lung resistance protein in chemo-naive patients and in relapsed disease. Lung Cancer 2006; 54: 235-40.
3. Savaraj N, Wu CJ, Xu R, Lampidis T, Lai S, Donnelly E, et al. Multidrug-resistant gene expression in small-cell lung cancer. Am J Clin Oncol 1997; 20:398-403.

Aspirin induced COX-2 over-expression in monocytes of aspirin-intolerant patients

Morgan T, Bajrović N, Košnik M, Korošec P
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Through decades of investigation researchers found different biochemical abnormalities in aspirin-intolerant (AI) patients. Cysteinyl-leukotrienes, prostaglandins, different prostanoid receptors and many other related substances have been studied. However, all of the differences so far found appear to be unspecific and a clear picture of the pathogenesis of AI was not proposed yet. Similarly, the diagnosis of aspirin intolerance still relies on provocation testing.
Since the cyclooxygenases 1 and 2 (COX-1 and COX-2) are the key enzymes involved in prostaglandin synthesis, we hypothesized that derangements in their expression could be present in aspirin-intolerant patients.
Our aim was to examine the dynamics of COX-1 and COX-2 expression in whole blood monocytes in healthy and aspirin-intolerant patients.

Materials and Methods. Cyclooxygenase expression was evaluated by flow cytometry through intracellular staining of whole blood monocytes with anti-COX-1 and anti-COX-2 antibodies. Enzyme expression was monitored after *in vitro* stimulation with lipopolysaccharide (LPS) and/or aspirin in 19 aspirin-intolerant patients (eight aspirin-sensitive asthmatics and 11 urticaria-angiooedema patients) and 14 healthy controls.

Results. We found statistically significant COX-2 overexpression after stimulation with LPS and aspirin (mean (range): 78.8 (44.9-92.3); P=0.0002) in comparison to LPS alone (65.9% (33.6-82.6)) in aspirin-intolerant patients. A comparable, but lower up-regulation was also observed after aspirin stimulation alone (median (range): 2.1% (0.5-15.9); P=0.004) in comparison with baseline values (1% (0.1-5.4)). There was no significant difference in COX-2 expression between LPS and aspirin stimulation (mean (range): 61.8% (26.8-89.2); P=0.09) and LPS stimulation (55.5% (28.1-74.3), nor between aspirin stimulation alone (median (range): 0.5% (0-8.6); P=0.8) and baseline values (0.4% (0-5.4)) in healthy control subjects. Consistent with its role as a housekeeping enzyme, COX-1 expression showed no such patterns.

Conclusions. These findings suggest that aspirin-induced COX-2 over-expression may be involved in aspirin intolerance.

Evaluation of clinical interventions made by pharmacists in cancer services

Knez L, Laaksonen R, Duggan C, Nijjar R
Barts and The London NHS Trust, UK

Background. The role of pharmacists has been changing and expanding in the UK in the last decades. Cancer has been identified as a priority area for improvement of services in the 21st century NHS. These developments emphasise the need to explore the contribution of pharmacists to the care of cancer patients.

Materials and Methods. Clinical interventions made by oncology pharmacists were recorded on six cancer wards and the Chemotherapy Production Unit (CPU) at St. Bartholomew's Hospital in London, UK, by two researchers during 25 ward visits and nine visits at the CPU. An expert panel of pharmacy staff was used to reach consensus on the prime reason and clinical significance of the recorded interventions, and was compared with an assessment of a sample of the interventions made by a consultant medical oncologist to further validate the rankings.

Results. Pharmacists made 115 interventions on 340 cases; the vast majority (95%) were accepted by medical practitioners. Problems related to "drug and therapy" (38%) and "dose, frequency and duration" (35%) most commonly required interventions. The panel rated 64% of interventions to have a significant, very significant or potentially life saving effect on patient care. While the panel and the consultant reached agreement on the significance rating of 17% of the interventions in the sample, both rated 77% of the interventions to be significant, very significant or potentially life saving. At the CPU, most interventions were made on cancer therapy and were more significant, than those made on the wards on mainly support therapy (Mann-Whitney U, z = 2.116, p=0.033). Pharmacists of higher grades contributed more to care of complex patients (2 = 67.332, p < 0.0005), whose therapy required more significant interventions (2 = 12.131, p = 0.002).

Conclusions. The study demonstrated that pharmacists' contributions to patient care is related to the level of practice and expertise. The interventions improve the standard of patient care, reduce risk and prevent major toxicity, showing that contribution of pharmacists is required for high quality services.

References
Pharmaceutical Journal 2008; 280:277-80.

Evaluation of the use of bronchodilators in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease

Erjavec J[1], Knez L[1], Škrgat-Kristan S[1], Mrhar A[2], Košnik M[1]
[1]University Clinic of Respiratory and Allergic Diseases, Golnik
[2]University Ljubljana, Faculty of Pharmacy, Ljubljana

Background. Inhaled bronchodilators (BD) form the mainstay of pharmacotherapy for aeCOPD. Current guidelines on COPD recommend an increase in the dose and/or frequency of short-acting BD (SBD), whereas the role of long-acting BD (LBD) is not established. A prospective, randomized study was undertaken to assess the efficacy and safety of SBD against concomitant use of SBD and LBD in patients hospitalized with aeCOPD.

Materials and Methods. Patients with aeCOPD were identified the next working day and randomized in group 1: treated with SBD; or group 2: treated with SBD and LBD. The observed outcomes were: length of hospital stay due to aeCOPD, improvement in the rate of breathlessness defined by the patients using a modified Borg scale (MBS), and occurence of side effects.

Results. The study included 30 patients; 13 patients (11 men, 2 female; mean age 70 years) in group 1, and 17 patients (13 men, 4 female; mean age 72 years) in group 2. The median COPD GOLD stage in group 1 was III (severe disease), whereas the median COPD stage in group 2 was IV (very severe). One patient in group 1 and six patients in group 2 were on long term oxygen therapy (LTOT) at home. Statistically significant differences between groups were recorded in the severity of COPD (2 test, p=0,001). Patients in group 1 had a longer duration of hospital stay (8,2 days) than patients in group 2 (7,5 days). Although the difference in hospital stay was not statistically significant (Mann-Whitney, p>0,05), these results indicate that the concomitant use of short and long-acting BD may shorten the duration of hospital stay. However, while interpreting these results we have to take into account the difference in the severity of the disease between groups. In fact, excluding patients on LTOT from analyses, the difference in hospital stay between group 1 (average 7,2 days) and group 2 (average 7,0 days) was smaller. In group 1, patient dyspnea improved on average for 4 MBS points, and for 4,5 MBS points in group 2. (Mann-Whitney, p>0,05). Nine patients (69%) in group 1 and 13 patients in group 2 (76%) complained of at least one side effect (2 test, p>0,05). The higher occurrence of side effects in group 2 may be the consequence of the use of the additional LBD or of the higher severity of the disease.

Conclusions. Although our study did not find any statistically significant benefit of including LBD in aeCOPD therapy, some trends which need further exploration were seen.

References

1. Global Initiative for Chronic Obstructive Lung Disease, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, updated 2007 (www.goldcopd.org).
2. Šuškovič S., Košnik M, Fležar M, Šifrer F, Eržen D, Kern I, et al.: Strokovna izhodišča za smernice za obravnavo bolnika s KOPB, Zdrav. vest. 2002; 71: 697-702.

Optimisation of methyldigoxin therapy at the University Clinic Golnik

Oblak E[1], Morgan T[1], Lainščak M[1], Košnik M[1], Mrhar A[2]
[1]University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia
[2]University Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia

Background. Methyldigoxin (Md) is a lipophilic derivate of digoxin, which has been used in therapy of heart failure (HF) and chronic atrial fibrillation (CAF) for decades (1,2). Therapeutic drug monitoring (TDM) is a useful tool, which helps doctors to individualise pharmacotherapy with this drug. However, TDM without a proper indication, wrong sampling time and consecutive misinterpretation of the result may significantly limit its benefits.
The main goal of our research was the evaluation of Md therapy and determination of most useful sampling time for Md TDM in our institution.

Materials and Methods. Patients hospitalized between September 1, 2006 and December 31, 2006 being diagnosed CAF or/and HF were included in retrospective study. Md serum concentrations (S_{Md}), indications for Md TDM and appropriateness of blood sampling time were assessed from patients' medical files. Appropriateness criteria were: blood sampling at least 6 hours after last Md administration and at least 6 days after first initiation of Md (3). In the one-month prospective study inpatients with Md therapy were included. S_{Md} was determined 1 hour, 6 hours (C_{ss6h}) and 24 hours (C_{ss24h}) after the daily dose of Md. Paired samples T test for variables C_{ss6h} and C_{ss24h} was made.

Results. In retrospective part 145 patients with CAF and/or HF were included. Sixty-four of them were receiving Md and all further data are related to this group of patients. Thirty were diagnosed CAF, 33 CAF with HF and one patient HF only. Patients, in whom Md was initiated in hospital, had inappropriate TDM of Md in 68%. In 2006, 739 S_{Md} were determined in 465 patients. Twenty-five S_{Md} (in 22 patients) were above 2,6 nmol/L. In prospective study 20 patients were included, 65% of them were female and 35% male with similar median age of 76 years. Median S_{Md} after 1, 6, 24 hours were 1.629, 1.107, 1.070, respectively. Patients were divided in two subgroups: group A was receiving 0,1mg of Md and group B 0,05mg of Md once daily. Differences between C_{ss6h} and C_{ss24h} were statistically insignificant for both groups ($N(A) = 14$; $p < 0.05$, $N(B) = 4$; $p < 0.05$).

Conclusions. TDM of Md was not adequately performed. New hospital guidelines for Md TDM were made as a result of our research.

References
1. ESC Guidelines for the diagnosis and treatment of Chronic Heart Failure (update 2005)

2. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation
3. Mara RM, Stephan K, Raymond GS: Appropriateness of digoxin level monitoring. Swiss Med Wkly 2002; 132:506-12.

Drug dosage regimen adjustment in patients with kidney failure according to estimations of glomerular filtration rate

Sabotin M[1], Mrhar A[2], Meško Brguljan P[1]
[1]University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia
[2]Faculty of Pharmacy, University Ljubljana, Slovenia

Background. Considering only serum creatinine concentration (S_{cr}) renal failure can be overlooked, likewise the need for drug dosage adjustment in renal impairment. Endogenous creatinine clearance (ECC) has in the past been seen as more sensitive method for detection of renal dysfunction than S_{cr}. However, ECC is overall impractical as a routine determination in clinical practice in all patients. GFR estimating equations provide a more accurate assessment of the level of kidney function than S_{cr} alone (1). Furthermore, such equations have been shown to be more reliable estimates of GFR than 24-urinary ECC (2). Our aim was to find out whether drug dosage adjustment according to ECC or estimated GFR (eGFR) was comparable.

Materials and Methods. We performed a prospective study and calculated eGFR from the first hospital S_{cr} measurement in 2208 co-morbid patients using abbreviated 4-variable Modification of Diet in Renal Disease Study (MDRD) equation. 300 patients had eGFR<60 mL/min/1,73 m^2 and in 103 we measured ECC. Consequently data from 72 patients (38 male, 34 female; age=74±10) with stable S_{cr} were used in statistic analyses. Drug dosage regimen was examined to ascertain frequency of necessity of drug dosage adjustment according to 4 different GFR determinations: ECC, calculated GFR using MDRD, Cockcroft-Gault (C&G) and Cockcroft-Gault equation with lean body mass (C&G(LBM)). Statistical analysis included correlation comparison and McNemar's test of distribution of patients into GFR intervals for drug dosage adjustments (=0,05).

Results. Reciprocal values of S_{cr} showed the lowest correlation with ECC (0,714). Equation based GFR estimations showed high correlations with ECC (C&G(0,786), MDRD(0,829), C&G(LBM)(0,833); p<0,01). Fisher's z-test of correlation coefficients comparison showed that no equation had precedence over another. Distributions of patients into two GFR intervals (>60 mL/min, <60 mL/min) showed no statistically significant difference comparing ECC distribution with distribution according to MDRD and C&G equation (p(MDRD)=0,18; p(C&G)=0,38; =0,05). The difference was statistically significant comparing ECC with C&G(LBM) distribution ($p=4,4*10^{-6}$; =0,05). Frequency of necessity of drug dosage adjustment according to 4 different GFR determinations was: ECC(10), C&G(9), MDRD(7).

Conclusions. C&G(LBM) equation highly underestimated GFR. MDRD equation and C&G equation performed equally well to ECC values in co-morbid patients. Renal function determination and drug dosage regimen adjustments according to C&G and MDRD equation were comparable to ECC.

References

1. Stevens LA, Coresh J, Feldman HI, Greene T, Lash PJ, Nelson RG, et al. Evaluation of the modification of diet in renal disease study equation in a large diverse population, J Am Soc Nephrol 2007; 18:2749-57.
2. Lamb EJ, Tomson CRV, Roderick PJ. Estimating kidney function in adults using formulae. Ann Clin Biochem 2005; 42:321-45.

Efficiency analysis of the clinical pathway for the treatment with low molecular weight heparins at the University Clinic Golnik

Jančar P[1], Morgan T[1], Lainščak M[1], Mrhar A[2], Košnik M[1]
[1]University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia
[2]University Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia

Background. In our hospital low-molecular-weight heparins (LMWHs) are prescribed most commonly for the prevention of venous thromboembolism (VTE), treatment of VTE, treatment of acute coronary syndrome and for the prevention of stroke in patients with atrial fibrillation. Our aim was to analyze LMWHs treatment practice at the University Clinic Golnik two years after the clinical pathway was introduced into clinical practice.

Materials and Methods. We performed a retrospective and a prospective analysis. The following parameters were recorded: basic patient characteristics, reason for LMWH prescription, risk factors for VTE, dosing of LMWH, duration of treatment, treatment complications and contraindications for the treatment. Based on these data we assessed the correctness of LMWH prescription and compared the group treated according to the clinical pathway and the group that was not.

Results. In the prospective analysis 870 patients were enrolled: 388 of them had an indication for the treatment with LMWHs, 89% of which received LMWH. Only 68 patients (8%) were treated according to the clinical pathway. Thirty eight percent of patients were treated correctly each day of their hospital stay. Patients were treated correctly 61% of the duration of their hospital stay. Patients were more often treated too short (22%) with too low doses (24%). Side effects were observed in 2% of patients. The statistical analysis showed no statistically significant difference between the two groups. The comparison of the retrospective and prospective analysis showed no statistically significant difference in the pathway use (9% and 8 %, respectively).

Conclusions. The patients treated according to the clinical pathway were not treated better than the patients not treated according to the clinical pathway. Our clinical pathway does not improve the quality of treatment with LMWH. We recommend improvements of the clinical pathway and further education of the physicians.

Year in review: pulmonary arterial hypertension

Salobir B
Department of Pulmonary Diseases and Allergy, University Clinical Center, Ljubljana, Slovenia

Pulmonary arterial hypertension (PAH) is a severe condition characterized by a progressive remodeling of small pulmonary arteries leading to elevated pulmonary vascular resistance and right ventricular failure. Its pathogenesis is complex, to date not completely understood, and includes both genetic and environmental factors. PAH may occur either in the setting of a variety of underlying medical conditions (non-idiopathic PAH) or as a disease that uniquely affects the pulmonary circulation (idiopathic and familial PAH). Since Revised nomenclature and classification of PAH proposed at the Third World Conference on Pulmonary Hypertension, held in Venice in 2003, and formulation of American College of Chest Physicians guidelines for the approach to diagnosis and management of PAH in 2004, there has been a marked progress in PAH treatment, with several important clinical trials already published in the literature. Thus last year a subcommittee of the original ACCP expert panel published an update to the treatment guidelines, based on these recent developments in PAH management, which influences on the way physicians now approach the treatment of PAH (1). In accordance with this important document several other issues regarding survival of the PAH patients, initiatives for early disease detection and for registries of PAH patients arose in the last year, and many papers on current and novel treatment approaches based on the new knowledge about pathophysiology of PAH were published. In this review we will mainly focus on the latter, but we will also discuss investigations conducted in the last year, which will influence the future PAH management. These and several other issues regarding the future in PAH were also discussed on the Fourth World Symposium on Pulmonary Hypertension, held in Dana Point in California in February 2008. The reports from this important symposium will be published in the near future.

Current treatment options for PAH in the last year

Five agents targeting three major pathways involved in the pathogenesis of PAH are currently approved and recommended by new ACCP guidelines (1). These include prostacyclin agonists epoprostenol, treprostinil and iloprost; endothelin-1 receptor antagonist bosentan (sitaxsentan and ambrisentan are at present not included in the guidelines); and the phosphodiesterase-5 (PDE5) inhibitor sildenafil.

In regard with the effectiveness of prostacylines it was shown in an animal model of PAH that the cardiac output improvement is achieved only by decreasing pulmonary arterial resistance without any detectable effect of prostacycline on the right ventricular function. Thus a rationale exists to add positive inotropic drugs to prostacyclin therapy in patients from the functional class IV, who present with right ventricular decompensation (2). In regard with the safety of bosentan recent results of two stud-

ies (large European post-marketing surveillance study - 1583 patients with idiopathic, 3040 with non-idiopathic PAH and long-term study in adults with PAH associated with congenital heart disease) showed that it is safe and well tolerated, with the incidence of severely elevated aminotrasferase similar to that reported in previous randomized controlled clinical trials (3, 4). The double-blind, placebo-controlled, multicentric trial on 185 patients with PAH showed that bosentan could be beneficial in NYHA class II patients with PAH (5). It was also shown that sildenafil improves health related quality of life of PAH patients in a 12-week, double-blind, placebo-controlled study and an open-label extension (6).

New ACCP recommendations for treatment of PAH in the last year

In the last year new update to the ACCP treatment guidelines was published in Chest journal (1).
In regard with the effectiveness of calcium channel blockers (CCB) in patients with idiopathic PAH a new favorable response in acute vasodilating test (AVT) with either epoprostenol or nitric oxide is now defined as a fall in PAPm equal or greater than 10 mmHg to a PAPm equal or lower than 40 mmHg (7, 1). CCB should be used only in patients who reach these new criteria with AVT. The initial reassessment of safety and efficacy should be done already after 3 months of therapy; if CCB are not effective, they should be discontinued and other drugs for PAH should be used (1).
For NYHA functional class II patients the recommended drug is sildenafil; for "early" class III patients either oral bosentan or sildenafil (listed in no order of preference) while in more advanced class III patients prostanoids (epoprostenol iv or inhaled iloprost) may be required (1). For class IV patients epoprostenol iv is strongly recommended (all grade A). Terprostinil in sc form is moderately recommended (grade B) for advanced class III patients, otherwise it is only weakly recommended (grade C) in sc. or iv. form in all other functional classes (1).
It is strongly recommended to perform thorough diagnostic evaluation, to look for possible underlying causes and contributing factors, to evaluate not only functional class according to symptoms, cardiopulmonary hemodynamics and 6-minute walk test, but also side-effect profile, drug-drug interactions and cost-benefit analysis when deciding on the appropriate treatment for each individual patient. Thus referral to specialized centers continues to be strongly recommended (1).

Still low survival of PAH patients: importance of early PAH detection and PAH registries

Although in less than 10 years PAH treatment has evolved from the state of "no hope" to one in which several drugs can be used to prolong survival and improve quality of life, contemporary registries and first meta-analysis of PAH trials on prostacyclines, ETRAs and PDE5 agonists emphasize that PAH is still a progressive and fatal disease. Contemporary registries indicate that survival rates have increased, but remained low (8-12). Moreover first meta-analysis showed that pharmacologic interventions were associated with only non-significant reduction in all-cause mortality (RR 0,70; 95% CI 0,41-1,22) and that a significant improvement in exercise capacity and dyspnea status were not found to be predictive of survival benefits (13).
Since it is already known for several years that survival on treatment with epoprostenol and possibly other drugs as well is strongly depended on the severity of the disease at the baseline (NYHA functional class) these discouraging results are most probably due to the late disease detection, observed in all current registries (14, 8-12). Furthermore, these results also showed that - yet unidentified - subgroups of patients with PAH benefit from current treatment diversely and that mechanisms beyond endothelial dysfunction associated with decreased prostacyclin and NO production and increased ET-1 production may be involved in non-responders.
According to these results immediate strategies for registries and screening programs for early detection of the disease, especially in the high risk populations (based on cardiac echo-Doppler, functional evaluation of dyspnea with spiroergometry and followed by right-heart catheterization if PAH is suspected) should be implemented all over the world on the national levels (15, 16).

Novel treatment options for PAH in the last year

In several already published and ongoing phase 2 and 3 clinical trails novel combinations of current drugs, including combination of inhaled iloprost on the top of bosentan or sildenafil, sildenafil on the

top of bosentan and vice versa, to name only a few, as well as novel drugs targeting the same three pathways implicated in the pathogenesis of PAH (such as oral terprostinil and beraprost from prostanoid group, ambrisentan and sitaxsentan from ETRAs group and tadafil from PDE5 group), are tested (17-22). The main aim of these trials is to improve effectiveness and/or tolerability of drugs for PAH and to implement the use of PAH medications for patients with PAH associated with other diseases.
In the last year it was shown that thyrosine kinase inhibitors imatinib and sunitinib, already used in patients with resistant PAH, might be cardiotoxic and on-going multicentric randomized trial about cardiac safety of these drugs is currently underway (23, 24).
Studies which will determined the efficacy of serotonin transporter inhibitors and efficacy of combination therapy with aspirin and simvastatin are underway and will be published soon (22).
Until additional evidence is available, the use of novel drugs, add-on or combination therapy might be considered in the context of enrollment into clinical trials (1, 19, 22).

The future of PAH

In the last year several important original and review articles showed that current treatment of PAH might be effective also in some subgroups of patients with PAH, associated with other diseases such as chronic pulmonary thromboembolic disease, pulmonary fibrosis, liver diseases and hemoglobinopathias, while similar studies in other diseases also associated with PAH such as thyroid diseases are still lacking (25-29). In the last year several studies about novel mechanisms for developing PAH on the level of vascular tone modulation with agents such as relaxin and adrenomodulin, on the level of modulation of ion channels, as well as on the level of impaired apoptosis and repair of pulmonary arterial endothelial and smooth muscle cells showed, that in the future PAH treatment will go far beyond current therapies with prostacyclins, ETRAs and PDE5 inhibitors (30-38). In addition these studies implicate that "second hit" in genetically predisposed persons is extremely important in the development of PAH. These "second hits", which might also be new targets for therapy of PAH, are not yet well recognized but are probably involved in the majority of cases with oxidative stress and inflammation (39-45).

Conclusions

Despite tremendous advances in the understanding of PAH pathophysiology and treatment possibilities in the past, which led to new treatment guidelines, published last year, the disease prognosis is still very poor, not only as a consequence of treatment failure, occuring in many patients, but also due to late recognition of this rare disease. In the last year several new studies showed that novel treatment options will go far beyond current treatment with prostacyclins, ETRAs and PDE5 inhibitors targeting vascular proliferation and apoptosis and preventing "second hits", responsible for PAH development in genetically predisposed persons.

References

1. Badesh DB, Abman SH, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension: Updated ACCP evidence-based clinical practice guidelines. Chest 2007; 131:1917-28.
2. Kerbaul F, Brimioulle S, Rondelet B, Dewachter C, Hubloue I, Naeije R. How prostacyclin improves cardiac output in right heart failure in conjunction with pulmonary hypertension. Am J Resp Crit Care Med 2007; 175:846-50.
3. Humbert M, Segal ES, Kiely DG, et al. Results of European post-marketing surveillance of bosentan in pulmonary hypertension. Eur Respir J 2007; 30: 338-44.
4. Diller GP, Dimopoulos K, Kaya M, et al. Long-term safety, tolerability and efficacy of bosentan in adults with pulmonary arterial hypertension associated with congenital heart disease. Heart 2007; 93:974-6.
5. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomized controlled trial. Lancet. 2008; 371:2093-100.
6. Sildenafil improves health-related quality of life in patients with pulmonary arterial hypertension. Chest. 2008;133:183-9.
7. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005; 111: 3105-11.

8. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006; 173: 1023-30.
9. Peacock A, Murphy NF, McMurray JJV, et al. An epidemiological study of pulmonary arterial hypertension in Scotland. Eur Resp J 2007; 30:104-9.
10. Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension: 1982-2006. Eur Resp J 2007; 30:1103-10.
11. Jing ZC, Xu XQ, Han ZY, et al. Registry and survival in Chinese patients with idiopathic and familial pulmonary arterial hypertension. Chest 2007; 132:373-9.
12. McGoon MD, Barst RJ, Doyle RL, et al. REVEAL registry: treatment history and treatment at baseline. Chest 2007; 132:631.
13. Macchia A, Marchioli R, Marfidi R, et al. A meta-analysis of trials of pulmonary hypertension: a clinical condition looking for drugs and research methodology. Am Heart J 2007; 153:1037-47.
14. McLaughlin V, Schillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002; 106:1477-82.
15. Humbert M, Khaltev N, Bousquet J, Souza R. Pulmonary hypertension: from an orphan disease to a public health problem. Chest 2007; 132:365-7.
16. Bousquet J, Dahl R, Khaltaev N. Global alliance against chronic respiratory diseases. Allergy 2007; 62:216-22.
17. Mathai SC, Girgis RE, Fisher MR, et al. Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension. Eur Respir J 2007; 29:469-75.
18. Rubin JL, Simonneau G, Hoeper MM, et al. Bosentan improves hemodynamics in patients receiving background sildenafil treatment: results from EARLY, a randomized, double-blind, placebo-controlled study in patients with mildly symptomatic pulmonary arterial hypertension. Abstract. Chest 2007; 132:487S.
19. Preston IR. Combination therapies in pulmonary arterial hypertension. Advances in pulmonary hypertension 2008; 7:235-42.
20. Ouidz RJ. Long-term ambrisentan therapy provides sustained benefit in patients with pulmonary arterial hypertension. Chest 2007; 132:474a.
21. Ambrisentan for the management of pulmonary arterial hypertension. Clin Ther. 2008; 30:825-33.
22. Safdar Z. Phase 2 and 3 clinical trials in pulmonary arterial hypertension. Advances in pulmonary hypertension 2008; 7:228-34.
23. Atallah E, Durand JB, Kantarjian H, Cortes J. congestive heart failure is rare event in patients receiving imatinib therapy. Blood 2007; 110:1233-1237.
24. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoicity associated with tyrosine kinase inhibitor sunitinab. Lancet 2007; 110:1233-7.
25. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med. 2008; 177:1122-7.
26. Idiopathic pulmonary fibrosis and pulmonary hypertension: connecting the dots. Am J Respir Crit Care Med. 2007; 175:875-80.
27. Hepatopulmonary syndrome and portopulmonary hypertension: what's new? Acta Gastroenterol Belg 2007; 70:203-9.
28. Inhaled iloprost for hepatopulmonary syndrome: improvement of hypoxemia. Eur J Gastroenterol Hepatol. 2007; 19:1140-3.
29. Gladwin MT, Kato MD. Hemolysis associated endothelial dysfunction and pulmonary hypertension, an emerging cause of death in the hemoglobinopathias. Advances in pulmonary hypertension 2007; 6: 23-30.
30. The vascular actions of relaxin. Adv Exp Med Biol 2007; 612:65-87.
31. Elevated plasma adrenomedullin and vascular manifestations in patients with systemic sclerosis. J Rheumatol 2007; 34:2224-9.
32. Potassium channel diversity in the pulmonary arteries and pulmonary veins: implications for regulation of the pulmonary vasculature in health and during pulmonary hypertension. Pharmacol Ther. 2007; 115:56-69
33. Potassium channels in the regulation of pulmonary artery smooth muscle cell proliferation and apoptosis: pharmacotherapeutic implications. Br J Pharmacol 2008; 153(Suppl 1):S99-S111.
34. Hyperproliferative apoptosis-resistant endothelial cells in idiopathic pulmonary arterial hypertension. Am J Physiol Lung Cell Mol Physiol 2007; 293:L548-54.
35. Circulating angiogenic precursors in idiopathic pulmonary arterial hypertension. Am J Pathol 2008; 172:615-27.
36. Reduced number and activity of circulating endothelial progenitor cells in patients with idiopathic pulmonary arterial hypertension. Respir Med 2008; 102:1073-9.

37. Circulating endothelial progenitor cells in patients with Eisenmenger syndrome and idiopathic pulmonary arterial hypertension. Circulation 2008; 117:3020-30.
38. Endothelial progenitor cells: new perspectives and applications in cardiovascular therapies. Expert Rev Cardiovasc Ther 2008; 6: 687-701.
39. Mitochondrial metabolism, redox signaling, and fusion: a mitochondria-ROS-HIF-1alpha-Kv1.5 O2-sensing pathway at the intersection of pulmonary hypertension and cancer. Am J Physiol Heart Circ Physiol 2008; 294:H570-8.
40. Oxidant and redox signaling in vascular oxygen sensing: implications for systemic and pulmonary hypertension. Antioxid Redox Signal 2008;10:1137-52.
41. Pulmonary arterial remodeling induced by a Th2 immune response. J Exp Med 2008; 205:361-72.
42. The nuclear factor of activated T cells in pulmonary arterial hypertension can be therapeutically targeted. Proc Natl Acad Sci U S A 2007; 104:11418-23.
43. Enhancement of pulmonary vascular remodelling and inflammatory genes with VIP gene deletion. Eur Respir J 2008; 31:135-9.
44. Raised LIGHT levels in pulmonary arterial hypertension: potential role in thrombus formation. Am J Respir Crit Care Med 2008; 177:202-7.

Chronic thromboembolic pulmonary hypertension

Birtič D, Drinovec I
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the leading causes of severe pulmonary hypertension. The disease is notoriously underdiagnosed, and the true prevalence is still unclear. CTEPH is characterized by intraluminal trombus organisation and fibrous stenosis or complete obliteration of pulmonary arteries. The consequence is an increased pulmonary vascular resistance resulting in pulmonary hypertension and progressive right heart failure. It was belived that 0,1% to 0,5% of patients who survive an episode of acute pulmonary embolism develop CTEPH. Persistent obstruction of pulmonary arteries may result in elevated pulmonary artery pressures and high shear stress in those areas of the pulmonary vasculature that were spared from trombembolic occlusion. Progression of pulmonary hypertension would result in progresive pulmonary vascular remodelling, resulting in a small vessel disease. The management of CTEPH has changed over recent years with the growth of pulmonary endarterectomy surgery and the availability of disease- modifying therapies.
Our aim was to investigate the natural history of patients diagnosed and treated for CTEPH between 1998 and 2008 in our clinic, the treatment options and the prognosis of CTEPH.

Materials and Methods. We performed a retrospective analysis of all cases diagnosed and treated in our clinic from March 1998. Information regarding baseline characteristics, treatment and follow-up was subsequently collected from hospital records.

Resuts. We identified 13 patients diagnosed and treated in our clinic. The female / male ratio was 1 : 1,6 in favour of man. The median age at diagnosis was 56.1 years (+/- 20.9 years). The average mean pulmonary artery preassure measured by right heart catheterization at diagnosis was 38,7 mmHg and the average pulmonary vascular resistance was 524 dyne.s.cm^5. Three patients (23%) were treated with bosentan, 4 (31%) with sildenafil and 2 (15%) with inhaled iloprost. Four patients (31%) have been treated with a calcium channel blocker. Two patients are receiving combined therapy; one with iloprost, bosentan and sildenafil and another with bosentan and sildenafil. Only one patient was proposed for pulmonary endarterectomy (PEA).

Conclusions. Treatment of CTEPH requires a multidisciplinary approach and may involve surgery, medical treatment, or both. However many aspects of the patogenesis of CTEPH are poorly understood and the diagnostic aproach to these patients has not been standardised. We also do not have

sufficient information about the long - term course of patients treated with new medical options or PEA. We need to establish a strategy for long-term follow-up of this patients.

References

1. Hopper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. Circulation 2006; 113:2011-20.
2. Condliffe R, Kiely DG, Gibbs SR, Corris PA . Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2008; 177:1122-7.
3. Lang IM. Chronic thromboembolic pulmonary hypertension: not so rare after all. N Engl J Med 2004; 350: 2236 –8.

Improved options for surgical treatment of chronic thromboembolic pulmonary hypertension

Harlander M, Salobir B, Turel M
Department of Pulmonary Diseases and Allergy, University Clinical Centre, Ljubljana, Slovenia

Background. With a possibility of pulmonary thromboendarterectomy (PTEA) nowadays chronic thromboembolic pulmonary hypertension (CTEPH) became potentially curable disease. Improvements in operative techniques developed over last years approved PTEA as a treatment of choice also for patients with more distal (segmental and even subsegmental) thromboemboli (TE) (Jamieson type III disease). Since experienced centres recently reported perioperative mortality of less than 5% and good long term results, superior to those of lung transplantation (LUTX) [1,2] it is strongly advised that all CTEPH patients should be referred to experienced surgical team that can evaluate accessibility of TE for removal [1]. Further, good preparation of patient for surgery is essential to ensure the best possible outcome. Our aim is to present first successful surgical treatment of Slovene patient with distal type III CTEPH.

Case presentation. A forty-three-year-old man suffered deep vein thrombosis of right calf 13 years ago. Progressive dyspnoea thereafter has been attributed to obesity (BMI 37) and physical inactivity. In 2002 his condition abruptly worsened due to massive pulmonary embolism. After systemic thrombolysis mean pulmonary arterial pressure (mPAP) remained increased (54 mmHg) and pre-existent chronic TE at the level of segmental pulmonary arteries were confirmed (type III). Both PTEA and LUTX were judged to risky at that time by surgeons at AKH Vienna. Chronic anticoagulation and reduction of body weight was indicated. He remained stable under strict medical control and managed to lose more than 20 kg in the next 5 years. Thereafter his condition deteriorated due to three episodes of severe right heart failure. Additional vasodilator therapy with sildenafil introduced after second deterioration showed almost no improvement. Surgical treatment was again proposed and accepted by the surgical team at AKH Vienna. The operation was successful and he is recovering well. We observed reduction in the mPAP, improvement of right ventricular function and NT-proBNP. Long term follow-up will show the actual success of the operation and LUTX still remains the rescue option for the patient.

Conclusion. Since PTEA is the only procedure with curative role for patients with CPTE and now possible also in patients with more distal TE it should be considered a treatment of choice in all eligible patients [1]. Medical treatment should be reserved for patients who cannot be treated surgically either due to intrinsic small vessel disease (type IV) or contraindications for operation [3].

References

1. Madani MM, Jamieson SW. Surgical Treatment of Chronic Thromboembolic Pulmonary Hypertension. Advances in pulmonary hypertension 2007; 6:83-91.

2. Bonderman D, Skoro-Sajer N, Jakowitsch J, Adlbrecht C, Dunkler D, Taghavi S, Klepetko W, Kneussl M, Lang IM. Predictors of outcome in chronic thromboembolic pulmonary hypertension. Circulation. 2007; 115:2153-8.
3. Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, Hodgkins D, Goldsmith K, Hughes RJ, Sheares K, Tsui SS, Armstrong IJ, Torpy C, Crackett R, Carlin CM, Das C, Coghlan JG, Pepke-Zaba J. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med. 2008; 15; 177:1122-7.

Percutaneous mechanical thrombectomy in treatment of acute massive pulmonary embolism with acute pulmonary arterial hypertension and right ventricular dysfunction

Limpel Novak K, Popovič P
University Clinical Center, Clinical Institut of Radiology, Ljubljana, Slovenia

Background. Massive pulmonary embolism (PE) with acute pulmonary arterial hypertension (PAH) and right ventricular dysfunction (RVD) is associated with a high early mortality rate. The therapeutic alternatives for this condition include thrombolysis, surgical embolectomy, or percutaneous mechanical thrombectomy (PMT). We describe our experience using PMT in patients with massive PE, acute PAH and RVD with contraindications for thrombolytic therapy.

Materials and Methods. Eight patients (mean age, 69,7 ±3,5 years; range, 65-76 years; 6 men, 2 women) with massive PE initially diagnosed by computed tomography (CT) and confirmed by pulmonary angiography were treated with the PMT. All patients had acute onset of PE symptoms and all presented with hemodynamic compromise and dyspnea.

Results. All patients underwent thrombus aspiration. The Aspirex percutaneous thrombectomy device was used in 3 patients. Hemodynamic, angiographic and blood oxygenation parameters improved after the procedure.

Conclusions. Thrombolysis is a standard therapy for the patients in whom the risk of bleeding is not substantially increased. In patients who cannot receive thrombolysis, catheter thrombectomy is a promising alternative to effectively reverse acute PAH with RVD and improve the clinical outcome of these critically-ill patients.

Pulmonary arterial hypertension associated with overt hypothyroidism

Rener K
University Clinical Center, Ljubljana, Slovenia

Introduction. Thyroid disease has been suggested as a risk factor for pulmonary arterial hypertension (PAH), although it is yet unclear whether or not PAH is causally related to thyroid disease (1). Our aim is to present a patient with PAH which for the first time supports hypothesis that PAH and overt hypothyroidism (OH) are causally related through direct influence of thyroid hormone deficiency.

Case presentation. A thirty-six year old vegetarian-vegan, otherwise healthy female has developed cramps, disturbed consciousness and respiratory failure which needed artificial ventilation after prolonged intake of large amount of pure water. Head CT excluded brain pathology. Laboratory tests indicated mild megaloblastic anemia, OH and severe hyponatriemia, attributed to OH and pure water intoxication. After electrolyte correction, substitution of thyroxine and vitamin B12, her condition improved in a few days. Echocardiography (ECHO) demonstrated elevated pulmonary artery systolic pressure (PAPS) 50mmHg+CVP and small pericardial effusion. We did not perform right heart catheterization since the patient refused the procedure. V/P lung scan and chest CT with CT angiography excluded pulmonary embolisms and relevant lung diseases. Serology for HIV and connective tissue diseases was negative. Patient has not been taking any medication associated with PAH. Her condition completely resolved in six months of therapy with thyroxine and vitamin B12. Repeated ECHO showed normalization of PAPS and brain natriuretic peptide (from 1007 to 85 ng/L). The 6-minute walk test showed an improvement in the walking distance from 465 to 615 m. OH remained etiologically undefined, autoimmune reason was excluded and the most probable reason was iodine deficiency due to inadequate intake of iodized salt, the most important source of iodine.

Conclusion. Hypothyroidism by itself might be causally related to PAH, since it has already been proven that increased arteriolar smooth muscular cells contractility and lowered production of nitric oxide by vascular endothelial cells is caused by direct influence of thyroid hormone deficiency on vascular system (2,3). However, we could not find any significant data on this possible causal relation in existing literature concerning PAH. Our case, in whom important PAH which was not attributed to any other disease except OH and which completely resolved after treatment of OH, strongly supports this assumption, which might be clinically relevant.

References

1. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Forrtin TA, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension. ACCP Evidence-Based Clinical Practice. Chest 2004; 126: 14S-34S.
2. Biondi B. Cardiovascular effects of mild hypothyroidism. Thyroid 2007; 17:625-30.
3. Vargas F, Moreno JM, Rodriguez-Gomez I, Wagensteen R, Osuna A, Alvarez-Guerra M, et al. Vascular and renal function in experimental thyroid disorders. Eur J Endocrinol. 2006; 154:197-212.

Clinical presentation of patients with late diagnosis of chronic thromboembolic pulmonary hypertension

Cebin T, Salobir B, Terčelj M
Department of Pulmonary Diseases and Allergy, University Clinical Center, Ljubljana, Slovenia

Background. Chronic thromboembolic pulmonary hypertension (CTEPH) is one of more common cardiovascular diseases, yet it is severely under-diagnosed. A diagnosis of CTEPH is difficult to establish since there are no specific signs or symptoms associated with the disease. Easy fatigability and progressive dyspnea is a complaint common to all patients; haemoptysis can also occur at any time; exertional chest pain, near syncope or syncope and signs of right heart failure with lower extremity edema develop only later in the course of the disease. Thus main symptoms are often erroneously attributed to associated diseases, obesity, deconditioning, or psychogenic dyspnea (1).

Presentation of cases. In five our patients in whom the CTEPH was diagnosed after a longer history of clinical procedures, progressive dyspnea and other clinical symptoms of CTEPH were attributed to associated chronic lung disease (COPD in one and chronic bronchitis with haemoptyses in another two patients), or deconditioning due to physical inactivity (after poly-trauma with splenectomy in one and severe obesity and pain in right calf due to post-thrombotic syndrome in another patient). Only one of four patients had history of deep vein thrombosis and D-dimer was negative in 2 of 5 patients at the time of diagnosis.

Discussion and conclusion. CTEPH is a progressive disease with poor prognosis. However due to improved medical and surgical options the observed improvements in outcome during the modern treatment era reinforce the importance of identifying patients with this increasingly treatable condition (2). Unfortunately the period of diagnostic delay does not appear to have shortened substantially in patients with CTEPH over the last several years, emphasizing that the status of the pulmonary vascular bed should be considered in any patient with out-of proportion dyspnea as well as with other symptoms and signs such as syncope or haemoptysis even in the absence of documented venous thrombosis and negative D-dimer if no other compelling cause can be established (3).

References

1. Fedullo PF. Clinical manifestations and diagnosis of chronic thromboembolic pulmonary hypertension**.** In: Mandel J, Wilson KC, Eds: Up-To-Date, Last literature review version 16.1: Jan 2008 **|** this topic last updated: November 6, 2007.
2. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2008; 177:1122-7.
3. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004; 126:14S-34S.

Novosti 2007/2008 na področju difuznih intersticijskih pljučnih bolezni

Mušič E
Bolnišnica Golnik – Klinični oddelek za pljučne bolezni in alergijo, Slovenija

Difuzne intersticijske pljučne bolezni (DIPB) ostajajo zahteven problem v pulmologiji in so tudi s sodobnimi diagnostičnimi možnostmi še vedno odkrite večinoma že v napredovalih stopnjah fibroziranja. Sodobne slikovne tehnike omogočajo potrditev DIPB že v zgodnjih stopnjah. V možnostih terapije pa smo vsaj deloma lahko uspešni le v takem stadiju bolezni. Vsebinskih sprememb terapije zadnji 2 leti ni, interferon gama (IFN-) in biološka protitelesa so razočarali. Koristen dodatek ustaljeni terapiji predstavljajo antioksidanti. Zavzeto je stališče do transplantacije pljuč. Z novo klasifikacijo, ki smo jo predstavili na Golniškem simpoziju 2007, že dokaj dobro razmejujemo entitete z ugodnejšo in tiste s slabo prognozo (1). Po zadnji monografiji o DIPB iz leta 2007 smo tedaj predstavili tudi dopolnjeno in prirejeno klasifikacijo DIPB, po kateri je osvojena tudi fibroproliferativna hipoteza z zgodnjim vzburjenjem fibroblastov v začetni leziji alveolarnih epitelijskih celic (2). Ta klasifikacija je najenostavnejša doslej in vključuje:

1. DIPB znanih vzrokov : ekstrinzični alergijski bronhoalveolitis (EABA) in DIPB zaradi kajenja (respiratorni bronhiolitis/intersticijska pljučna bolezen (RB/IPB), histiocitoza Langerhansovih celic)
2. DIPB neznanih vzrokov : idiopatska pljučna fibroza (IPF), nespecifična intersticijska pljučnica (NSIP), akutna intersticijska pljučnica (AIP)
3. Granulomatoze
4. Redke DIPB : kriptogena organizirajoča pljučnica (KOP), limfocitna intersticijska pljučnica (LIP), limfangioleiomiomatoza, vaskulitisi, alveolarna proteinoza

V istem viru je povzeto, da je bronhoalveolarni lavat (BAL) po 25 letih lahko diagnostičen pri naslednjih boleznih (2):

- alveolarna proteinoza
- histiocitoza Langerhansovih celic
- EABA
- eozinofilna pnevmonija
- pljučna hemosideroza
- določene poklicne DIPB

O DIPB na Golniškem simpoziju 2007 (GS 2007)
Med slikovnimi metodami je visokoločljivostna računalniška tomografija (HRCT) pljuč ključna in obvezna pred odločitvijo za bronhoskopsko ali kirurško biopsijo pljuč (1). Požek in Marin sta ocenila korelacijo HRCT s testi pljučne funkcije pri DIPB, ki se med entitetami skoraj značilno razlikuje (1). Imunski mehanizmi pri DIPB so izjemno nazorno obdelani v sestavku Vizjakove na GS 2007, po-

udarek je na boleznih z odlaganjem imunskih kompleksov, sodelovanju komplementa, ANCA vaskulitisih. Omembe vredna je izvirna raziskava golniške skupine Korošca in sodelavcev z opozorilom na vlogo NKT celic v patogenezi EABA, ki je odmevala tudi kot mednarodna objava (3). Sistemske bolezni veziva s pogosto prizadetostjo pljuč je na GS 2007 predstavila Šipek Dolničarjeva.

EABA v strokovni literaturi

O predolgo spregledanem recidivno akutnem EABA poročamo leta 2008 v članku z naslovom »Extrinsic allergic alveoilitis from the bedroom« (5). Leta 2007 smo poročali o medikamentoznem obstruktivnem bronhiolitisu po sulfasalazinu z dobro regresijo po ukinitvi zdravila (42. Tagung der Gesellschaft für Atemwegs- und Lungenkrankheiten). Sicer pa so evropske novosti o EABA povzete v zbirnem članku »Recent advances in extrinsic allergic alveolitis«, po katerem je zadnja leta pogostejši predvsem alveolitis vlažilcev klimatskih naprav, farmarska pljuča pa po pogostnosti nazadujejo (4). Opozorjeno je na različne poteke EABA, pri čemer moramo razpoznati akutne oblike, ki potekajo kot pljučnica ali kot reverzibilna NSIP od malignega poteka kronično progresivnega EABA, kateri poteka lahko kot vzorec običajne intersticijske pljučnice ali organizirajoče pljučnice z epizodno sliko NSIP. Perzistenca tkivne nevtrofilne infiltracije je neugodna. Če so navzoči tudi granulomi, je potek ugodnejši. Opozorjeno je tudi na EABA pri strojnikih ter na etiološko vlogo mikobakterij v klimatskih napravah (4). Nemško združenje za EABA in njihovo združenje DGAKI sta izdala nove smernice za diagnostiko te bolezni (6). Ob EABA in sarkoidozi se opozarja na možnost kronične berilioze kot poklicne bolezni v avtomobilski industriji, elektroniki, proizvodnji računalnikov, v zobotehniki, metalurgiji, vojski, industriji gospodinjskih aparatov, športnih pripomočkov, izdelavi okrasja itd. Največ zmotnih diagnoz zaradi spregledane berilioze ostaja pod oznako sarkoidoza (7).

Kaj predstavlja idiopatska NSIP?

NSIP ni več le nejasna košara oz. vzorec različnih stadijev večih DIPB, možno celo EABA, ampak je tudi svojska entiteta kot idiopatska NSIP. V analizi 193 primerov z vzorcem NSIP, med katerimi jih je 67 ostalo kot idiopatska NSIP z vodilnima simptomoma dispnejo in kašljem, je večina imela dominantne spremembe v spodnjih pljučnih predelih, 46 v perifernih in 47 difuzno. V 87% je bil vzorec sprememb mrežast s trakcijskim bronhektazijami.in v 77% s krčenjem volumna. Histološko so bile celične spremembe v kombinaciji s fibrozo. Pet let jih je preživelo 82,3%. Take so značilnosti idiopatske NSIP kot bolezni zase, ki jo dobijo nekadilke srednjih let in ima zelo dobro prognozo (9,14).

EABA in IPF na Pneumoupdate 2007

Povzetek aktualnih stališč za EABA in IPF v svetu je podal Behr Jürgen, tudi avtor monografije o diagnostiki in terapiji DIPB iz 2003 (10). Poudaril je možnosti dokaj praktične opredelitve DIPB na podlagi izkušenj s HRCT, ki je danes temeljna metoda. DIPB neredko spremljajo do 2 cm povečane mediastinalne bezgavke. Raziskave IPF poudarjajo genetsko, familiarno dispozicijo pri do 20% primerov. Opažajo mutacije v surfaktantnih proteinih, pri čemer po okvari alveolarnega epitela nastaja interstcijsko vnetje. Pomanjkljiva sposobnost regeneracije epitela ima lahko še druge genetske vzroke in je oslabljena v starosti, ko je IPF pogostejša. Pri etiologiji še vedno domnevajo o vlogi virusov in celo o možni vlogi gastroezofagealne refluksne bolezni. Epidemiološko je zadnjih 20 let evidenten 3-kraten porast incidence IPF. Sedaj beležimo v Evropi prevalenco 20/100.000 prebivalcev, v starosti nad 75 let pa je le-ta 10-krat večja. V diagnostiki skušajo zasledovati potek in prognozo IPF in spremljajo letni upad difuzijske kapacitete, ki je pri korektni diagnozi pribl. 15%. Opozarjajo na kombinacije emfizema in IPF pri kadilcih. V serumu se določa citokin KL-6, ki odraža aktivnost IPF. To je mucinu podoben glikoprotein, ki ga izločajo pnevmociti-2 in bronhiolarne epitelne celice. Znatno povišana vrednost KL-6 kaže s 95% verjetnostjo na neugodno prognozo. Kot dejavnik za napoved prognoze je uporaben še 6-minutni test hoje. Čeprav se pomenu BAL ne pripisuje velike diagnostčne vloge (12), je izpostavljeno poročilo klinike Mayo, kjer so opazovali, da limfocitoza >20% napoveduje boljšo prognozo in ugodnejši odziv na terapijo glukokortikoid (GK) +/- azatioprin ali ciklofosfamid. Pri IPF ima kirurška biopsija diagnostično prednost pred transbronhialno biopsijo, če le ni kontraindikacij in če diagnoza ni možna že po znanih kliničnih, HRCT in funkcijskih kriterijih. V histološki sliki so fibroblastna žarišča tipičen ugotovek za IPF in kažejo na to, da so mezenhimske celice in izvence-

lični matriks samostojen, kompleksen sistem, ki se je vzburil k razvoju IPF. Raziskave tega procesa bi morale sprožiti tudi nove pristope v terapiji. Terapevtske izkušnje zadnjih 2 let kažejo, da le tisti primeri IPF, ki prve 3 mesece na najpogostejši terapiji glukokortikoid+citostatik kažejo zaznaven odziv, potekajo tudi v nadaljevanju ugodneje. Neprimerno je bolnika z IPF zdraviti samo z glukokortikoidom. Za izboljšanje kvalitete življenja bolnikov z IPF moramo zdraviti tudi neizogibno pulmonalno hipertenzijo in kronično pljučno srce. V terapiji DIPB neznane etiologije je že 2 leti najbolj odmevna študija IFIGENIA o vlogi N-acetilcisteina (NAC) v terapiji IPF, ki je pozitivno ocenila dodatno terapijo z dozo 3x600mg NAC skozi 1 leto. Bolniki z IPF so v študiji prejemali vzdrževalno terapijo s pronizonom (začetno 0,5mg/kg do vzdrževalnih 10mg/dan od 4. do 12. meseca) in azatioprin (2mg/kg/d). Rezultate so primerjali med skupino z dodanim NAC 3x600mg/dan in skupino brez dodanega NAC. Doseženi so bili skromno ugodni rezultati z 8% boljšo vrednostjo vitalne kapacitete in s 14% boljšo vrednostjo DLco v skupini z NAC. Zaključek je, da se z vplivom na razmerje oksidanti/antioksidanti delno zadržuje propadanje pljučne arhitekture in funkcije. Druge objave o terapiji IPF, pa tudi DIPB pri sistemski sklerozi (SS), priznavajo minimalno učinkovitost ciklofosfamida v zadrževanju fibroziranja in to bolj pri SS kot pri IPF, zlasti če spremembe pri SS začnemo tako zdraviti že v fazi sprememb z vzorcem NSIP. Pri tem sta za spremljanje učinkov bolj uporabna HRCT in pljučna funkcija kot BAL (8).

Kaj je akutno poslabšanje IPF?
Je pomemben del poteka IPF, na leto je takih epizod lahko več. Klinično je prisotna v enem mesecu akutno večja dispneja, poslabšanje hipoksemije, novi infiltrati v rentgenski sliki, odsotnost okužbe ali srčnega popuščanja. Poleg difuzne alveolarne okvare se pojavi tudi organizirajoča pljučnica, kar se lahko odzove na terapijo z GK in citostatikom. Zato je v taki epizodi smiselno vključiti višjo dozo GK in citostatik (15). Kadar najdemo v histološki sliki vzorec NSIP ali AIP obstaja diferencialno diagnostična možnost sistemske bolezni veziva (9, 15).

Transplantacija pljuč
Rezultati so manj ugodni kot pri KOPB. Pogoj je upoštevanje absolutnih in relativnih kontraindikacij. Indikacije pri IPF so:
- vsaj 1 izmed naslednjih kriterijev:
  - DLco <39%
  - upad FVC za >10% v zadnjih 6 mesecih
  - znižanje O_2 saturacije pod 88% med 6-minutnim testom hoje
  - satasta pljuča v HRCT

Indikacije pri fibrozirajoči NSIP so:
- DLco < 35% norme
- upad FVC > 10% ali DLco > 15% v zadnjih 6 mesecih.

Clinical year in review, ATS 2008
Na mednarodni konferenci ATS so analizirali zadnje objave o IPF, EABA, NSIP in opozorili še na nekaj člankov v zvezi z DIPB v zadnjem letu (11). Ugotavlja se, de je pogostnost IPF v porastu. Iščejo se specifični genotipi za razvoj te bolezni. IPF poteka ugodneje pri nekadilcih ali vsaj bivših kadilcih. Familiarnost pojavov IPF je aktualna. Pri kroničnem EABA je pomembno, ali je bolezen pričela z vzorcem NSIP ali manj ugodnim običajne intersticijske pljučnice. Obstajajo primeri EABA z enim izmed omenjenih vzorcev in anamnezo kritične ekspozicije, vendar so tipični parametri za EABA odsotni. Opisani so primeri, ko bolezen tudi po prenehanju ekspozicije poteka progresivno. Ne glede na omenjena dejstva kronični EABA poteka ugodneje kot IPF. NSIP kaže lahko potek idiopatske bolezni, ob čemer so prisotni nekateri pojavi kot pri sistemskih boleznih veziva (SBV) npr. artralgije, Raynaud fenomen, jutranja okorelost, suhost sluznic, disfagija, ANA v serumu, povišan CRP. Bolezen pa ne združuje kriterijev za SBV po ACR. Za pljučne manifestacije SBV pa velja, da spremembe pri RA večkrat potekajo z vzorcem običajne intersticijske pljučnice, NSIP vzorec pa je pogostejši pri polimiozitisu, zgodnjih stopnjah sistemske skleroze in pri Sjögrenovem sindromu (11, 12, 13). V obravnavi pljučnih manifestacij v sklopu različnih sistemskih vaskulitisov je nujno sodelovanje z revmatologi,

nefrologi, kar še posebej velja za sindrome vaskulitisov malih žil. Posebno zahtevno je še vedno poglavje hipereozinofilnega sindroma, ki spremlja različne bolezni in prizadene različne organske sisteme, tudi pljuča. Tedaj pride ob imunološko potrjeni diagnozi v poštev tudi terapija z biološkimi protitelesi (npr. imatinib) (16).

Zaključek

Nemogoče je predstaviti celotno literaturo zahtevnega strokovnega področja o DIPB. Povzamemo pa lahko izkušnje kliničnih in raziskovalnih zanesenjakov, ki vztrajajo na izkustvenih priporočilih za prakso in nam nakazujejo bodoča pota, da bi zaustavili pospešen porast DIPB z neugodno prognozo. Zelo praktični so zgledi povezovanja strokovnjakov in izmenjave ter preverjanja ocen in izkušenj. Študija sodelujočih ekspertov v diagnostiki IPF iz 6 evropskih držav, ki je prikazala individualna in konsenzualna vrednotenja HRCT in histoloških ugotovkov, je temeljila na smernicah ATS/ERS. Diagnozo so potrdili, če sta soglašala vsaj dva izmed treh ekspertov. IPF je bila konsenzualna diagnoza v 87,2% domnevnih primerov. Podan je zgled, da ta diagnoza zahteva sodelovanje več ekspertov iz specializiranih centrov (17). Stopnja progresije bolezni je ključni dejavnik v indikaciji za transplantacijo pljuč (18). IPF je bolezen s slabšo prognozo od mnogih karcinomov, pogojujejo jo različni vzroki in udeleženi so mnogi patološki mehanizmi s spremembami vnetnega procesa in razvojem brazgotinjenja (19). V bodoči terapiji IPF bodo tarča tisti celični receptorji npr. somatostatinski, ki zavirajo aktivacijo fibroblastov in pljučno fibrozo (20). Manj skrivnostna je patogeneza EABA, ki ima znatno boljšo prognozo, vendar pa manjši del primerov tudi napreduje v fibrozo (21). Raziskave o subpopulacijah T lmfocitov v subakutni in kronični obliki EABA nakazujejo, da se v kroničnem EABA spremeni funkcija T-limfocitov tako, da se obrne v smer aktivnosti Th-2, kar determinira kroničnost in fibrozo. Supernatanti celic pri kroničnem EABA, ki so jih stimulirali s kritičnim antigenom, so namreč vsebovali več interlevkina 4 in manj IFN- , torej se spet domneva vloga genetskih pogojev.

Literatura

1. Golniški simpozij 2007. Klinična imunologija, KOPB- zbornik predavanj.
2. Costabel U, du Bois RM, Egan JJ. Difuse parenchymal lung disease. Karger 2007.
3. Korosec P, Osolnik K, Kern I, Silar M, Mohorcic K, Kosnik M. Expansion of pulmonary CD8+CD56+ natural killer T-cells in hypersensitivity pneumonitis. Chest 2007; 132:1291-7.
4. Sennekamp J, Joest M. Recent advances in extrinsic allergic alveolitis. (Exogen-allergische alveolitis – neue Erkenntnisse). Pneumologie 2008; 62:51-4.
5. Marin A, Mušič E, Eržen R, Uršič V, Korošec P. Extrinsic allergic alveolitis (EAA) from the bedroom. Allergo J 2008; 17: sprejeto v tisk.
6. Sennekamp J, Muller-Wening D, Amthor M, Baur X, Bergmann KC, Kostabel U, et al. Empfehlungen zur diagnostik der exogen-allergischen alveolitis. Pneumologie 2007; 61:52-6.
7. Müller-Quernheim J, Gaede KI, Prasse A, Zissel G: Chronische Berylliose. Pneumologie 2007; 61:109-16.
8. Strange C, Bolster MB, Roth MD, Silver RM, Theodor A, Goldin J, et al. Bronchoalveolar lavage and response to cyclo-phosphamide in scleroderma interstitial lung disease. Am J Respir Crit Care Med 2008; 177:91-8.
9. Travis WD, Hunninghaker G, King TE Jr, Lynch DA, Colby TV, Galvin JR, et al. Idiopathic nonspecific interstitial pneumonia. Am J Respir Crit Care Med 2008; 177:1338-47.
10. Magnussen H, ed. Pneumo Update 2007, Wiesbaden , November 2007.
11. ATS 2008 Toronto: Clinical year in review.
12. Baughman RP, Costabel U, Meyer KC, eds. Bronchoalveolar lavage. Semin Respir Crit Care Med 2007; 28:473-572.
13. Clement P, Fürst DE, Wells AU, eds. Pulmonary complications of connective tissue disease. Semin Respir Crit Care Med 2007; 28:367-471.
14. Kinder BW, Collard HR, Koth L, Daikh DI, Wolters PJ, Elicker B, et al. Idiopathic nonspecific interstitial pneumonia. Am J Respir Crit Care Med 2007; 177: 691-7.
15. Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE Jr, et al. Acute exacerbation of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2007; 177: 636-97.
16. Peros-Golubicic T, Smojver-Jezek S. Hypereosinophilic syndrom: diagnosis and treatment. Curr Op Pulm Med 2007; 13:422-7.
17. Thomeer M, Demedts M, Behr J, Costabel U, Flower CD, Verschakelen J, et al. Multidisciplinary interobserver agreement in the diagnosis of idiopahic pulmonary fibrosis. Eur Respir J 2008; 31:585-91.

18. Mackay LS, Anderson RL, Parry G, Lordan J, Corris PA, Fisher AJ, et al. Pulmonary fibrosis: rate of disease progression as a trigger for referral for lung transplantation. Thorax 2007; 62:1069-73.
19. Maher TM, Wells AU, Laurent GJ. Idiopathic pulmonary fibrosis: multiple causes and multiple mechanisms. Eur Respir J 2007; 30:835-9.
20. Borie R, Fabre A, Prost F, Marchal-Somme J, Lebtahi R, Marchand-Adam S, et al. Activation of somatostatin receptors attenuates pulmonary fibrosis. Thorax 2008; 63:251-8.
21. Barrera L, Mendoza F, Zuniga J, Estrada A, Zamora AC, Melandro EI, et al. Functional diversity of T cell subpopulations in subacute and chronic hypersensitivity pneumonitis. Am J Respir Crit Care Med 2008; 177:44-55.

Diagnostic value of penetrating light NIR spectroscopy in idiopatic pulmonary fibrosis

Votruba J[1], Bruha T[1], Balaz T[2]
[1]Hospital Na Homolce, Prague, Czech Republic
[2] University of Defense, Brno, Czech Republic

We describe new method for noninvasive evaluation of lung parenchyma by NIR spectroscopy of penetrated light. Our technical solution consists of external source of NIR emission and NIR spectroscope with flexible cannula containing spectroscopic probe which is inserted into the working channel of the bronchoscope. Spectroscopic readings from the probe taken during bronchoscopic procedure bring information about the quality of lung parenchyma. Such an approach seems to be feasible in our preliminary study elucidating the NIR spectroscopy differences in UIP (KFA) contra healthy persons. Concerns about the interference of the chest wall tissues with spectroscopic readings have not been confirmed by our preliminary data.
Study population consisted of 12 healthy voluntiers and 7 patients with UIP. Results show good diagnostic value of the method in discrimination between normal and UIP afflicted tissue. When validated in further clinical studies this method could be easily integrated into diagnostic workup of DPLDs and eventually other disorders of lung parenchyma (pulmonary/non-pulmonary edema) due to its low cost, non-invasiveness and short procedure time.

References

1. American Thoracic Society, European Respiratory Society. American Thoracic Society/European thoracic Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002; 165:277-304.
2. Liebow AA, Carrington CB. The interstitial pneumonias, frontiers of pulmonary radiology. New York 1969: Grune and Stratton.

Determination of IgG, IgA and IgM in patients with lung tuberculosis

Vojnovska Z, Tomovska D
Clinical Hospital, Laboratory of Biochemistry, Bitola, Macedonia

Background. Tuberculosis is a contagious disease that usually affects humans and attacks the lungs. Immunoglobulins are structurally related proteins that differ in their functions, characteristics and reactions under stimulation with the antigen. In some pathological conditions the determination of the immunoglobulins can be useful for diagnosis.

Materials and Methods. The concentration of the immunoglobulins IgG, IgA, IgM, was determined in 20 patients (12 male and 8 female) with lung tuberculosis, between the age of 25 and 50 in serum with turbidimetric method, using sets from the firm RANDOX.

Results. The results gained were processed for:
IgG: x = 10,4g/L; SD = ± 5,5; KV = 22% p<0,05 R.V.(8-18)
IgA: x = 4,9g/lL; SD = ± 0,9; KV = 1,9% p<0,05 R.V.(0,9-4,5)
IgM: x = 1,33g/lL; SD = ± 0,6; KV = 3,0% p<0,05 R.V.(0,6-2,5)

Conclusion. The significantly higher values gained for IgA show presence of a specific infection in these patients diseased with lung tuberculosis.

The DOTS achievements in controlling TB in the Republic of Macedonia

Vidoevska A, Zakoska M, Talevski S, Ilievska Poposka B, Sandevski A, Vulovik Damjanovska M, Metodieva M
Institute for Lung Diseases and Tuberculosis, Skopje, Macedonia

Since year 2000, the control of TB in Macedonia has been organized following WHO recommendations and implementing all elements of DOTS.
The study is retrospective with analyses of the epidemiological indicators and the treatment results in patients with TB during the last 5 years.

Table 1. Epidemiological indicators (notification rate, prevalence rate and mortality)

Year	Prevalence rate	Notification rate	Mortality rate
2003	48.7	34.4	0.7
2004	50.4	33.6	0.9
2005	53.2	32.5	0.7
2006	47.5	31.0	1.7
2007	45.4	27.8	1.8

Conclusions. The results of the National strategy for control of TB is improving the epidemiological parameters for TB as well as improving the treatment effects.

Table 2. Treatment effects

	2003	2004	2005	2006
New pulmonary TB cases (ss+) -total	**200**	**189**	**176**	**181**
Successfully treated	163 (81.5%)	159 (84%)	148 (84%)	157 (87%)
Deceased	3 (1.5%)	3 (1.6%)	3 (1.7%)	9 (5%)
Treatment failure	4 (2%)	2 (1.1%)		1 (0.6%)
Treatment stopped	30 (15%)	25 (13.3%)	25 (14.3%)	14 (7.7%)
Relapses with pulmonary TB (ss+) - total	**36**	**50**	**39**	**24**
Successfully treated	27 (75%)	43 (86%)	29 (74.4%)	16 (66.7%)
Deceased	3 (8.3%)	5 (10%)	2 (5.1%)	5 (20.8%)
Treatment failure			2 (5.1%)	1 (4.2%)
Treatment stopped	6 (16.7%)			
6 (15.4%)	2 (8.3%)			
Transferred to		2(4%)		
Others	**12**	**23**	**64**	**21**
Successfully treated	8 (66.7%)	21 (91.3%)	34 (53%)	10 (47.6%)
Deceased	1 (8.3%)	2 (8.7%)	6 (9.5%)	5 (24%)
Treatment failure	1 (8.3%)		24 (37.5%)	2 (9.5%)
Treatment stopped	2 (16.7%)			3 (14.2%)
Still under treatment				1 (4.7%)

Laryngeal tuberculosis

Atanasova S, Ilievska Poposka B, Vidoevska A, Metodieva M, Pilovska K, Zakovska M
Institute for Lung Diseases and Tuberculosis, Skopje, Republic of Macedonia

Larynx is the most frequent localization of tuberculous infection in upper parts of respiratory system. In vast majority of cases the laryngeal tuberculosis is demonstrated as a complication of advanced lung tuberculosis. The high contagious rate and possible diagnostic failures, could be a reason for increased rate of infection in the general population.
Twenty-five patients with laryngeal tuberculosis, were treated in a period from 2003 to 2007 on the Institute for Lung Diseases and Tuberculosis, Skopje. Twenty-two of them were males (88%), the mean age was 45±17 years. In 11 patients (44%), the duration of the period from onset of symptoms till final diagnosis lasted longer than 6 months. The most likely symptoms were: progressive hoarseness (88%), cough (72%) and sore throat accompanied with disphagia (40%). Nineteen patients demonstrated a long-standing period of smoking (76%). In 23 patients (92%), there was a patohistologic confirmation of tuberculous laryngitis, after an endoscopic examination has been performed. Eighteen patients presented acid-fast bacilli on direct microscopy, and in 23 (92%) there was a positive sputum culture on Löwenstein-Jensen medium. According to radiological changes, cavitary bilateral tuberculosis was diagnosed in 6 patients (24%), whereas a chronic hematogenous form was detected in 17 (68%).
All the patients were treated using a standardized therapeutic regimen for newly detected cases, according to the protocol of WHO, combined with use of glucocorticoids. Bacteriologic conversion of sputum after 2 months from the beginning of treatment was achieved in 18 patients (72%). The initial phase of treatment was prolonged for 1 month in 15 patients (60%).
Although uncommon, laryngeal tuberculosis is a very important factor in spreading of the disease. Therefore, an early detection and proper treatment of these cases significantly decreases the risk of infection in the general population.

Pathogens isolated in hospitalized patients with ae-COPD

Polak D, Tomič V, Škrgat Kristan S
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. To investigate the spectrum of isolated bacteria in AE-COPD patients, to determine their antimicrobial susceptibility and to evaluate the empirical selection of antibiotics.

Material and Methods. Medical charts of patients with leading diagnosis of acute exacerbation of COPD hospitalized in University Clinic Golnik in 2007 were retrospectively analyzed.

Results. Twohundred and forty--two patients were eligible for inclusion. 95.5% of them had severe or very severe COPD. Good quality lower respiratory tract specimen (mostly sputum) was collected from 148 patients (60.9%). From respiratory samples of 60 patients (24.8% of all patients, 40.5% of those with good quality specimen) we isolated 77 bacterial strains. *Pseudomonas aeruginosa* (16 isolates), *Haemophilus influenzae* (15 isolates) and *Stenotrophomonas maltophilia* (9 isolates) were the most frequently isolated pathogens, followed by *Moraxella catarrhalis, Staphylococcus aureus* susceptible to methicillin, *Acinetobacter baumannii* (4 isolates each), *Streptococcus pneumoniae, Klebsiella oxytoca* and *Escherichia coli* (3 isolates each). Some other pathogens were isolated only once or twice each. 7% of *H. influenzae* isolates were resistant to ampicillin, and 20% to cotrimoxazole, with no resistance to macrolides and fluoroquinolones detected. None of *P. aeruginosa* isolates was resistant to ceftazidime, imipenem, ciprofloxacin and amikacin but 50% were resistant to cefotaxime and ceftriaxone. All *M. catarrhalis* isolates were resistant to ampicilline due to –lactamase production and were susceptible to all other antibiotics tested. *S. pneumoniae* showed no resistance to penicillin and other antibiotics tested. All *S. maltophilia* isolates were resistant to amoxicilline with clavulanic acid, cefotaxime and ceftriaxone, 11%, 22% and 22% resistant to gentamycin, ciprofloxacin and cotrimoxazole, respectively. 218 patients (90%) were treated with antibiotics. Amoxicilline with clavulanic acid was the most frequently prescribed empirical antibiotic treatment (44% of all cases), followed by moxifloxacin (28%) and ciprofloxacin, prescribed alone (9%) or in combination with ceftazidime (6%). In 15 patients (25% of those with positive culture) isolated pathogens were resistant to empirically chosen antimicrobial agent.

Conclusions. P. aeruginosa, *H. influenzae* and *S. maltophilia* were the most frequently isolated pathogens in COPD patients who were admitted in 2007 for acute exacerbation of the disease. Patients were treated with antimicrobial agents in accordance with current guidelines. In 75% of cases isolated pathogens were susceptible to empirical antibiotic therapy.

Kriteriji CURB-65 kot prognostični kazalec pri bakteremičnih bolnikih zdravljenih zaradi zunajbolnišnične pljučnice

Marin A, Mušič E, Eržen R, Tomič V
Bolnišnica Golnik – Klinični oddelek za pljučne bolezni in alergijo, Slovenija

Izhodišča. V ambulantni praksi uporabljamo za opredelitev teže pljučnice sistem CURB, pri bolnikih sprejetih v bolnišnico sistem PORT. Na osnovi CURB-65 kriterijev se odločimo, kako in kje bomo bolnika z zunajbolnišnično pljučnico (ZBP) zdravili. Želeli smo oceniti uporabnost CURB-65 kriterijev pri hospitaliziranih bolnikih z ZBP in pozitivno hemokulturo. Analizirali smo napovedno vrednost CURB-65 kriterijev, dolžino hospitalizacije in smrtnost.

Metode. Analiza je retrospektivna. Vanjo smo zajeli bolnike, ki so bili hospitalizirani v Bolnišnici Golnik – KOPA v letu 2006 zaradi ZBP in pri katerih smo povzročitelja ZBP izolirali iz hemokulture. Vsi podatki so iz bolniške dokumentacije. Zbrali smo podatke kot so: starost, spol, bakterija, ki je bila izolirana iz hemokulture, novonastala zmedenost ob sprejemu, koncentracija serumske sečnine, frekvenca dihanja, krvni tlak, serumski kreatinin, C-reaktivni protein (CRP), število levkocitov v krvi, dolžino hospitalizacije in izid zdravljenja. Pozitivni CURB-65 kriteriji so bili akutna zmedenost, serumska sečnina >8.3 mmol/l, frekvenca dihanja ≥30/min, diastolni krvni tlak ≤60 mmHg ali sistolni krvni tlak ≤90 mmHg in starost ≥65 let.

Rezultati. V analizo smo vključili 30 bolnikov, 21 (70%) moških. Povprečna starost bolnikov je bila 69,13 let (21 starejših od 65 let, razpon 42-92 let). Iz hemokultur smo izolirali: *Streptococcus pneumoniae* pri 10 bolnikih, *Klebsiella pneumoniae* pri 3 bolnikih, *Escherichia coli* pri 4 bolnikih, *Staphylococcus aureus* občutljiv za meticilin pri 3 bolnikih, pri 2 bolnikih *Haemophilus parainfluenzae*, pri po enem bolniku pa *Pseudomonas aeruginosa, Clostridium perfringens, Streptococcus constellatus, Streptococcus mutans, Peptostreptococcus prevotii, Morganella morganii, Enterobacter aerogenes* in *Micrococcus spp.* Povprečna doba hospitalizacije je bila 16,8 dni, smrtnost 23,3%. Bolnike smo razdelili po stopnjah CURB-65 kriterijev v 6 skupin (tabela 1).

Zaključek. CURB-65 kriteriji so dober napovednik pri ogroženih bolnikih. ZBP pri starejših bolnikih s pozitivnimi hemokulturami lahko poteka z blažjo obliko klinične slike. Višje vrednosti serumskega kreatinina so lahko tudi napovedni kriterij za izid. Najvišje CURB-65 skupine so slab prognostični dejavnik s smrtnostjo nad 50%.

Tabela 1. Korelacije med CURB-65 kriteriji in starostjo, serumskim kreatininom, CRP, številom levkocitom, dolžino hospitalizacije ter smrtnostjo pri bolnikih z ZBP in pozitivno hemokulturo.

Število pozitivnih CURB-65 kriterijev	Število bolnikov	Srednja vrednost serumskega kreatinina (umol/L)	Srednja vrednost CRP (mg/L)	Srednja vrednost števila levkocitov (x 10^9/L)	Srednja vrednost dolžine hospitalizacije (dni)	Smrtnost (%)
0	1	60,0	143,9	12,8	36,0	0%
1	4	49,8	34,1	16,0	12,0	0%
2	14	93,7	181,5	11,7	21,3	14%
3	8	122,9	213,2	13,8	12,0	13%
4	2	157,0	342,0	11,8	19,0	50%
5	1	355,0	434,9	5,2	1	100%

Utility of computed tomography and fiberbronchoscopy in patients with unexplained fixed airway obstruction

Regvat J, Kern I, Triller N, Škrgat Kristan S, Cesar R, Košnik M
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. In some patients despite detailed history, medical examinaton, lung function testing, noninvasive measurement of airway inflammation, and chest x-ray the cause of fixed airway obstruction cannot be established. Determination of correct diagnosis is necessary due to different treatment strategies and prognosis.
Our objective was to establish whether examination with computed tomography (CT) and/or fiberbronchoscopy (FB) contributed to diagnosis in such patients and how they influenced the treatment strategies.

Materials and Methods. Retrospective analysis was conducted for the period from November 2005 until November 2007. The data were collected from hospital information system BIRPIS. The analysis included patients with asthma, COPD, bronchiectasis or bronchiolitis as main diagnosis in hospital/ambulatory charts, with fixed obstruction in pulmonary function testing (FEV1/FVC < 0,7) and with performed CT and/or FB for determination of obstructive disease.

Results. In 2 years at least one examination was performed in 25 patients (62±14 years, 11 female). The CT and/or FB results influenced the treatment in 15 (60%) patients. In 5 patients new medication were introduced (twice for COPD, twice for asthma joined with emphysema and bronchiectasis, respectively, once for bronchiolitis). In 6 patients the therapy was subsequently changed (the diagnosis changed from COPD to asthma twice, from COPD to asthma with bronchiectasis once, twice from indeterminate diagnosis and unsuitable treatment to asthma, once from chronic asthma to bronchiolitis). In 4 cases we discontinued the therapy (the diagnosis changed from asthma to bronchiectasis three times, and once from asthma to tracheobronchomalacia with tracheobronchopathia osteochondroplastica and bronchiectasis).

Conclusions. CT and/or FB can be of use in establishing the cause of fixed obstruction after noninvasive approach has proved inconclusive. However, no examination (noninvasive or invasive) is 100% specific and sensitive for the diagnosis, so these patients should always be debated on multidisciplinary meetings with pneumologist, radiologist and pathologist.

How do patients with home long-term oxygen treatment live?

Globočnik M, Lainščak M, Kadivec S
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Background. Chronic obstructive pulmonary disease (COPD) is a lung disease, where lung function is gradually and irreversibly deteriorating and progressing over time. Today, COPD is one of the leading causes of death and its prevalence is even increasing. It is estimated that the number of COPD patients sums to 600 million or 4 - 7% of adult white population. Symptoms such as fatigue, dyspnea and coughing are experienced during everyday activity. This, of course, has a major influence on the quality of life. Even though the latter is the most desired result of the treatment it is usually very poorly evaluated. In the course of COPD treatment a long-term oxygen home treatment is the treatment of choice when a patient suffers from permanent respiratory insufficiency, i.e. pO_2 less than 7.3 kPa or with pO_2 values ranging between 7.3 – 8.0 kPa with signs of a chronic cor pulmonale. It has been established that the survival rate in COPD patients has significantly improved if the patients receiving extra oxygen for at least 17 hours a day.

Current literature on patient view and experience of COPD is scarse. A majority of them deal with the impact of COPD symptoms on the lives of patients, whilst the effects of those factors that patients themselves feel as being crucial for better or worse quality of their lives remain neglected. In 2007, Williams et al. from New Zealand studied the performance of those COPD patients who were subjected to long-term oxygen home treatment. Based on qualitative method and in-depth interviews with patients they tried to establish what truly mattered to them. Severe physical restrictions of COPD patients may lead to lesser social mobility and social isolation. In the study patients showed a strong desire to be actively included in different social activities despite their physical limitations. Even though most of their activities were limited to closed quarters or to the safety of their home environment, walking, driving and housekeeping were pointed out as the activities, which would help them keep their independence and integrity. Feelings of social isolation were bridged over by various social activities (holidays, social interaction).

Materials and Methods. We interviewed COPD patients on long-term oxygen home treatment. Potential participants were found in the 2007 study. The patients were all from the Gorenjska region and less than 80 years of age. All patients agreed to be interviewed. Qualitative method and a semi-structured interview were used. The data were collected by a semi-structured interview lasting anywhere from 35 to 50 minutes. All interviews were carried out by a same interviewer at the

patients' homes. All patients completed the interview although some had shortness of breath. The main focus of the interview was patient's experience with the disease. It also discussed important factors of life. The basis for determining important factors was the 2007 study by Williams et al. Open-type questions gave the patients opportunity to talk about their experience with an individual factor. The demographic data such as age, sex, degree of disease and the time passed from establishing the diagnosis were gathered in the course of the interview and with the help of disease register.

Results. Five men and three women participated in the study. All eight patients had oxygen concentrators, four had portable oxygen tanks. They received from 1 to 3 litres of oxygen per minute. Some patients characteristics, technical details about long-term oxygen treatment, data on physical performance and psychological view of the COPD are reported in Table 1.

Discussion. Our results allow additional insight into the everyday life of COPD patients. The participants pointed out heavy breathing and coughing as the two most disturbing symptoms that gravely influence their lives. Both symptoms are in particularly expressed in advanced stages of the disease. However, physical activity was seen equally important for better quality of life as it kept them actively involved in their home and greater social environment. Walking, housekeeping, taking care of others and pursuing one's hobbies gave them a sense of independence and usefulness and, last but not least, a sense of meaningful life and their identity. The COPD patients tried to maintain contact with the immediate and broader environs in various ways: by telephone, visiting and socializing regardless of their ever present symptoms and restrictions imposed by the oxygen concentrator. Being able to drive a car gave them a very strong feeling of independence and creativity. A sense of social isolation and loneliness was stronger with patients who were mostly limited to their quarters. Such patients were more pessimistic as well. The reasons for lesser mobility of the COPD patients lay mostly in the oxygen concentrator, which couldn't be moved, and poor use of portable oxygen tanks due to high costs. We are aware that the results of our study are limited to a small sample. From the personal perspective of patients the study has shed some light on those aspects that are important to them. Due to shortness of breath patients often experience physical restrictions that result in lesser mobility and social isolation. Besides these restrictions patients often experience restrictions caused by their need for oxygen therapy. They mostly pointed out a feeling of being tethered to their home.

Conclusion. For a COPD patient the stress on the importance of not being still and keeping physically active is never enough. The more active they get, the longer they will live. Oxygen home therapy has to be seen positively. In spite of it and because of it a patient can continue to live fully and diversely. Respiratory rehabilitation opens many new possibilities as well. It enables patients to socialize with people with same problems, but most importantly, it gets them physically involved. A high level of physical fitness and a portable oxygen tank are those two pillars that keep a COPD patient alive.

References

1. Williams V, Bruton A, Ellis – Hill C, McPherson K. What really matters to patients living with chronic obstructive pulmonary disease? An exploratory study. Chron Respir Dis 2007; 4:75-88.
2. Okubadejo AA, Shea LO, Jones PW, Wedzicha JA. Home assessment of activities of daily living in patients with severe chronic obstructive pulmonary disease on long term oxygen therapy. Eur Resp J 1997; 10:1572-5.
3. Drummond MB. Oxygen therapy in COPD: What do we know. Am J Resp Crit Care Med 2007; 176:321-6.
4. Bratkovič M, Kadivec S, Globočnik M, Škrgat S. Kako zares poteka zdravljenje s kisikom na domu. V Zdravstvena obravnava bolnika z obstruktivno boleznijo pljuč in alergijo. Zbornik predavanj: program za medicinske sestre in zdravstvene tehnike. Golnik, Bled, 2007.

Patient Activity	SB	ŠA	SM	RA	KM	KJ	MA	PL
Age	51	73	78	73	78	75	67	75
Litres per minute	1	1.5	2	1	2	2	3	2
Portable oxygen tank	yes	no	no	yes	no	yes	yes	no
Personal care (1 – 3)	washes herself alone 3	washes herself alone, needs help with washing her head 2	washes herself alone, needs help with washing her head 2	washes herself alone 3	washes himself alone 3	washes himself alone 3	washes himself alone 3	his wife washes him and puts on his clothes 1
Walking/day (1 – 10)	4 km 10	in the 3	0.5 km 5	3-4 km 8	3-4 km 8	farming 10	100 - 200 m 4	in the apartment 3
Driving a car	yes	no	no driving licence	no	no	yes, and a tractor also	yes	no
Taking care of others (1 – 10)	babysitting her grand-daughter 9	cooks for her son 8	sewing for friends, feeding chickens 10		makes brunch for his daughter every day 7			
Housekeeping (1 – 10)	cooks for all family, tidies up 8	cooks for herself and her son, tidies up 6	cooks for herself, tidies up 5	during the day in the retirement home 2	cooks for himself, tidies up 5	makes brandy, feeds chickens, goes in the stable, saws wood 10		
Fear (1 – 10)		not very optimistic 6			fears the concentrator may break down 8			wants to die 10
Plans (1 – 10)	To climb Kredarica 10				wants to write a book 7			

Do patients with end stage COPD need more structured palliative care than patients with lung cancer?

Lunder U
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Palliative care is often related only to the management of patients in the terminal stages of a malignant disease. It has been slowly recognized that patients with non-malignant terminal diseases have similar needs or even more difficult ones to cope with in comparison to patients with a malignant disease (1). The physical and psychosocial burden of COPD has largely been ignored and for a long time these patients have been excluded from palliative care programs, hospice and community care (2). The scale of suffering for patients with COPD is beginning to emerge (3). Although a few patients receive intensive medical and nursing care at the end of life, even with artificial ventilation, most die slowly in hospital wards, at home or in nursing homes. The definition of palliative care states it is an active total care for patients with a life limiting disease, and their families, by a multi-professional team, when the disease is no longer responsive to curative or life-prolonging treatment (4). This article discusses the comparative studies of needs of patients with end stage COPD and those with lung cancer, in order to introduce criteria for patients with COPD to get more appropriate palliative care to enhance their quality of life.

Patients' viewpoint comparison in COPD and cancer

1) COPD has a different disease trajectory to cancer, commonly having multiple admissions with exacerbations for approximately last 5 years and particularly in the last year of life (4).
2) Physical symptoms of pain, dyspnoea, cough, anorexia, emesis and constipation are comparable with those of lung cancer patients (5).
3) Psychosocial symptoms: (6) low mood is found to the same extent as, or often is worse than, in cancer.
4) Quality of life measurement: (7) COPD patients probably suffer as much as lung cancer patients, but COPD patients remain ill for longer, so it could be argued the total amount of their suffering to be greater.
5) Communication of terminal disease is less open with COPD patients than with cancer patients (8).
6) Mobility: COPD patients become house bound and isolated from society for a longer period of time in the terminal phase than lung cancer patients.
7) COPD patients and their carers are less likely to receive terminal care in hospitals or in their homes from palliative care knowledgeable professionals.
8) As 90% of COPD patients are smokers or ex-smokers they are likely to experience the stigma associated with smoking-related illnesses, similar to lung cancer (9).

Cancer patients are currently better cared for, probably due to a much more clear distinction and criteria of the progressive stage of malignant disease. The best current knowledge about managing physical symptoms should be easily transferred from cancer to non-cancer. Unfortunately the use of analgesic and sedating drugs is still associated with myths and fears among professionals. COPD in advanced stage is often accompanied by more than one physical symptom and often also by fatigue, depression and delirium. But the main difficulty for health professionals is probably to determine when the patient with COPD has reached the terminal phase and at which point it is appropriate to discuss the subject of death and end-of-life issues (9).

When the patient with COPD has reached the terminal stage?
Emerging profile of prognosis of dying within a year (10):
- Best FEV1<30% of predicted
- Declining performance in ADL
- Uninterrupted walk distance less than a few steps
- 1 urgent hospitalization in past year
- Left-heart and/or other comorbid diseases
- Older age
- Depression
- Unmarried

Common distressing end-stage COPD physical symptoms (10)
Emerging symptoms are of subjective nature (self reported), with a poor clinician accuracy and difficult symptom measurement. There are several measurement instruments suggested: Memorial Symptom Assessment Scale, Rotterdam Symptom Checklist, Visual Analogue Scale (VAS 1/10), Dyspnea Assessment.
Most common physical symptoms in advanced COPD are: dyspnoea, cough (wet or productive), pain, constipation, depression and anorexia. General principles of palliation are guiding to determine and treat underlying cause, relieve symptoms without adding any new problems, to consider if treatment is worthwhile for the patient and their family and to discuss all reasonable treatment options.

Psychosocial and spiritual care
Intensity of patients' and families' emotions and spiritual quests while moving within the progression of the disease can be a huge problem. Most common psychological issues are low mood, insomnia, anxiety, fatigue and lethargy. Psycho-social support and medical treatments should be considered. It is essential to recognize the importance of open but sensitive discussion of dying, about stopping futile treatments, advance care planning and preferences in symptom control. Spiritual care in accordance with patient's cultural and religious beliefs needs to be offered.

Conclusion
Broadening medical care to integrate palliative care in patients with progressive chronic illness is a major challenge for health care. Providing palliative care to patients with end-stage COPD is just as essential as for those with a malignant disease. The biggest barrier for patients with COPD to receive palliative care on time and in full range is probably a difficulty of judging the prognosis. Communication and forming a relationship is an essential factor with both the patient and those close to them, to identify and discuss issues or concerns they may have. Opportunities to discuss prognosis in COPD are likely to arise as the disease progresses and, since 90% of all care in the last year of life is received at home, GP's inevitably have a significant role in the care of many of these patients (11).

References
1. Edmonds P, Karlson S, Khan S, Addington-Hall J. A comparison of the palliative care needs of patients dying from COPD and lung cancer. Palliat Med 2001; 15:287-95.

2. Gott CM, Ahmedzai SH, Wood C. How many inpatients at an acute hospital have palliative care needs? Palliat Med 2001; 15:451-60.
3. Lynn J, Ely E, Zhong Z, McNiff KL, Dawson NV, Connors A, et al. Living and dying with chronic obstructive pulmonary disease. J Am Geriatric Soc 2000; 48:S910-S1000.
4. Watson M, Lucas C, Hoy A, Back I. Oxford Handbook of Palliative Care. Oxford University Press 2005, New York.
5. Booth S, Wade R, Johnson M, Kite S, Swannick M. Expert Working Group of the Scientific Committee of the Association of Palliative Medicine. The use of oxygen in the palliation of breathlessness. A report of the expert working group of the scientific Committee of the Association of Palliative Medicine. Resp Med 2004; 98:66-77.
6. Elkington H, White P, Addington-Hall J, Higgs R, Pettinary C. The last year of life of COPD: a qualitative study of symptoms and services. Resp Med 2004; 98:439-45.
7. Guthrie SJ, Hill KM, Muers MF. Living with severe COPD. A qualitative exploration of the experience of patients in Leeds. Resp Med 2001; 95:196-204.
8. Curtis JR, Engelberg RA, Wenrich MD, Au DH. Communication about palliative care for patients with chronic obstructive pulmonary disease. J Pal Care 2005; 21:57-64.
9. Russell SJF, Russell REK. Challenges in end-of-life communication in COPD. Breathe 2007; 4:133-9.
10. Specialist Palliative Care Referral Guidelines and Symptom Control for Patients with End-stage Chronic Respiratory Disease. (Working Party, Chair: Littlewood CM) Liverpool, August 2006.
11. Elkington H, White P, Higgs R, Pettinari CJ. GP's views of discussions of prognosis in severe COPD. Family Practice 2001; 18:440-4.

Use of atrial natriuretic hormone as the serum marker of cardiac decompensation in patients with dyspnea

Prnjavorac B, Ajanovic E, Sejdinovic R, Mehic J, Fejzic J
General Hospital Tesanj, Bosnia and Herzegovina

Background. Chronic obstructive pulmonary diseases are problem of health care worldwide. Actually, very clear guidelines are available and used by most of physicians involved in pulmonary care. Most of patients belong to aged population. So, many diseases were diagnosed on most of them. Clinicians have problem if some of the symptoms of different diseases overlap. Dyspnea is caused mostly by bronchoobstruction or a result of cardiac decompensation. We tested usefulness of measurement of atrial natriuretic hormone for that clinical purpose.

Material and Methods. We followed up the patients in period of first six months of 2008 treated in Department of Internal Medicine in our hospital. We performed analysis of atrial natriuretic peptide by measurement of its precursor B-form of atrial natriuretic peptide (pro-BNP), blood cell counts, lipid status, uric acid, fibrinogen, blood gas analysis.

Results. In this period we have 1086 discharged patients. Out of them 74 have been discharged as obstructive pulmonary diseases, 166 with diagnoses of different degree of heart failure, and 41 with both of these diagnoses. In 38 of them with dyspnea for which we could not exactly diagnose only bronchoobstruction or cardiac decompensation. Many of symptoms overlapped. For the purpose to establish as much as possible precise diagnoses we performed measurement of pro-BNP for the patients in whom we could not were sure either obstructive bronchitis or heart failure is main cause of dyspnea. If only bronchoopstruction was cause of the dyspnea no high level of pro-BNP was shown. But, if heart failure took much more important role of dyspnea pro-BNP level was higher.

Conclusions. Measurement of pro-BNP level is very useful marker to diagnose heart failure component in patients with dyspnea.

Tracheoesophageal fistula - an unusual diagnosis in an adult

Peposhi I
University Hospital of Lung Diseases, Tirana, Albania

Esophageal atresia and tracheoesophageal fistulas are the most common and most important developmental anomalies of the esophagus. The three less common types of tracheoesophageal fistula are when: (1) the atretic upper esophagus communicates with the trachea, (2) both upper and lower segments of the atretic esophagus communicate with the trachea, and (3) a nonatretic esophagus communicates with the trachea in an H-type configuration. Because these types have in common the communication between upper esophagus and trachea, they all present clinically with signs and symptoms of recurrent (aspiration) pneumonia. Distinguishing among types, however, should not be difficult. Esophageal atresia accompanied by proximal tracheoesophageal fistula presents in infancy as recurrent pneumonia, and the presence or absence of bowel gas on a plain radiograph indicates whether an accompanying distal tracheoesophageal fistula exists. In contrast, in those with an H-type tracheoesophageal fistula without esophageal atresia, the diagnosis can be delayed until childhood or, at times, adulthood. In some instances, confirmation of the type of configuration is obtained by esophagography or bronchoscopy.

Case report
A 17-year-old female, lifelong nonsmoking, presented in our clinic with increasing cough especially during drinking, purulent sputum, mild dysphagia, wheezing during night, and increasing of symptoms. She was given a diagnosis of asthma and recurrent respiratory infections until 7 years old. She was referred to the pulmonary department at 10 years of age for bronchiectasis and recurrent pneumonia treated with antibiotic, mucolytic, bronchodilators and vitamins, she improved a little and was sent to our hospital's pulmonary department for further investigations, further evaluation of her symptoms. Her physical examination was unremarkable except for pectus excavatum, in auscultation bronchial rales. CT scan revealed bilateral cylindrical bronchoectasis with pneumonia. Spirometry after treatment is normal.
Because of the very abnormal CT scan, a flexible bronchoscopy was performed. As the bronchoscope was passed between the vocal cords, a fleeting glimpse of a defect involving the posterior wall of the proximal trachea was noted during inspiration. A small (5 x 5 mm) round, mature opening of a tracheoesophageal fistula valve-like was noted only with deep inspiration (Fig. 1). The patient was diagnosed with a H-type tracheoeosofageal fistula and referred to thoracic surgery.

Discusion
The incidence of tracheoesophageal fistula itself is not exceedingly uncommon (2.86–4.1 per 10,000), but the adult presentation and type of fistula is rare (1) (10). Congenital tracheoesophageal com-

munication can be also in association with otherwise normal esophagus (5,11). In this situation, survival into adult life is possible because of the lack of early signs and symptoms related to regurgitation and aspiration (11). Anatomically, the fistulas are usually obliquely oriented, the esophageal end being distal to the upper airway communication. It has been proposed that this arrangement – possibly aided by contraction of mural smooth muscle during swallowing - explain the frequent mildness of respiratory symptoms and the delay in diagnosis until adulthood (11). The fact that aspiration is less common in adults could be attributed to either the elongation of the esophagus relative to the trachea, or to a sphincter or valve-like mechanism of the fistula itself (1, 8). Clues to the existence are often noted when the patient is pressed for details of childhood symptoms such as choking and recurrent respiratory infections. Our patient had a diagnosis of bronchoectasis and recurrent bilateral pneumonia. There has been only 1 prior case of tracheoesophageal fistula diagnosed after abnormal CT scans leading to investigation (4).The prognosis is good after reparative surgery (11).

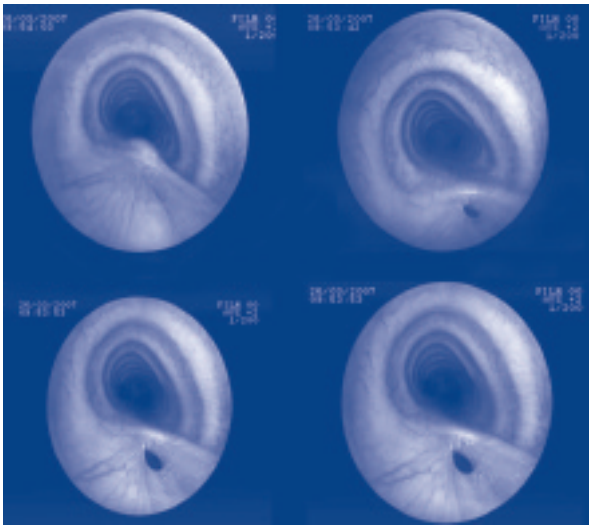


Fig.1. Tracheoesophageal fistula

References

1. Gildea TR, Choure AJ, DeCamp MM, Mehta AC, Arroliga AC. Tracheoesophageal fistula: an unusual presentation of upper airway obstruction. J Bronchol 2005; 12:156–7.
2. Weaver K, Folch EE, Dent LL, Flenaugh EL. Cuff pressure tracheal necrosis. J Bronchol 2006; 13:212–3.
3. Bertelsen S. Congenital oesophago-tracheal fistulas in the adult. Scand J Thorac Cardiovasc Surg 1970; 4:80–2.
4. Acosta JL, Battersby JS. Congenital tracheoesophageal fistula in the adult. Ann Thorac Surg 1974; 17:51–7.
5. Moorhead JM, Reid RA, Vontz FK. Congenital tracheoesophageal fistula in an adult. South Med J 1982; 75:1030–1.
6. Peat SJ, Paes T, Howard ER, et al. Congenital tracheo-oesophageal fistula in an adult. Br J Surg 1989; 76:412.
7. Azoulay D, Regnard JF, Magdeleinat P, et al. Congenital respiratory–esophageal fistula in the adult. Report of nine cases and review of the literature. J Thorac Cardiovasc Surg 1992; 104:381–4.
8. Ramaswamy S, Sharma SK, Mitra DK, et al. Congenital tracheooesophageal fistula in a young adult. Aust N Z J Surg 1992; 62:594–5.
9. Heitmiller RF, Nikoomanesh P, Ravich WJ. Esophageal motility in an adult with a congenital H-type tracheoesophageal fistula. Dysphagia 1990; 5:138–141.
10. Depaepe A, Dolk H, Lechat MF. The epidemiology of tracheo-oesophageal fistula and oesophageal atresia in Europe. EUROCAT Working Group.Arch Dis Child 1993; 68:743–8.
11. Fraser R, Colman N, Muller N, Pare P. Sinopsis of diseases of the chest. 3rd ed. 2005. 198-9.
12. Duhamel and Harrell. Clinical atlas of airway diseases; Bronchoscopy, radiology, and pathology 2005; Tracheoesophageal fistulas p.148.

Primerjava treh vrst lokalnih anestezij pri bronhoskopiji z upogljivim instrumentom

Perdija Ž[1], Križmarić M[2]
[1]Univerzitetni klinični center, Maribor
[2]Univerza Maribor, Fakulteta za zdravstvene vede, Maribor

Uvod. Bronhoskopija z upogljivim bronhoskopom je danes sodobna in nezamenljiva metoda pregleda dihalnih poti. Poseg se izvaja v lokalni anesteziji in je večinoma enostaven in varen za bolnike. Kljub napredku tehnologije in izboljševanju opreme za bronhoskopijo je to še vedno agresivna diagnostična metoda, ki je povezana z določenim tveganjem oz. neželenimi posledicami posega. Preiskava je neboleča, je pa pogosto zelo neprijetna za preiskovance. Pred preiskavo je potrebno anestezirati zgornje in spodnje dihalne poti. Za anestezijo spodnjih dihalnih poti se uporabljajo različne vrste anestezije. V naši ustanovi uporabljamo anestezijo skozi delovni kanal (»spray as you go«), transkrikoidno anestezijo in anestezijo z razprševanjem anestetika s pomočjo razpršilca pred preiskavo.

Material in metode. V raziskavi smo primerjali tri vrste lokalne anestezije, ki se uporabljajo pred bronhoskopijo z upogljivim inštrumentom. Uporabili smo »real life« obliko raziskave, kar pomeni, da smo v raziskavo vključevali vse bolnike, ki so bili predvideni za bronhoskopijo brez posebej definiranih vključitvenih in izključitvenih kriterijev (kot npr. podatki o boleznih, zdravilih). Vključili smo bolnike napotene na bronhoskopijo na Oddelek za pljučne bolezni Univerzitetnega kliničnega centra Maribor po predhodnem pisnem soglasju bolnika. Za ocenjevanje smo uporabljali vprašalnike. V študiji smo ocenjevali prenašanje lokalne anestezije in bronhoskopije s strani bolnikov ter oceno strokovnega tima o težavnosti posega. Želeli smo ugotoviti, katera vrsta lokalne anestezije je bolj ugodna za bolnike ter bolj ustrezna za posamezne skupine bolnikov, kje se pojavlja manj težav pri posegu, oceniti refleks kašlja med bronhoskopijo ter celotno porabo anestetika.

Rezultati. V raziskavo smo vključili na diagnostično bronhoskopijo napotene bolnike v obdobju 6 mesecev. Vključili smo 272 bolnikov, 198 moških in 74 žensk. Starost bolnikov je bila med 20 in 82 let. Povprečna starost je bila 57,8 let. Razlike v starosti preiskovancev v posameznih skupinah anestezij niso bile statistično pomembne. Glede izobrazbe je bilo s končano srednjo šolo 136 bolnikov (50%), osnovno šolo 112 (41%) ter z visoko oz. višjo izobrazbo 24 (9%) bolnikov. Aktivnih kadilcev je bilo 80 (29%), bivših kadilcev 110 (41%) in nekadilcev 82 (30%). Kriterij za nekadilce je bil vsaj eno leto brez kajenja pred posegom.
Anestezijo z razprševanjem anestetika s pršilom smo uporabili pri 56 bolnikih (21%), transkrikoidno anestezijo pri 105 bolnikih (39%) in anestezijo z razprševanjem anestetika skozi delovni kanal inštrumenta pri 111 bolnikih (41%).

Pri ocenjevanju prenašanja anestezije oz. neugodja ob dajanju lokalnega anestetika pred posegom smo ugotovili statistično pomembno razliko v korist transkrikoidne anestezije (p<0,001), kar pomeni, da so bolniki ocenili transkrikoidno anestezijo kot najmanj neprijetno. Med preostalima dvema vrstama anestezije ni bilo opaziti statistično pomembne razlike. Pri ocenjevanju kašlja nismo ugotovili pomembne razlike glede na uporabljeno metodo anestezije. Poseg so lažje prenašali bolniki, ki so prejemali anestetik z razprševanjem. Razlika je bila statistično pomembna (p<0.038) v primerjavi z dajanjem anestetika skozi delovni kanal. Po ocenah strokovnega tima so bronhoskopije lažje prenašali bolniki, ki so prejemali transkrikoidno anestezijo v primerjavi z anestezijo skozi delovni kanal (p=0.005).
Skupna količina uporabljenega anestetika, ne upoštevajoč lidokain gela, katerega so prejeli vsi bolniki pred posegom v približno enaki količini, je bila izrazito povečana pri anesteziji z razprševanjem anestetika. Povprečna količina porabljenega anestika je bila 22.14±6.46 ml, kar je statistično pomembno več v primerjavi z obema drugima metodama anestezije. Najmanj anestetika je bilo uporabljenega pri transkrikoidni anesteziji.
Ugotavljali smo, ali obstajajo statistične razlike med spoloma glede ocene prenašanja posamezne vrste anestezije, prenašanja bronhoskopije, refleksa kašlja in količine uporabljenega anestetika. Večinoma ni razlik med spoloma, razen pri prenašanju bronhoskopije po transkrikoidni anesteziji. Moški so bronhoskopijo ocenili lažje (1,75+/- 0,46), pri ženskah je ta vrednost večja (2,04+/-0,58), kar je statistično pomembno (p=0,011).
Med bolniki z osnovno in višjo šolo ni nobenih statističnih razlik glede na prenašanje posega in anestezije, tako da izobrazba tu ne igra vlogo. Razlike smo dobili le pri anesteziji skozi delovni kanal, kjer bolniki s srednjo šolo lažje prenašajo anestezijo v primerjavi z bolniki z osnovno šolo (srednja šola: 1.74±0.59, osnovna šola: 2.02±0.58) p=0.016.
Ocena refleksa kašlja, prenašanja anestezije in bronhoskopije ter težave pri bronhoskopiji niso statistično signifikantne glede na tip uporabljenega instru-menta. Ocene prav tako niso statistično signifikantne med skupinami aktivnih kadilcev, bivših kadilcev in nekadilcev.
Imeli smo tri komplikacije, vse tri so bile pri transkrikoidni anesteziji. Od komplikacij smo zabeležili dve močnejši krvavitvi ter eno omotico po bronhoskopiji. Krvavitev je zabeležena pri bivšem kadilcu z osnovno šolo ter pri eni bolnici po pljučni biopsiji. Omotica je bila pri aktivni kadilki stari 58 let. Pri njej so bile tudi opravljene biopsije. Vse krvavitve so se ustavile brez dodatnih posegov, zaradi tega bolniki niso potrebovali dodatnega zdravljenja. Omotica je tudi bila prehodna in je minila brez dodatnega zdravljenja. Komplikacije, ki smo jih zabeležili, so bile posledica bronho-skopskih posegov (biopsija pljuč) in sodijo v pričakovane dogodke. Menimo, da niso posledica anestezije. Pri nobeni metodi nismo zabeležili komplikacije, ki bi bila posledica uporabljene metode.

Zaključki. Z našo raziskavo ugotavljamo prednosti transkrikoidne anestezije, posebej pri moških, zato bi to metodo anestezije priporočali pri večini bolnikov pri bronhoskopiji. Pri bolnikih, ki zaradi objektivnih razlogov ne bi mogli imeti opravljene transkrikoidne anestezije, bi po naših podatkih priporočali metodo z razprševanjem anestetika preko posebnega pršilnika, vendar bi pri tem morali upoštevati, da se bo uporabila večja količina anestetika. Metoda »spray as you go« se je pokazala kot metoda z največ pomanjkljivostmi. Glede na spol, starost, izobrazbo, vrsto inštrumenta ter kajenje nismo ugotovili bistvenih razlik pri prenašanju katerekoli metode anestezije ter bronhoskopije, razen boljšega prenašanja transkrikoidne anestezije pri moških.

Literatura

1. Fry WA. Techniques of topical anesthesia for bronhoscopy. Chest 1978: 73: 694-6.
2. Graham DR, Hay JG, Clague J, Nisar M, Earis JE. Comparison of three different methods used to achieve local anesthesia for fiberoptic bronchoscopy. Chest 1992; 102: 704-7.
3. Middleton RM, Shah A, Kirkpatrick MB. Topical nasal anesthesia for flexible bronchoscopy. A comparison of four methods in normal subjects and in patients undergoing transnasal bronchoscopy. Chest 1991; 99: 1093-6.
4. Korttila K. Local anesthetic techniques for bronchoscopies. Acta Anaesthesiol Belg 1984; 35 Suppl: 389-97.
5. Norley J, Lander C. Topicalization, oxygenation, and suction via a single-channel fiberoptic bronchoscope. Anesthesiology 1986; 65: 116.

6. Yank V, Rennie D. Disclosure of researcher contributions: a study of original research articles in The Lancet. Ann Intern Med 1999 Apr 20; 130: 661-70.
7. Prakash UBS, Offord KP, Stubbs SE. Bronchoscopy in North America: the ACCP survey. Chest 1991; 100: 1668–75.
8. Kirkpatrick MB. Lidocaine topical anaesthesia for flexible bronchoscopy. Chest 1989; 96: 965–7.
9. Kinnear WJM, Reynolds L, Gaskin D, Macfarlane JT. Comparison of transcricoid andbronchoscopic routes for administration of local anaesthesia before fiberoptic bronchoscopy. Thorax 1988; 43: 805P–5.
10. Webb AR, Fernando SSD, Dalton HR, Arrowsmith JE, Woodhead MA, Cummin ARC. Local anaesthesia for fibreoptic bronchoscopy: transcricoid injection or the »spray as you go« technique? Thorax 1990; 45: 474–7.
11. Fry WA. Techniques of topical anaesthesia for bronchoscopy. Chest 1978; 73: Suppl: 694–6.
12. Dierkesmann R, Dobbertin I. Different techniques of bronchoscopy. In: Strausz. Pulmonary endoscopy and biopsy techniques. ERS Monograph 1998; 3: 1–21.
13. British Thoracic Society. British thoracic society guidelines on diagnostic flexible bronchoscopy. Thorax 2001; 56: Suppl 1: i1–i21.
14. Reed AP. Preparation of the patient for awake flexible fiberoptic bronchoscopy. Chest 1992; 101: 244–53.
15. Triller N, Eržen D, Debeljak A in sod. Primerjava anestezije skozi delovni kanal bronhoskopa s transkrikoidno lokalno anestezijo z atropinom ali brez v premedikaciji-randomizirana študija. Zdrav Vestn 2001; 70: 534-5.

APHECOM - The impact of air pollution on asthma occurrence

Hočevar Grom A[1], Otorepec P[2], Medina S[2]
[1]IVZ RS, Ljubljana, Slovenia
[2]InVs, Paris, France

Aphecom is a multicity project that studies impact of air pollution on respiratory health.

Long-term average exposure to air pollution determines both the risks of chronic effects of pollution on health, such as impaired development of lung function, and the frequency of acute effects, such as the aggravation of asthma or incidence of respiratory symptoms. This indicator is also well correlated with the risk of a wide range of health effects, including increased mortality, in adults.

New evidence suggests that proximity to traffic (distance from highways, traffic density within certain distance of the residence) correlates with development of asthma risk and exacerbation of existing disease. Chronic pathologies are superimposed by acute exacerbations.

Other important task of project is to reveal the importance of other susceptibility factors for asthma (eg. parental asthma, movers).

The main objectives of projects are: whether traffic air pollution exposure has impact on development and exacerbation of asthma and what the importance of susceptibility factors for development of asthma is.

The study has two important phases; identification of people living in vicinity of busy roads, levels of air pollution at different distances and risk calculations.
In second phase a sample of asthma patients will be analaysed according to possible selected ecological and biological factors.

It is a multicentic study with participation of 8 EU countries and a number of big cities.
The final results will be avaiable in fall of 2010.

Treatment of chronic sarcoidosis with methotrexate

Grm Zupan S, Osolnik K
University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Introduction. Although corticosteroids (CS) remain the initial drug for most patients with sarcoidosis who require therapy, several steroid-sparing alternatives are possible. In chronic sarcoidosis the »second line« therapy can be used in addition to oral CS. Methotrexate (MTX) is most commonly used cytotoxic agent for treatment of chronic disease. It is metabolized in liver, cleared by kidney, a small part by biliary tract. Due to its several possible side effects: inhibition of hematopoesis (anemia, aplastic anemia, leukopenia, trombocytopenia), hepatitis (acute and chronic hepatotoxicity), MTX-induced pulmonary disease (fibrosis, pneumonitis), kidney damage (acute renal failure), GIT symptoms (nausea, vomiting, diarrhea, ulcerative stomatitis), skin changes (toxic epidermal necrolysis, erithema multiforme), careful monitoring is recommended.

Materials and Methods. We reviewed KOPA Golnik medical records of 14 patients (10 female: av. age 49,2 years; 4 male: av. age 46,5 years) with chronic pulmonary sarcoidosis treated with MTX.

Results. MTX therapy was started in cases of chronic pulmonary sarcoidosis and sarcoidosis with multiorgan involvement (lung, skin, nervous sistem, kidney). In six patients side-effects of CS therapy were found before starting therapy with MTX (steroidal diabetes 1, osteoporosis 2, mental changes 1, worse pre-existing diabetes 3, disfunction of adrenal gland 1), in three cases relapses occured when lowering the dose of CS, in four the CS therapy alone was uneffective. Five patients are still on therapy.
Average duration of MTX therapy in 9 patients was 15,2 months (range 3 months – 54 months). In all patients CS-dose was lowered during the MTX therapy.
In 13 patients MTX 10 mg was used once weekly, in one case 7,5 mg once weekly.
Side effects, except in one case (abdominal pain, nausea, pruritus), were not noticed. Liver enzymes, kidney function tests, whole blood count and chest x-ray showed no significant pathology during therapy.

Conclusions. Due to our data MTX is a quite safe drug for chronic sarcoidosis. Before starting the therapy liver enzymes, kidney function tests, whole blood count and chest X-ray are needed. Later, monthly blood count and every 1 - 2 months other tests are advised.

Tridimenzionalno spremljanje sprememb volumna prsnega koša med mirnim dihanjem

Jezeršek M[1], Fležar M[2], Možina J[1]
[1]Fakulteta za strojništvo, Univerza v Ljubljani, Ljubljana, Slovenija
[2]Bolnišnica Golnik – Klinični oddelek za pljučne bolezni in alergijo, Slovenija

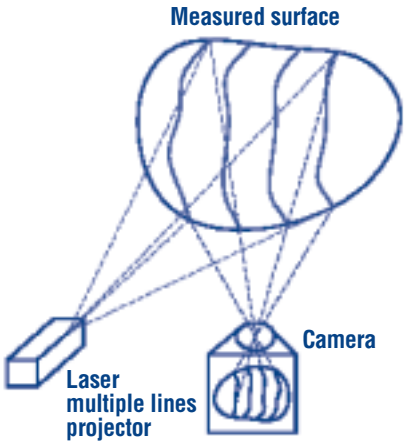
Neinvazivno merjenje pljučne mehanike s pomočjo optičnih metod predstavlja izziv in novost v fiziologiji dihanja, saj tako spirometri kot druge naprave potrebujejo sodelovanje bolnika pri dihanju. Približki optičnih metod meritvam, ki jih beležijo spirometri so dandanes že dobro razviti in omogočajo tako opazovanje globine in frekvence dihanja, kot kalibracijo sprememb volumna prsnega koša na znane volumne izmerjene s spirometri. Predvsem otroška populacija do starosti petih let in starejši bolniki so taki, katerim ne moremo izmeriti klasičnih parametrov pljučne funkcije s spirometri in kjer je omenjena metodologija potencialno primernejša za spremljanje frekvence in globine dihanja.

Opis metodologije

Glavni elementi merilne metodologije so opisani na sliki1.

Slika1: Grafična ponazoritev sprememb gibanja prsnega koša v barvah ob bolnikovi postelji

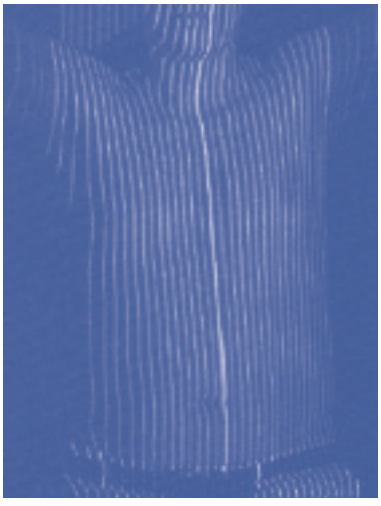
Metodologija zajema kamero in projektor, ki projicira na steno prsnega koša tanke črte v obliki mreže, katere zazna kamera. Deformacija mreže ob spremembah oblike prsnega koša pri dihanju izkorišča računalniški algoritem, ki na podlagi ukrivljenosti črt izračuna spremembe površine oz. spremembe v volumnu ter premike v smeri, ki jih zaznava kamera. Vidno polje, ki si ga z aparatom izmerimo zajema 400x400 milimetrov širine in dolžine ter lahko fokusira do 50 milimetrov v globino, kar pomeni premikanja v smeri proti kameri. Shematsko je princip detekcije projicirane mreže na prsni koš prikazan na sliki 2.



Slika 2: Princip projekcije na steno prsnega koša in detekcija na kameri.

Kalibracija natančnost aparata

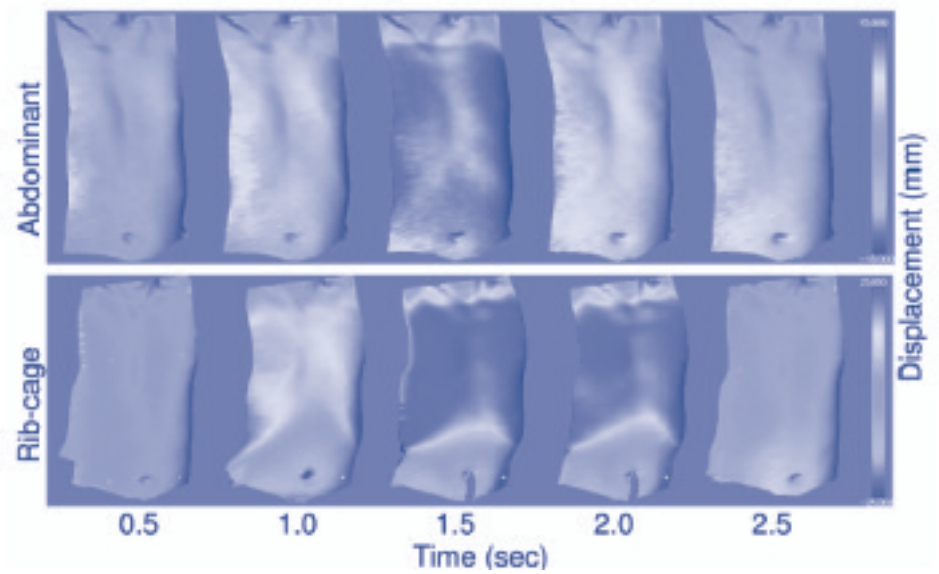
Pri kalibraciji smo uporabljali znane volumne, ki jih je bolnik vdahnil preko pnevmotahografa in pri nastavitvah kamere smo upoštevali optične lastnosti kamere, ki omogoča natančnost +/- 0,5 milimetra spremembe globine oz. deformacije črte. Omenja natančnost omogoča zaznavati že spremembe v volumnu prsnega koša, ki so manjše od 100 mililitrov.



Slika 3: Prikaz principa projekcije laserske mrežice na trup prostovoljca. Ob tem so roke iztegnjene, tako da se podoba fokusira na določene regije opazovanja.

Rezultati

Preliminarne meritve na zdravih prostovoljcih so pokazale možnost kalibracije aparata na znane volumne in detekcijo premikov torakalne in abdominalne stene med dihanjem. Grafično smo uspeli na barvni lestvici nazorno prikazati abdominalni in torakalni način dihanja.



Slika 4: V barvni skali prikazan premik prsnega koša pri vdihu in izdihu pri normalnem dihanju (zgornji del slike) in pri izrazitem dihanju s steno prsnega koša (spodnji del slike). Spremembe volumna oz. premikanja prsnega koša v osi proti kameri so prikazane na barvni lestvici.

Zaključek

Z metodo smo uspeli slediti spremembam gibanja prsnega koša in s pomočjo računalniškega algoritma prikazati omenjene spremembe z barvno lestvico, ki vizualno opisuje prispevke različnih delov prsnega koša pri gibanju in opazovanje načina dihanja teh bolnikov. Pričakujemo, da bo sistem uporaben pri fizioterapevtskem delu – učenju pravilnega dihanja s feed-back metodo in pri bolnikih, ki ne sodelujejo pri klasični preiskavi pljučne funkcije. Sistem bo v naslednji fazi omogočal tudi klinično uporabo testiranja.

Literatura

1. Gilbert R, Auchincloss JH, Brodsky J, Boden W. Changes in tidal volume, frequency, and ventilation induced by their measurement. J Appl Physiol 1972; 32:252-4.
2. Binks AP, Banzett RB, Duvivier C. An inexpensive, MRI compatible device to measure tidal volume from chest-wall circumference. Physiol Meas 2007; 28:149–59.
3. Kondo T, Inocchieri S, Baldwin DN, Nelle M, Frey U. Noninvasive monitoring of chest wall movement in infants using laser. Pediatr Pulmonol 2006.
4. Drummond GB, Duffy ND. A video-based optical system for rapid measurements of chest wall movement. Physiol Meas 2001; 22:489-503.
5. Groote AD, Wantier M, Cheron G, Estenne M, Paiva M. Chest wall motion during tidal breathing. J Appl Physiol 1997; 83:1531-7.
6. Jezeršek M, Gruden V, Možina J. Highspeed measurements of steel-plate meformations during laser surface processing. Optics Express 2004; 12:4905-11.
7. Jezeršek M, Možina J. A laser anamorph profilometer. Stroj vestn 2003; 49:76-89.
8. Bracun D, Jezeršek M, Diaci J. Triangulation model taking into account light sheet curvature. Meas Sci Technol 2006; 17:2191-6.

Beležke:

Beležke:

Beležke:

Beležke:

Beležke:

Beležke:

Beležke:

Izvedbo kongresa so omogočili:

Astra Zeneca

Glaxo SmithKline

Medis

Bayer

Alcon

Boehringer Ingelheim

Eli Lilly

Ewopharma

HAL

IRIS

Krka

Lek

LKB

Novartis

Nycomed

Olympus

Pfizer

Pliva

Pulmodata

Sapio plini

Schering Plough

Torrex Chiesi

PREPROSTO
2x na dan
in nič več!

Seretide®
salmeterol/flutikazonpropionat

ZA BOLNIKE S SIMPTOMI

kljub zdravljenju z zdravilom Flixotide®

ZDRAVILO SERETIDE®

omogoča dolgoročno preprečevanje simptomov [1, 2]

PREPROSTO.

Zjutraj in zvečer 1 vdih Seretide® 250.

ali drugih IKS.

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

IME ZDRAVILA

SERETIDE DISKUS 50 µg/100 µg/odmerek odmerjeni prašek za inhaliranje
SERETIDE DISKUS 50 µg/250 µg/odmerek odmerjeni prašek za inhaliranje
SERETIDE DISKUS 50 µg/500 µg/odmerek odmerjeni prašek za inhaliranje

KAKOVOSTNA IN KOLIČINSKA SESTAVA

Vsak posamezni odmerek zdravila SERETIDE DISKUS vsebuje 50 mikrogramov salmeterola (v obliki salmeterolijevega ksinafoata) in 100, 250 ali 500 mikrogramov flutikazonpropionata.
Pomožne snovi: laktoza
Vsak posamezni odmerek zdravila SERETIDE DISKUS (ne glede na jakost) vsebuje največ do 12,5 mg laktoze monohidrata.
Laktoza monohidrat (vsebuje mlečne proteine)

FARMACEVTSKA OBLIKA

Prašek za inhaliranje, odmerjen

KLINIČNI PODATKI

Terapevtske indikacije

ASTMA

Če je uporaba kombiniranega zdravila (kombinacije dolgodelujočega agonista adrenergičnih receptorjev beta-2 in inhalacijskega kortikosteroida) primerna, je zdravilo SERETIDE indicirano za redno zdravljenje astme pri:

- bolnikih, katerih simptomi astme z uporabo inhalacijskega kortikosteroida in občasno uporabo (po potrebi) kratkodelujočega inhalacijskega agonista adrenergičnih receptorjev beta-2 niso zadostno nadzorovani, ali
- bolnikih, katerih simptomi astme so že zadostno nadzorovani z uporabo obeh, inhalacijskega kortikosteroida in dolgodelujočega agonista adrenergičnih receptorjev beta-2.

Opomba: Zdravilo SERETIDE DISKUS 50 µg/100 µg/odmerek ni primerno za uporabo pri odraslih in otrocih s hudo astmo.

KRONIČNA OBSTRUKTIVNA PLJUČNA BOLEZEN (KOPB)

Zdravilo SERETIDE je indicirano za simptomatsko zdravljenje bolnikov z zmerno do zelo hudo KOPB (forsirani ekspiracijski volumen v 1. sekundi; FEV$_1$ < 60 % pričakovane normalne vrednosti) in anamnezo ponavljajočih se poslabšanj, ki imajo signifikantne simptome bolezni kljub rednemu zdravljenju z bronhodilatatorjem.

Odmerjanje in način uporabe

Zdravilo SERETIDE DISKUS je namenjeno izključno za inhaliranje.
Bolnikom je treba pojasniti, da bo optimalna korist zdravila SERETIDE DISKUS dosežena le, če ga bodo uporabljali vsakodnevno, tudi takrat, ko nimajo simptomov bolezni.
Bolniki morajo biti pod rednim zdravniškim nadzorom, da bi tako jakost zdravila SERETIDE, ki ga uporabljajo, ostala optimalna ves čas zdravljenja. Jakost zdravila SERETIDE lahko spremeni le zdravnik. **Odmerek je treba postopno zmanjševati do najmanjšega odmerka, ki še zagotavlja učinkovito nadzorovanost simptomov bolezni. Če se nadzorovanost simptomov vzdržuje z uporabo najmanjše jakosti kombinacije dvakrat na dan, se lahko v naslednji fazi zdravljenja poskusi z uporabo inhalacijskega kortikosteroida samega.** Bolnikom, ki potrebujejo zdravljenje z dolgodelujočim agonistom adrenergičnih receptorjev beta-2 se alternativno lahko predpiše uporaba zdravila SERETIDE enkrat na dan, če zdravnik meni, da bo s takšno uporabo nadzorovanost bolezni ostala zadovoljiva. V primeru uporabe zdravila enkrat na dan mora bolnik, ki ima simptome predvsem ponoči, uporabiti odmerek zdravila zvečer, bolnik, ki pa ima simptome predvsem podnevi, pa mora odmerek zdravila uporabiti zjutraj.
Bolnikom je treba predpisati jakost zdravila SERETIDE, ki vsebuje odmerek flutikazonpropionata, primeren resnosti bolezni. Zdravniki se morajo zavedati, da je pri bolnikih z astmo flutikazonpropionat tako učinkovit kot drugi inhalacijski kortikosteroidi že v približno polovičnem mikrogramskem dnevnem odmerku. Na primer, odmerek 100 mikrogramov flutikazonpropionata je približno enakovreden odmerku 200 mikrogramov beklometazondipropionata (z vsebnostjo CFC) ali budezonida. Če posamezen bolnik potrebuje zdravljenje z odmerkom, ki je izven priporočenega režima odmerjanja, mu je treba predpisati primeren odmerek agonista adrenergičnih receptorjev beta in/ali kortikosteroida.

Priporočeni odmerki

ASTMA

- ***Odrasli in mladostniki, stari 12 let in starejši***

- Ena inhalacija 50 mikrogramov salmeterola in 100 mikrogramov flutikazonpropionata dvakrat na dan, ali
- ena inhalacija 50 mikrogramov salmeterola in 250 mikrogramov flutikazonpropionata dvakrat na dan, ali
- ena inhalacija 50 mikrogramov salmeterola in 500 mikrogramov flutikazonpropionata dvakrat na dan.

Pri odraslih ali mladostnikih z zmerno persistentno astmo (bolniki z vsakodnevnimi simptomi, vsakodnevno uporabo olajševalca in zmernim do hudim zmanjšanjem pretoka zraka), pri katerih je nujno treba doseči hitro nadzorovanost astme, se lahko razmisli o kratkotrajni poskusni uporabi zdravila SERETIDE kot začetnega vzdrževalnega zdravljenja. V takšnih primerih je priporočeni začetni odmerek ena inhalacija 50 mikrogramov salmeterola in 100 mikrogramov flutikazonpropionata dvakrat na dan. Ko je dosežena nadzorovanost astme je treba zdravljenje ponovno ovrednotiti in presoditi o primernosti zmanjšanja odmerka in zdravljenju z inhalacijskim kortikosteroidom samim. Bolniki, pri katerih se odmerek zmanjša ali uvede zdravljenje z inhalacijskim kortikosteroidom samim, morajo biti pod rednim zdravniškim nadzorom.
V primeru odsotnosti enega ali dveh kriterijev za opredelitev nadzora bolezni očitna korist pri začetnem vzdrževalnem zdravljenju, v primerjavi z uporabo inhalacijskega flutikazonpropionata samega, ni bila dokazana. Pri večini bolnikov inhalacijski kortikosteroidi na splošno ostajajo zdravila prvega izbora. Zdravilo SERETIDE ni namenjeno začetnemu zdravljenju blage astme. Jakost zdravila SERETIDE 50/100 mikrogramov ni primerna za odrasle in otroke s hudo astmo. Pri bolnikih s hudo astmo je pred uvedbo katere koli fiksne kombinacije priporočljivo določiti ustrezni odmerek inhalacijskega kortikosteroida.

- ***Otroci, stari 4 leta in starejši***

- Ena inhalacija 50 mikrogramov salmeterola in 100 mikrogramov flutikazonpropionata dvakrat na dan.

Največji dovoljeni odmerek flutikazonpropionata, ki ga lahko prejmejo otroci z zdravilom SERETIDE DISKUS je 100 mikrogramov dvakrat na dan.
Podatki o uporabi zdravila SERETIDE pri otrocih, mlajših od 4 let, niso na voljo.

KOPB

- ***Odrasli***

- Ena inhalacija 50 mikrogramov salmeterola in 500 mikrogramov flutikazonpropionata dvakrat na dan.

Posebne skupine bolnikov

Pri starostnikih in bolnikih z okvaro ledvic odmerka ni treba prilagajati. Podatki o uporabi zdravila SERETIDE pri bolnikih z okvaro jeter niso na voljo.

Uporaba DISKUS-a

Bolnike je treba natančno poučiti o pravilni uporabi DISKUS-a.
Bolnik DISKUS najprej odpre in ga s premikom vzmeti pripravi za uporabo. Ustnik nato vstavi v usta in ga obda z ustnicami. Med inhalacijo se iz DISKUS-a sprosti prašek, ki ga bolnik vdihne v pljuča. Po uporabi mora bolnik DISKUS ustrezno zapreti. Število odmerkov na DISKUS-u kaže število preostalih odmerkov.
Za podrobnejša navodila glejte Navodila za uporabo, ki so priložena zdravilu.

Kontraindikacije

Alergija na (preobčutljivost za) katero koli zdravilno učinkovino ali pomožno snov.

Posebna opozorila in previdnostni ukrepi

Običajno mora zdravljenje astme potekati po stopenjskem programu. Bolnikov odziv je treba nadzirati tako klinično kot s testi pljučne funkcije.
Zdravila SERETIDE DISKUS se ne sme uporabljati za zdravljenje akutnih simptomov astme. V takšnih primerih morajo bolniki uporabiti kratkodelujoči bronhodilatator s hitrim nastopom delovanja. Bolnike je treba poučiti, da morajo imeti zdravilo za lajšanje akutnih astmatičnih napadov (akutnih poslabšanj astme) vedno na voljo.
Zdravljenja z zdravilom SERETIDE se ne sme uvesti med akutnim poslabšanjem astme oziroma če bolezen pomembno in hitro napreduje.
Med zdravljenjem z zdravilom SERETIDE se lahko pojavijo resni neželeni dogodki, povezani z astmo, in poslabšanja astme. Bolnikom je treba pojasniti, da naj v takšnih primerih nadaljujejo z uporabo zdravila, vendar pa naj poiščejo zdravniško pomoč, če simptomi astme ostanejo nenadzorovani ali se po začetku uporabe zdravila SERETIDE poslabšajo.
Pogostejša uporaba kratkodelujočih bronhodilatatorjev za lajšanje simptomov kaže na slabšo nadzorovanost bolezni. Takšni bolniki potrebujejo ustrezno zdravniško obdelavo.
Nenadno in progresivno poslabšanje nadzorovanosti astme je lahko smrtno nevarno. Takšni bolniki potrebujejo urgentno zdravniško oskrbo. Morda bo potrebno zdravljenje z večjim odmerkom kortikosteroida. Bolnik potrebuje zdravniški pregled tudi, če trenutni odmerek zdravila SERETIDE ne zagotavlja zadostne nadzorovanosti astme. Pri bolnikih z astmo ali KOPB bo morda potrebno uvesti dodatno zdravljenje s kortikosteroidi.
Ko je dosežena nadzorovanost astme, je treba presoditi o primernosti postopnega zmanjšanja odmerka zdravila SERETIDE. Pomembno je, da so bolniki po zmanjšanju odmerka pod rednim zdravniškim nadzorom. Bolnik mora uporabljati najnižji še učinkoviti odmerek zdravila SERETIDE
Pri bolnikih z astmo se zaradi nevarnosti poslabšanj, zdravljenje z zdravilom SERETIDE ne sme prekiniti nenadoma. Odmerek zdravila je treba zmanjševati postopoma, pod zdravniškim nadzorom. Tudi pri bolnikih s KOPB je opustitev zdravljenja lahko povezana s simptomatsko dekompenzacijo in ga mora zato nadzirati zdravnik.
Tako kot vsa inhalacijska zdravila, ki vsebujejo kortikosteroide, je treba tudi zdravilo SERETIDE uporabljati previdno pri bolnikih, ki imajo pljučno tuberkulozo.
Zdravilo SERETIDE lahko pri visokih terapevtskih odmerkih v redkih primerih povzroči aritmije, npr. supraventrikularno tahikardijo, ekstrasistole in atrijsko fibrilacijo ter blago prehodno zmanjšanje serumskega kalija. Zdravilo SERETIDE je treba zato uporabljati previdno pri bolnikih, ki imajo hujšo kardiovaskularno bolezen, vključno z motnjami srčnega ritma, sladkorno boleznijo, hipertiroidizmom (tirotoksikozo), nezdravljeno hipokaliemijo ali predispozicijo za nizke vrednosti serumskega kalija.
Zelo redko so poročali o povečanih vrednostih glukoze v krvi , kar je treba pri pacientih pri predpisovanju zdravila bolnikom, ki imajo v anamnezi sladkorno bolezen.
Tako kot pri zdravljenju z drugimi inhalacijskimi zdravili se lahko tudi pri zdravljenju z zdravilom SERETIDE pojavi paradoksni bronhospazem, ki se kaže s pojavom piskajočega dihanja takoj po uporabi odmerka. Uporabo zdravila SERETIDE DISKUS je treba nemudoma opustiti, opraviti ponoven pregled bolnika in po potrebi uvesti alternativno zdravljenje.
Zdravilo SERETIDE DISKUS vsebuje laktozo (do 12,5 miligramov/odmerek). Pri osebah, intoleratnih za laktozo, takšna količina običajno ne povzroča težav.
Pri prehodu na zdravljenje z zdravilom SERETIDE je potrebna previdnost, še posebej pri bolnikih, pri katerih obstaja kakršen koli sum na oslabljeno delovanje nadledvične žleze zaradi predhodnega zdravljenja s sistemskimi kortikosteroidi.
Sistemski učinki se lahko pojavijo pri zdravljenju s katerim koli inhalacijskim kortikosteroidom, še posebej v primeru velikih odmerkov, predpisanih za daljše obdobje. Verjetnost pojava sistemskih učinkov pa je vendarle veliko manjša kot pri zdravljenju s peroralnimi kortikosteroidi. Možni sistemski učinki vključujejo Cushingov sindrom in z njim povezane značilnosti, supresijo nadledvične žleze, zastoj rasti pri otrocih in mladostnikih, zmanjšanje kostne gostote, katarakto in glavkom. **Pomembno je torej, da so bolniki pod rednim zdravniškim nadzorom, in da se odmerek inhalacijskega kortikosteroida zmanjša do najmanjšega odmerka, ki še zagotavlja učinkovito nadzorovanost bolezni.**
Pri otrocih, ki se dolgotrajno zdravijo z inhalacijskim kortikosteroidom je priporočljivo opraviti redne meritve telesne višine.
Dolgotrajno zdravljenje bolnikov z visokimi odmerki inhalacijskih kortikosteroidov lahko posledično povzroči supresijo nadledvične žleze in akutno adrenalno krizo. Še posebno tveganje lahko obstaja pri otrocih in mladostnikih, mlajših od 16 let, ki se zdravijo z visokimi odmerki flutikazonpropionata (običajno ≥ 1.000 mikrogramov/dan). Zelo redko so poročali tudi o primerih pojava supresije nadledvične žleze in akutne adrenalne krize pri bolnikih, ki so se zdravili s flutikazonpropionatom v odmerkih od 500 do < 1.000 mikrogramov. Okoliščine v katerih lahko pride do pojava akutne adrenalne krize vključujejo travmo, kirurški poseg, okužbo ali kakršno koli nenadno zmanjšanje odmerka. Simptomi so običajno nejasni in lahko vključujejo anorekzijo, abdominalno bolečino, hušanje, utrujenost, glavobol, navzeo, bruhanje, hipotenzijo, zmanjšano stopnjo zavesti, hipoglikemijo in epileptične napade. Med obdobjem stresa ali načrtovanega kirurškega posega bo morda potrebno dodatno zdravljenje s sistemskimi kortikosteroidi.
Zaradi koristi zdravljenja z inhalacijskim flutikazonpropionatom se zmanjša potreba po zdravljenju s peroralnimi kortikosteroidi. Pri bolnikih, ki so se predhodno zdravili s peroralnimi kortikosteroidi pa lahko tveganje za okvarjeno adrenalno rezervo traja še znaten čas. Tveganje obstaja tudi pri bolnikih, ki so v preteklosti nujno potrebovali zdravljenje z visokimi odmerki kortikosteroidov. Takšno možnost rezidualne okvare je potrebno vedno upoštevati pri urgentnih in načrtovanih posegih, ki lahko izzovejo stres. Morda bo potrebno ustrezno kortikosteroidno zdravljenje. Pred načrtovanimi posegi bo o obsegu okvare nadledvične žleze morda potrebno pridobiti mnenje ustreznega specialista.
Ritonavir lahko znatneje poveča koncentracijo flutikazonpropionata v plazmi. Sočasni uporabi se je torej potrebno izogibati, razen v primerih, ko morebitna korist za bolnika prevlada nad tveganjem za pojav sistemskih kortikosteroidnih nežeželenih učinkov. Večje tveganje za pojav sistemskih nežeželenih učinkov obstaja tudi pri uporabi flutikazonpropionata v kombinaciji z drugimi močnimi zaviralci CYP3A.
V študijah pri bolnikih s KOPB, ki so prejemali zdravilo SERETIDE, so pogosteje poročali o pljučnici. Pri bolnikih s KOPB morajo biti zdravniki pozorni na možen pojav pljučnice, saj se klinični znaki pljučnice in poslabšanja osnovne bolezni pogosto prekrivajo.
Podatki iz obsežnega kliničnega preskušanja (SMART; *"The Salmeterol Multi-Center Asthma Research Trial"*) kažejo, da pri bolnikih afroameriškega porekla obstaja večje tveganje za pojav resnih respiratornih dogodkov ali smrtnih izidov pri uporabi salmeterola v primerjavi s placebom. Povezava s farmakogenetskimi ali drugimi dejavniki ni znana. Bolnikom črnega afriškega ali afrokaribskega izvora je treba pojasniti, da naj nadaljujejo z uporabo zdravila, vendar pa naj poiščejo zdravniško pomoč, če simptomi astme ostanejo nenadzorovani ali se med uporabo zdravila SERETIDE poslabšajo.

Medsebojno delovanje z drugimi zdravili in druge oblike interakcij

Izogibati se je treba uporabi tako neselektivnih kot selektivnih zaviralcev adrenergičnih receptorjev beta, razen v primerih, ko je njihova uporaba utemeljena in nujno potrebna.
Sočasna uporaba drugih zdravil z beta adrenergičnim delovanjem ima lahko aditiven učinek.
V območjih okoliščinah so po inhalacijskem odmerjanju dosežene zelo nizke koncentracije flutikazonpropionata v plazmi, kar je posledica znatne presnove prvega prehoda in visokega sistemskega očistka s citokromom P450 3A4 v črevesju in jetrih. Klinično pomembne interakcije s flutikazonpropionatom so zato malo verjetne.
Pri zdravih osebah, ki so v študiji medsebojnega delovanja z drugimi zdravili prejemale flutikazonpropionat intranazalno so ugotovili, da so se zaradi ritonavirja (zelo močan zaviralec citokroma P450 3A4) v odmerku 100 mg dvakrat na dan plazemske koncentracije flutikazonpropionata povečale za več stokrat, serumske koncentracije kortizola pa posledično znatno zmanjšale. Za inhalacijski flutikazonpropionat podatki sicer niso na voljo, vendar pa lahko pričakujemo znatno povečane vrednosti flutikazonpropionata v plazmi. Poročali so o primerih Cushingovega sindroma in supresije nadledvične žleze. Sočasni uporabi flutikazonpropionata in ritonavirja se je torej potrebno izogibati, razen v primerih, ko morebitna korist za bolnika prevlada nad povečanim tveganjem za pojav sistemskih glukokortikoidnih nežeželenih učinkov.
Pri zdravih prostovoljcih, ki so bili vključeni v manjšo študijo so ugotovili, da se je zaradi ketokonazola (nekoliko manj močan zaviralec CYP3A) izpostavljenost flutikazonpropionatu po eni sami inhalaciji slednjega povečala za 150 %. To je imelo za posledico močnejše zmanjšanje kortizola v plazmi kot pa pri uporabi flutikazonpropionata samega. Pri sočasnem zdravljenju z drugimi močnimi zaviralci CYP3A, kot je itrakonazol se tudi pričakuje, da se bo sistemska izpostavljenost flutikazonpropionatu povečala. Obstaja tveganje za pojav sistemskih nežeželnih učinkov. Priporočamo previdnost. Če je le možno, se je dolgotrajnemu zdravljenju s tovrstnimi zdravili potrebno izogibati.

Nosečnost in dojenje

O uporabi salmeterola in flutikazonpropionata pri nosečnicah in doječih materah je premalo podatkov, da bi lahko podali oceno o možnih škodljivih učinkih. Pri študijah na živalih so se po dajanju agonistov adrenergičnih receptorjev beta-2 in glukokortikosteroidov pojavile anomalije plodov.
Zdravilo SERETIDE se sme nosečnicam predpisati le, če pričakovana korist za mater prevlada nad kakršnim koli možnim tveganjem za plod.
Nosečnicam se sme predpisati le najmanjši še učinkovit odmerek flutikazonpropionata, ki še zagotavlja zadovoljivo nadzorovanost astme.
Podatkov o izločanju zdravila z materinim mlekom ni. Tako salmeterol kot flutikazonpropionat se izločata z mlekom pri doječih podganah. Zdravilo SERETIDE se sme doječim materam predpisati le, če pričakovana korist za mater prevlada nad kakršnim koli možnim tveganjem za dojenega otroka.

Vpliv na sposobnost vožnje in upravljanja s stroji

Študij o vplivu na sposobnost vožnje in upravljanja s stroji niso izvedli.

Neželeni učinki

Zdravilo SERETIDE vsebuje salmeterol (v obliki salmeterolijevega ksinafoata) in flutikazonpropionat, zato lahko pričakujemo vrsto in resnost neželenih reakcij, ki so povezane z vsako posamezno učinkovino. Zaradi sočasne uporabe obeh zdravilnih učinkovin, se dodatni neželeni dogodki niso pojavili.
Zelo pogosti: Glavobol
Pogosti: Kandidoza ustne votline in žrela, pljučnica*, tremor, palpitacije, draženje žrela, hripavost/disfonija, mišični krči
Občasni: Preobčutljivostne kožne reakcije, tahikardija
Zelo redki: Angioedem (predvsem edem obraza in orofaringealni edem), respiratorni simptomi (dispneja in/ali bronhospazem), anafilaksijske reakcije, vključno z anafilaktičnim šokom, Cushingov sindrom in z njim povezane značilnosti, supresija nadledvične žleze, zastoj rasti pri otrocih in mladostnikih, zmanjšanje kostne gostote, katarakta in glavkom, hiperglikemija, anksioznost, motnje spanja in vedenjske spremembe, vključno s hiperaktivnostjo ter razdražljivostjo (predvsem pri otrocih), aritmije (vključno z atrijsko fibrilacijo, supraventrikularno tahikardijo in ekstrasistolami), paradoksni bronhospazem., artralgija, mialgija
*Pogosta poročila pri placebu
Poročali so o farmakoloških neželenih učinkih zdravljenja z agonisti adrenergičnih receptorjev beta-2, kot so tremor, palpitacije in glavobol. Običajno so bili prehodni in so se pri rednem zdravljenju ublažili.
Zaradi flutikazonpropionata se lahko pri posameznih bolnikih pojavi hripavost in kandidoza (soor) ustne votline in žrela. Otoje, hripavost in pojavnost kandidoze se lahko ublaži z izpiranjem ustne votline po uporabi zdravila. Simptomatska kandidoza se lahko, ob sočasnem nadaljevanju zdravljenja z zdravilom SERETIDE DISKUS, zdravi z lokalnimi protiglivičnimi zdravili.
V študijah pri bolnikih s KOPB so poročali o pljučnici.
Možni sistemski učinki lahko vključujejo Cushingov sindrom in z njim povezane značilnosti, supresijo nadledvične žleze, zastoj rasti pri otrocih in mladostnikih, zmanjšanje kostne gostote, katarakto in glavkom.
Zelo redko so poročali o pojavu hiperglikemije.
Tako kot pri zdravljenju z drugimi inhalacijskimi zdravili se lahko pojavi paradoksni bronhospazem.

Preveliko odmerjanje

Podatkov o primerih prevelikega odmerjanja zdravila SERETIDE med kliničnimi preskušanji ni, vendar pa so v nadaljevanju podani podatki o prevelikem odmerjanju posamezne zdravilne učinkovine.
Znaki in simptomi prevelikega odmerjanja salmeterola so tremor, glavobol in tahikardija. Prednostni antidot je kardioselektivni zaviralec adrenergičnih receptorjev beta, ki pa ga je pri bolnikih z bronhospazmom v anamnezi potrebno uporabljati previdno. Če se mora zdravljenje z zdravilom SERETIDE prekiniti zaradi prevelikega odmerjanja agonista adrenergičnih receptorjev beta, bo morda potrebno zagotoviti ustrezno nadomestno zdravljenje s kortikosteroidom. Lahko se pojavi tudi hipokaliemija, zato bo morda potrebno nadomeščanje kalija.
Akutno: Akutna uporaba inhalacijskega flutikazonpropionata v odmerkih, ki so večji od priporočenih, lahko povzroči začasno supresijo nadledvične žleze. Nujni ukrepi zaradi tega običajno niso potrebni, saj se adrenalna funkcija v nekaj dneh povrne, kar se lahko ugotovi z merjenjem koncentracije kortizola v plazmi.
Za kronično preveliko odmerjanje inhalacijskega flutikazonpropionata glejte podatke o tveganju za supresijo nadledvične žleze v poglavju 4.4. Morda bo potreben monitoring adrenalne rezerve. V primeru prevelikega odmerjanja flutikazonpropionata se lahko zdravljenje z zdravilom SERETIDE nadaljuje, in sicer z odmerki, ki zadostujejo za nadzorovanje simptomov.

Inkompatibilnosti

Navedba smiselno ni potrebna.

Vrsta ovojnine in vsebina

Prašek za inhaliranje se nahaja v dvojnem traku, ki je sestavljen iz osnovne PVC folije in povrhnje folije, ki se še preluknja. Dvojni trak je vstavljen v napravo iz lite plastike (DISKUS). Vsak DISKUS vsebuje 60 odmerkov. DISKUS je na voljo v škatli.

IMETNIK DOVOLJENJA ZA PROMET

GSK d.o.o., Ljubljana, Knezov štradon 90, 1000 Ljubljana, Slovenija

DATUM ZADNJE REVIZIJE BESEDILA

20. 4. 2007

Seretide Diskus je zaščitena blagovna znamka GlaxoSmithKline Group of Companies. Pred predpisovanjem, prosimo preberite celoten povzetek glavnih značilnosti zdravila. Za vse morebitne nadaljnje informacije o tem zdravilu se lahko obrnete na imetnika dovoljenja za promet z zdravilom:

GSK d.o.o., Ljubljana, Knezov štradon 90, 1000 Ljubljana, tel: + 386 (0)1 280 25 00, medical.x.si@gsk.com

Reference:

1. Bateman ED et al. Am J Respir Crit Care Med 2004; 170: 836–44.
2. Woodcock AA et al. Prim Care Respir J 2007; 16: 155–61.

GSK d.o.o., Ljubljana
Knezov štradon 90
1001 Ljubljana

Tel. (386 1) 28 02 500
Faks (386 1) 28 02 550
www.gsk.com

07-08-SER-A-035-J

Seretide - **edina** fiksna kombinacija IGK/LABA, indicirana za zmerno do zelo hudo KOPB

Razširitev indikacije na FEV_1 < 60 %

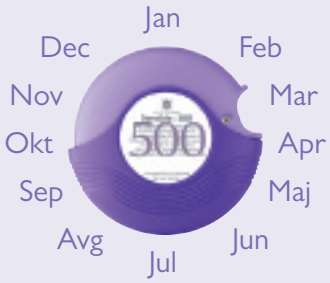
Seretide je namenjen KOPB bolnikom, ki so simptomatski

kljub rednemu zdravljenju z bronhodilatatorji in imajo FEV_1 < 60 % pričakovane vrednosti ter ponavljajoča poslabšanja v anamnezi.

Z zdravilom Seretide se bolniki počutijo bolje dlje časa

(v primerjavi s kontrolno skupino).[1]

Za dolgotrajno izboljšanje kakovosti življenja **predpišite vzdrževalno zdravljenje z zdravilom Seretide 50/500** dvakrat dnevno.



Zjutraj in zvečer 1 vdih

RAZŠIRITEV INDIKACIJE
SAMO ZA SERETIDE

Seretide®
salmeterol/flutikazonpropionat
Živite življenje

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

1. IME ZDRAVILA

SERETIDE DISKUS 50 µg/100 µg/odmerek odmerjeni prašek za inhaliranje
SERETIDE DISKUS 50 µg/250 µg/odmerek odmerjeni prašek za inhaliranje
SERETIDE DISKUS 50 µg/500 µg/odmerek odmerjeni prašek za inhaliranje

2. KAKOVOSTNA IN KOLIČINSKA SESTAVA

Vsak posamezni odmerek zdravila SERETIDE DISKUS vsebuje 50 mikrogramov salmeterola (v obliki salmeterolijevega ksinafoata) in 100, 250 ali 500 mikrogramov flutikazonpropionata.
Pomožne snovi: laktoza monohidrat

3. FARMACEVTSKA OBLIKA

Prašek za inhaliranje, odmerjen

4. TERAPEVTSKE INDIKACIJE

ASTMA

Prosimo, preberite celoten povzetek glavnih značilnosti zdravila.

KRONIČNA OBSTRUKTIVNA PLJUČNA BOLEZEN (KOPB)

Zdravilo SERETIDE je indicirano za simptomatsko zdravljenje bolnikov z zmerno do zelo hudo KOPB (forsirani ekspiracijski volumen v 1. sekundi; FEV_1 < 60 % pričakovane normalne vrednosti) in anamnezo ponavljajočih se poslabšanj, ki imajo signifikantne simptome bolezni kljub rednemu zdravljenju z bronhodilatatorjem.

5. ODMERJANJE IN NAČIN UPORABE

ASTMA

Prosimo, preberite celoten povzetek glavnih značilnosti zdravila.

KOPB

Odrasli: Ena inhalacija 50 mikrogramov salmeterola in 500 mikrogramov flutikazonpropionata dvakrat na dan.

6. KONTRAINDIKACIJE

Alergija na (preobčutljivost za) katero koli zdravilno učinkovino ali pomožno snov .

7. POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI

Običajno mora zdravljenje astme potekati po stopenjskem programu. Bolnikov odziv je treba nadzirati tako klinično kot s testi pljučne funkcije. Zdravila SERETIDE DISKUS se ne sme uporabljati za zdravljenje akutnih simptomov astme. V takšnih primerih morajo bolniki uporabiti kratkodelujoči bronhodilatator s hitrim nastopom delovanja. Zdravljenja z zdravilom SERETIDE se ne sme uvesti med akutnim poslabšanjem astme oziroma če bolezen pomembno in hitro napreduje. Med zdravljenjem z zdravilom SERETIDE se lahko pojavijo resni neželeni dogodki, povezani z astmo, in poslabšanja astme. Nenadno in progresivno poslabšanje nadzorovanosti astme je lahko smrtno nevarno. Takšni bolniki potrebujejo urgentno zdravniško oskrbo. Morda bo potrebno zdravljenje z večjim odmerkom kortikosteroida. Pomembno je, da so bolniki po zmanjšanju odmerka pod rednim zdravniškim nadzorom. Bolnik mora uporabljati najnižji še učinkoviti odmerek zdravila SERETIDE. Pri bolnikih z astmo se zaradi nevarnosti poslabšanj, zdravljenje z zdravilom SERETIDE ne sme prekiniti nenadoma. Odmerek zdravila je treba zmanjševati postopoma, pod zdravniškim nadzorom. Tudi pri bolnikih s KOPB je opustitev zdravljenja lahko povezana s simptomatsko dekompenzacijo in ga mora zato nadzirati zdravnik. Tako kot vsa inhalacijska zdravila, ki vsebujejo kortikosteroide, je treba tudi zdravilo SERETIDE uporabljati previdno pri bolnikih, ki imajo pljučno tuberkulozo. Zdravilo SERETIDE lahko pri visokih terapevtskih odmerkih v redkih primerih povzroči aritmije, npr. supraventrikularno tahikardijo, ekstrasistole in atrijsko fibrilacijo ter blago prehodno zmanjšanje serumskega kalija. Zdravilo SERETIDE je treba zato uporabljati previdno pri bolnikih, ki imajo hujšo kardiovaskularno bolezen, vključno z motnjami srčnega ritma, sladkorno bolezen, hipertiroidizem (tirotoksikozo), nezdravljeno hipokaliemijo ali predispozicijo za nizke vrednosti serumskega kalija.
Zelo redko so poročali o povečanih vrednostih glukoze v krvi (glejte poglavje 9. Neželeni učinki), kar je treba upoštevati pri predpisovanju zdravila bolnikom, ki imajo v anamnezi sladkorno bolezen. Tako kot pri zdravljenju z drugimi inhalacijskimi zdravili se lahko tudi pri zdravljenju z zdravilom SERETIDE pojavi paradoksni bronhospazem, ki se kaže s pojavom piskajočega dihanja takoj po uporabi odmerka. Uporabo zdravila SERETIDE DISKUS je treba nemudoma opustiti, opraviti ponoven pregled bolnika in po potrebi uvesti alternativno zdravljenje. Zdravilo SERETIDE DISKUS vsebuje laktozo (do 12,5 miligramov/odmerek). Pri osebah, intolerantnih za laktozo, takšna količina običajno ne povzroča težav. Pri prehodu na zdravljenje z zdravilom SERETIDE je potrebna previdnost, še posebej pri bolnikih, pri katerih obstaja kakršen koli sum na oslabljeno delovanje nadledvične žleze zaradi predhodnega zdravljenja s sistemskimi kortikosteroidi. Sistemski učinki se lahko pojavijo pri zdravljenju s katerim koli inhalacijskim kortikosteroidom, še posebej v primeru velikih odmerkov, predpisanih za daljše obdobje. Verjetnost pojava sistemskih učinkov pa je vendarle veliko manjša kot pri zdravljenju s peroralnimi kortikosteroidi. Možni sistemski učinki vključujejo Cushingov sindrom in z njim povezane značilnosti, supresijo nadledvične žleze, zastoj rasti pri otrocih in mladostnikih, zmanjšanje kostne gostote, katarakto in glavkom. **Pomembno je torej, da so bolniki pod rednim zdravniškim nadzorom, in da se odmerek inhalacijskega kortikosteroida zmanjša do najmanjšega odmerka, ki še zagotavlja učinkovito nadzorovanost bolezni.**
Pred načrtovanimi posegi bo o obsegu okvare nadledvične žleze morda potrebno pridobiti mnenje ustreznega specialista.
Podatki iz obsežnega kliničnega preskušanja (SMART; "*The Salmeterol Multi-Center Asthma Research Trial*") kažejo, da pri bolnikih afroameriškega porekla obstaja večje tveganje za pojav resnih respiratornih dogodkov ali smrtnih izidov pri uporabi salmeterola v primerjavi s placebom. Povezava s farmakogenetskimi ali drugimi dejavniki ni znana. Bolnikom črnega afriškega ali afrokaribskega izvora je treba pojasniti, da naj nadaljujejo z uporabo zdravila, vendar pa naj poiščejo zdravniško pomoč, če simptomi astme ostanejo nenadzorovani ali se med uporabo zdravila SERETIDE poslabšajo.

8. MEDSEBOJNO DELOVANJE Z DRUGIMI ZDRAVILI IN DRUGE OBLIKE INTERAKCIJ

Izogibati se je treba uporabi tako neselektivnih kot selektivnih zaviralcev adrenergičnih receptorjev beta, razen v primerih, ko je njihova uporaba utemeljena in nujno potrebna.
Sočasna uporaba drugih zdravil z beta adrenergičnim delovanjem ima lahko aditiven učinek.
V običajnih okoliščinah so po inhalacijskem odmerjanju dosežene zelo nizke koncentracije flutikazonpropionata v plazmi, kar je posledica znatne presnove prvega prehoda in visokega sistemskega očistka s citokromom P450 3A4 v črevesju in jetrih. Klinično pomembne interakcije s flutikazonpropionatom so zato malo verjetne.
Pri zdravih osebah, ki so v študiji medsebojnega delovanja z drugimi zdravili prejemale flutikazonpropionat intranazalno so ugotovili, da so se zaradi ritonavirja (zelo močan zaviralec citokroma P450 3A4) v odmerku 100 mg dvakrat na dan plazemske koncentracije flutikazonpropionata povečale za več stokrat, serumske koncentracije kortizola pa posledično znatno zmanjšale. Za inhalacijski flutikazonpropionat podatki sicer niso na voljo, vendar pa lahko pričakujemo znatno povečane vrednosti flutikazonpropionata v plazmi. Poročali so o primerih Cushingovega sindroma in supresije nadledvične žleze. Sočasni uporabi flutikazonpropionata in ritonavirja se je torej potrebno izogibati, razen v primerih, ko morebitna korist za bolnika prevlada nad povečanim tveganjem za pojav sistemskih glukokortikoidnih neželenih učinkov.
Pri zdravih prostovoljcih, ki so bili vključeni v manjšo študijo so ugotovili, da se je zaradi ketokonazola (nekoliko manj močan zaviralec CYP3A) izpostavljenost flutikazonpropionatu po eni sami inhalaciji slednjega povečala za 150 %. To je imelo za posledico močnejše zmanjšanje kortizola v plazmi kot pa pri uporabi flutikazonpropionata samega. Pri sočasnem zdravljenju z drugimi močnimi zaviralci CYP3A, kot je itrakonazol se tudi pričakuje, da se bo sistemska izpostavljenost flutikazonpropionatu povečala. Obstaja tveganje za pojav sistemskih neželenih učinkov. Priporočamo previdnost. Če je le možno, se je dolgotrajnemu zdravljenju s tovrstnimi zdravili potrebno izogibati.

9. NEŽELENI UČINKI

Zdravilo SERETIDE vsebuje salmeterol (v obliki salmeterolijevega ksinafoata) in flutikazonpropionat, zato lahko pričakujemo vrsto in resnost neželenih reakcij, ki so povezane z vsako posamezno učinkovino. Zaradi sočasne uporabe obeh zdravilnih učinkovin, se dodatni neželeni dogodki niso pojavili.
Infekcijske in parazitske bolezni: kandidoza ustne votline in žrela, pljučnica.
Bolezni imunskega sistema: preobčutljivostne reakcije z naslednjimi manifestacijami - preobčutljivostne kožne reakcije, Angioedem (predvsem edem obraza in orofaringealni edem). Respiratorni simptomi (dispneja in/ali bronhospazem). Anafilaksijske reakcije, vključno z anafilaktičnim šokom.
Bolezni endokrinega sistema: Cushingov sindrom in z njim povezane značilnosti, supresija nadledvične žleze, zastoj rasti pri otrocih in mladostnikih, zmanjšanje kostne gostote, katarakta in glavkom.
Presnovne in prehranske motnje: hiperglikemija.
Psihiatrične motnje: anksioznost, motnje spanja in vedenjske spremembe, vključno s hiperaktivnostjo ter razdražljivostjo (predvsem pri otrocih).
Bolezni živčevja: glavobol, tremor.
Srčne bolezni: palpitacije, tahikardija, aritmije (vključno z atrijsko fibrilacijo, supraventrikularno tahikardijo in ekstrasistolami).
Bolezni dihal, prsnega koša in mediastinalnega prostora: draženje žrela, hripavost/disfonija, paradoksni bronhospazem.
Bolezni mišično-skeletnega sistema in vezivnega tkiva: mišični krči, artralgija, mialgija.

Poročali so o farmakoloških neželenih učinkih zdravljenja z agonisti adrenergičnih receptorjev beta-2, kot so tremor, palpitacije in glavobol. Običajno so bili prehodni in so se pri rednem zdravljenju ublažili. Zaradi flutikazonpropionata se lahko pri posameznih bolnikih pojavi hripavost in kandidoza (soor) ustne votline in žrela. Oboje, hripavost in pojavnost kandidoze se lahko ublaži z izpiranjem ustne votline po uporabi zdravila. Simptomatska kandidoza se lahko, ob sočasnem nadaljevanju zdravljenja z zdravilom SERETIDE DISKUS, zdravi z lokalnimi protiglivičnimi zdravili.
V študijah pri bolnikih s KOPB so poročali o pljučnici. Možni sistemski učinki lahko vključujejo Cushingov sindrom in z njim povezane značilnosti, supresijo nadledvične žleze, zastoj rasti pri otrocih in mladostnikih, zmanjšanje kostne gostote, katarakto in glavkom (glejte poglavje *7. Posebna opozorila in previdnostni ukrepi*). Zelo redko so poročali o pojavu hiperglikemije.
Tako kot pri zdravljenju z drugimi inhalacijskimi zdravili se lahko pojavi paradoksni bronhospazem.

10. FARMAKOLOŠKE LASTNOSTI

10.1 Farmakodinamične lastnosti

Farmakoterapevtska skupina: Adrenergiki in druge učinkovine za obstruktivne pljučne bolezni, oznaka ATC: R03AK06

Klinična preskušanja zdravila SERETIDE pri zdravljenju KOPB

TORCH (TOwards a Revolution in COPD Health) je bila tri leta trajajoča študija, katere cilj je bil pri bolnikih s KOPB oceniti učinek zdravljenja s Seretide Diskusom 50/500 mcg dvakrat na dan, salmeterolijev ksinafoat Diskusom 50 mcg dvakrat na dan, flutikazon propionat (FP) Diskusom 500 mcg dvakrat na dan ali s placebom na umrljivost zaradi vseh vzrokov. Bolniki z zmerno do hudo KOPB z izhodiščnim (pred uporabo bronhodilatatorja) FEV_1 < 60 % pričakovane normalne vrednosti so bili randomizirano razporejeni v dvojno slepe skupine. V času študije je bilo bolnikom dovoljeno uporabljati zdravila, ki so jih sicer običajno uporabljali za zdravljenje KOPB, z izjemo drugih inhalacijskih kortikosteroidov, dolgo delujočih bronhodilatatorjev in dolgo delujočih sistemskih kortikosteroidov. Status preživetja po 3 letih je bil določen za vse bolnike, ne glede na to, če so študijsko zdravilo morda prenehali jemati. Primarni cilj študije je bil ugotoviti zmanjšanje umrljivosti zaradi vseh vzrokov po 3 letih uporabe Seretida v primerjavi s placebom.
1 p-vrednost prilagojena zaradi 2 vmesnih analiz primerjave primarne učinkovitosti iz log-rank testa, stratificiranega glede na kadilski status. Seretide Diskus je v primerjavi s placebom zmanjšal tveganje za smrt ob katerem koli času tekom 3 let za 17,5 % (razmerje tveganja 0,825 (95 % CI 0,68 do 1,00, p = 0,052), vsi prilagojeni za začasno analizo). Zmanjšanje tveganja za smrt ob katerem koli času tekom 3 let je bilo pri salmeterolijevem ksinafoatu v primerjavi s placebom 12 % (p = 0,180), v skupini, ki je uporabljala FP pa je v primerjavi s placebom prišlo do 6 % porasta tveganja (p = 0,525).

Podporna analiza, ki je uporabila Coxov model sorazmernih tveganj, je za uporabo Seretida v primerjavi s placebom ugotovila razmerje tveganj 0,811 (95 % CI 0,670 do 0,982, p = 0,031), kar predstavlja 19 % zmanjšanje tveganja za smrt ob katerem koli času v obdobju 3 let. Model je bil prilagojen glede na pomembne faktorje (kadilski status, starost, spol, področje, izhodiščni FEV, in ITM (BMI)). Dokazov, da bi ti faktorji vplivali na učinek zdravljenja, ni bilo. Odstotek bolnikov, ki so v teku 3 let umrli zaradi s KOPB povezanih vzrokov, je znašal 6,0 % pri placebu, 6,1 % pri salmeterolijevem ksinafoatu, 6,9 % pri FP in 4,7 % pri Seretidu. Seretide Diskus je v primerjavi s placebom zmanjšal število zmernih do hudih poslabšanj za 25 % (95 % CI 19 % do 31 %; p < 0,001). Seretide Diskus je v primerjavi s salmeterolijevem ksinafoatom zmanjšal število poslabšanj za 12 % (95 % CI 5 % do 19 %; p = 0,002) in v primerjavi s FP za 9 % (95 % CI 1 % do 16 %; p = 0,024). Salmeterolijev ksinafoat in FP sta v primerjavi s placebom pomembno zmanjšala število poslabšanj, in sicer za 15 % (95 % CI 7 % do 22 %; p < 0,001) salmeterolijev ksinafoat in za 18 % (95 % CI 11 % do 24 %; p < 0,001) FP. Z zdravljem povezana kakovost življenja, merjena po vprašalniku St. George Respiratory Questionnaire (SGRQ) je bila v primerjavi s placebom izboljšana pri vseh oblikah aktivnega zdravljenja. Povprečna vrednost izboljšanja v dobi 3 let za Seretide Diskus je v primerjavi s placebom znašala -3,1 enote (95 % CI -4,1 do -2,1; p < 0,001). V primerjavi s salmeterolijevim ksinafoatom je izboljšanje znašalo -2,2 enoti (p < 0,001) in v primerjavi s FP -1,2 enoti (p = 0,017). V triletnem obdobju zdravljenja so bile FEV, vrednosti višje pri osebah, zdravljenih s Seretidom, kakor pri osebah, ki so prejemale placebo (povprečna razlika v obdobju 3 let je bila 92 ml; CI: 75 do 108 ml; p < 0,001). Seretide Diskus je bil v izboljšanju FEV_1 učinkovitejši tudi od salmeterolijevega ksinafoata (povprečna razlika 50 ml, p < 0,001) in od FP (povprečna razlika 44 ml, p < 0,001). Ocenjena triletna verjetnost pljučnice kot neželenega učinka zdravila je bila za placebo 12,3 %, za salmeterolijev ksinafoat 13,3 %, za FP 18,3 % in za Seretide Diskus 19,6 % (razmerje tveganja za Seretide Diskus v primerjavi s placebom: 1,64; 95 % CI 1,33 do 2,01, p < 0,001). Porasta s pljučnico povezanih smrti ni bilo; v času zdravljenja je bilo število primarno pljučnici pripisanih smrti sledeče: 7 pri placebu, 9 pri salmeterolijevem ksinafoatu, 13 za FP in 8 za Seretide Diskus. Ni bilo statistično pomembne razlike v verjetnosti za zlom kosti (5,1 % placebo, 5,1 % salmeterolijev ksinafoat, 5,4 % FP in 6,3 % Seretide Diskus); razmerje tveganja za Seretide Diskus v primerjavi s placebom: 1,22 (95 % CI: 0,87 do 1,72, p = 0,248). Pogostnost očesnih bolezni, bolezni kosti in motnje HPA (hipotalamus-hipofiza-nadledvična žleza) osi je bila nizka in med posameznimi načini zdravljenja razlike ni bilo. Dokazov o porastu neželenih učinkov na srcu v skupini, ki je prejemala salmeterolijev ksinafoat, ni bilo. S placebom nadzorovana klinična preskušanja, ki so trajala 6 oziroma 12 mesecev, so pokazala, da se z redno uporabo zdravila SERETIDE DISKUS 50 µg/500 µg izboljša pljučna funkcija, ublaži zasoplost in zmanjša pogostnost uporabe olajševalca. V primerjavi s placebom se je tveganje za poslabšanja KOPB v 12-mesečnem obdobju zmanjšalo iz 1,42 na leto na 0,99 na leto. Tudi tveganje za poslabšanja, ki zahtevajo zdravljenje s peroralnimi kortikosteroidi se je v primerjavi s placebom pomembno zmanjšalo (iz 0,81 na 0,47 na leto).

11. FARMACEVTSKI PODATKI

11.1 Seznam pomožnih snovi: Laktoza monohidrat
11.2 Rok uporabnosti: 18 mesecev

12. IMETNIK DOVOLJENJA ZA PROMET

GSK d.o.o., Ljubljana, Knezov štradon 90, 1000 Ljubljana, Slovenija

13. DATUM ZADNJE REVIZIJE BESEDILA 20. 4. 2007

Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila.
Popolne informacije o zdravilu so na voljo pri imetniku dovoljenja za promet z zdravilom.
Seretide® in Diskus® sta zaščiteni blagovni znamki GlaxoSmithKline Group of companies.

Literatura:

1. Calverley PMA et al. New Engl J Med 2007; 356(8): 775-789.

GSK d.o.o., Ljubljana
Knezov štradon 90
1001 Ljubljana

Tel. (386 1) 28 02 500
Faks (386 1) 28 02 550
www.gsk.com

09-07-SER-C-012J

Današnje alergije cvetijo tudi na urbanih vrtovih

Nad alergijo z optimalno terapijo

Xyzal®
LEVOCETIRIZIN 5 mg

NOVO Na listi

Xyzal®, optimalen antihistaminik za zdravljenje današnjih alergij, ker:

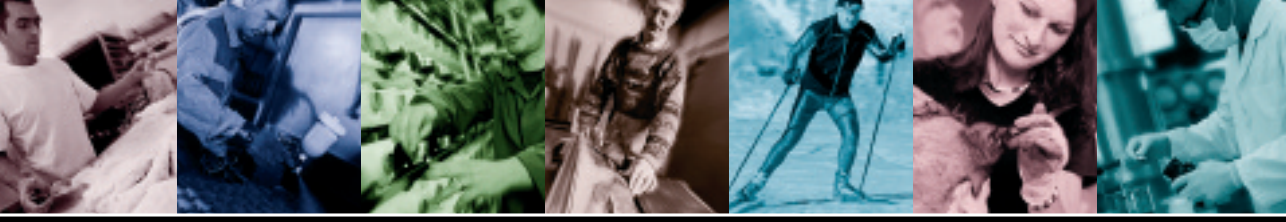
- današnje alergije zahtevajo učinkovit in varen antihistaminik[2]
- superiorno in zanesljivo zavre simptome alergijskega rinitisa, vključno z nosno kongestijo[3, 5-8]
- učinkovito zmanjša simptome kronične idiopatske urtikarije[4, 9, 10]
- izboljša kakovost življenja bolnikom z alergijo[1]
- njegov dober varnostni profil omogoča dolgotrajno zdravljenje[4,6,2]

1. Van Hoecke H, Allergy 2006; 61: 705-711, **2.** Allergy 2007, **3.** Day JH et al. J Clin Pract 2004; 58: 109-118, **4.** Grant JA et al. Ann Allergy Asthma Immunol 2002; 88: 190-197, **5.** Van Cauwenberg A, ERS poster 2005, **6.** Bachert C et al. J Allergy Immunol, 2004; 114: 838-44, **7.** Patou J et al. Clin Exp Allergy 2006; 36: 972-81, **8.** Jorissen M et al. B-ENT 2006; 255-262, **9.** Frossard N et al. EADV Congress 2006, **10.** Kapp A et al. Int J Dermatol 2006; 45: 469-474

Pred predpisovanjem zdravila Xyzal® preberite povzetek temeljnih značilnosti zdravila, ki ga dobite pri naših strokovnih sodelavcih.

MEDIS
www.medis.si

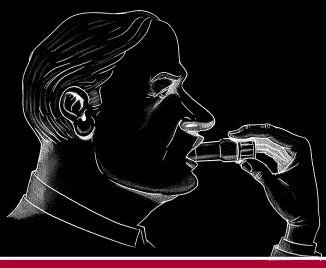
ucb
THE ALLERGY COMPANY



Twisthaler®

Enostaven vdihovalnik za zdravljenje astme

BREZ DOPLAČILA



1 *Twist* odpri

Odstranite zaščitni pokrov z inhalatorja tako, da ga zavrtite v obratni smeri urinega kazalca.

Števec bo to zaznal in številka se bo zmanjšala za eno enoto.

Zdravilo je pripravljeno za vdih.

2 vdihni

Izdihnite zrak do maksimalnega izdiha. Nato vstavite v usta ustnik inhalatorja Twisthaler® in vdihnite hitro in globoko. Inhalator nato odstranite iz ust, vdih pa zadržite še približno 10 sekund.

Priporočamo, da po vsaki uporabi ustnik obrišete s suhim robčkom.

3 *Twist* zapri

Po vsakem vdihu inhalator Twisthaler® zaprite z zaščitnim pokrovom tako, da ga zavrtite v smeri urinega kazalca. Pri tem rahlo potiskajte navzdol, dokler ne zaslišite, da se je zaskočil.

Puščica in števec na pokrovu se morata poravnati, kajti le tako je pokrov dobro nameščen in pripravljen za naslednji vdih zdravila.

Če morate inhalirati še en odmerek zdravila, ponovite zgornje korake.
Po vsakem inhaliranju si usta izperite z vodo. Inhalatorja Twisthaler® ne odpirajte po nepotrebnem!

Na vdih 1 2 3

Enostavno – v treh korakih do nadzora astme!

Schering - Plough CE AG

Dunajska 22, 1000 Ljubljana
telefon 01 300 10 70, faks: 01 300 10 70

Če želite podrobnejša pojasnila o vdihovalniku Twisthaler®, se pogovorite z zdravnikom.

Oblikovanje: Klemen Lavrih; Fotografije: Urban Modic; Marec 2005

Air ... Avelox®.

Avelox® moksifloksacin

Prvi razred pri okužbah dihal.

Vstopite, vzletite, dihajte bolje.

Kratkoročno:
Akutna epizoda apKOPB

- Hitro in učinkovito obvlada simptome poslabšanja, t. j. dispnejo, gnojni izmeček in količino izmečka.

Dolgoročno:
Ponovitev apKOPB

- Manj poslabšanj, ohranitev delovanja pljuč in kakovosti življenja.

Avelox® 400 mg filmsko obložene tablete
Avelox® 400 mg/250 ml raztopina za infundiranje
Sestava: 1 filmsko obložena tableta vsebuje 436,8 mg moksifloksacinijevega klorida; 250 ml raztopine za infundiranje (1 steklenica) vsebuje 436,8 mg moksifloksacinijevega klorida, kar ustreza 400 mg moksifloksacina. Avelox® 400 mg filmsko obložene tablete so na voljo v pakiranju, ki vsebuje 5 ali 7 filmsko obloženih tablet. **Terapevtske indikacije:** Filmsko obložene tablete so indicirane za zdravljenje naslednjih bakterijskih okužb, če jih povzročajo bakterije občutljive za moksifloksacin: akutne eksacerbacije kroničnega bronhitisa: 5 0 dni; pljučnice, pridobljene v domačem okolju, razen hudih oblik: 10 dni; akutnega vnetja obnosnih votlin: 7 dni; Raztopina za infundiranje je indicirana za zdravljenje: pljučnice, pridobljene v domačem okolju, ki jih povzročajo bakterije, občutljive za moksifloksacin (pri bolnikih, pri katerih je potrebno začetno parenteralno zdravljenje): 7–14 dni; zapletenih okužb kože in kožnih struktur: 7–21 dni. **Odmerjanje in način uporabe:** Odmerjanje (odrasli) 400 mg moksifloksacina, ki ga infundiramo enkrat na dan. Zdravljenje pljučnice, pridobljene v domačem okolju, se lahko začne z infuzijami in nadaljuje s tabletami, ki se jih daje peroralno (če je klinično indicirano). Zdravljenje zapletenih okužb kože in kožnih struktur je treba začeti z intravenskimi oblikami ter nato nadaljevati s filmsko obloženimi tabletami Avelox, 400 mg. Način uporabe Za intravensko uporabo; neprekinjeno infundiranje naj traja 60 minut. Če je indicirano, lahko raztopino za infundiranje dajemo preko T-cevke, skupaj s kompatibilnimi raztopinami za infundiranje. **Kontraindikacije**: znana preobčutljivost za moksifloksacin, druge kinolone ali katerokoli od pomožnih snovi, nosečnost in dojenje, otroci in mladostniki v obdobju rasti, bolniki z boleznimi kit v anamnezi ali z motnjami, ki so posledica zdravljenja s kinoloni. Zaradi varnostnih razlogov je uporaba zdravila Avelox® kontraindicirana pri bolnikih s/z: prirojenim ali dokazano pridobljenim podaljšanjem dobe QT, motnjami elektrolitskega ravnotežja, zlasti z neizboljšano hipokaliemijo, klinično pomembno bradikardijo, klinično pomembnim srčnim popuščanjem in zmanjšano iztisno frakcijo levega prekata, simptomatskimi aritmijami v anamnezi. Zdravilo Avelox® se ne sme uporabljati sočasno z drugimi zdravili, ki podaljšujejo interval QT. **Posebna opozorila in previdnostni ukrepi**: Bolniki z motnjami centralnega živčnega sistema morajo kinolone uporabljati previdno, saj lahko povzročijo epileptične napade ali znižajo prag njihovega pojava. Če se pojavijo motnje vida ali kakršnekoli očesne spremembe, mora bolnik takoj obiskati oftalmologa. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij**: Pri sočasni uporabi moksifloksacina in naslednjih zdravil ne moremo izključiti aditivnega učinka na podaljšanje intervala QT: antiaritmiki razreda IA ali antiaritmiki razreda III nevroleptiki, triciklični antidepresivi, nekatera protimikrobna zdravila (sparfloksacin, eritromicin IV, pentamidin, antimalariki, predvsem halofantrin), nekateri antihistaminiki (terfenadin, astemizol, mizolastin), drugi (cisaprid, vinkamin IV, bepridil, difemanil). **Neželeni učinki**: Vsi neželeni učinki zdravila (razen navzeje in driske) so se pojavili pri manj kot 3 % bolnikov. Pogosto (1–10 %): bolečine v trebuhu, glavobol, omotičnost, navzeja, driska, bruhanje, dispepsija, pri bolnikih s sočasno hipokaliemijo: podaljšana doba QT, spremembe okusa, nenormalne vrednosti jetrnih funkcijskih testov (predvsem zmerno zvečanje vrednosti AST/ALT in/ali bilirubina), reakcije na mestu injiciranja. **Način izdajanja:** Zdravilo se izdaja le na recept. **Zadnja revizija besedila:** 31.10.2007 **Podrobnejše informacije o zdravilu dobite pri imetniku dovoljenja za promet**: Bayer d.o.o., Bravničarjeva 13, Ljubljana **www.bayer.si**

Bayer HealthCare
Bayer Schering Pharma

Za bolnike z astmo

FOSTER®

formoterol + beklometazon

Ekstra fina fiksna kombinacija, s katero dosežete urejeno **astmo**

- **1–2 vpiha 2x na dan**
- **Delci mikronske velikosti zagotavljajo veliko pljučno depozicijo**
- **Velika učinkovitost, dokazana v primerjalnih raziskavah**

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA
Foster 100/6 mikrogramov na sprožitev inhalacijska raztopina pod tlakom

SESTAVA: Vsak določeni odmerek (iz ventila) vsebuje: 100 mikrogramov beklometazondipropionata in 6 mikrogramov formoterolijevega fumarata dihidrata. **POMOŽNE SNOVI:** norfluran (HFA-134a), brezvodni etanol, klorovodikova kislina. **PAKIRANJE:** Vsebuje 1 tlačni vsebnik, ki omogoča 120 sprožitev. **INDIKACIJE:** Foster je indiciran za redno zdravljenje astme, kadar je primerna uporaba kombiniranega zdravila (inhaliranega kortikosteroida in dolgodelujočega agonista beta,): - pri bolnikih, neustrezno urejenih z inhaliranimi kortikosteroidi in inhaliranim kratkodelujočim agonistom beta,, uporabljanim »po potrebi« ali - pri bolnikih, ki so že ustrezno urejeni z inhaliranimi kortikosteroidi in dolgodelujočimi agonisti beta,. **ODMERJANJE:** Foster je namenjen samo za inhalacijsko uporabo. Foster ni primeren za zdravljenje akutnih napadov astme. Foster ni namenjen za začetno vodenje astme. Odmerjanje sestavin zdravila Foster je individualno in ga morate prilagoditi izrazitosti bolezni. **Priporočila za odmerjanje pri odraslih, starih 18 let in več:** Ena ali dve inhalaciji dvakrat na dan. Največji dnevni odmerek so 4 inhalacije na dan. Priporočila za odmerjanje pri otrocih in mladostnikih, mlajših od 18 let: Z zdravilom Foster ni izkušenj pri otrocih in mladostnikih, mlajših od 18 let. Dokler ne bo na voljo več podatkov, zdravila Foster ni priporočljivo uporabljati pri otrocih in mladostnikih, mlajših od 18 let. **KONTRAINDIKACIJE:** Znana preobčutljivost za beklometazondipropionat, formoterolijev fumarat dihidrat in/ali katerokoli pomožno snov. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Foster morate uporabljati previdno pri bolnikih z motnjami srčnega ritma, zlasti z atrioventrikularnim blokom tretje stopnje ali tahiaritmijami, idiopatsko subvalvularno aortno stenozo, hipertrofično obstruktivno kardiomiopatijo, hudo boleznijo srca, akutnim miokardnim infarktom, ishemično boleznijo srca, kongestivnim srčnim popuščanjem, okluzivnimi boleznimi žil, zlasti arteriosklerozo, arterijsko hipertenzijo ali anevrizmo, podaljšanim intervalom QTc, tirotoksikozo, diabetes mellitusom, feokrpmocitomom, nezdravljeno hipokaliemijo, pljučno tuberkulozo, glivičnimi ali virusnimi okužbami dihal. Če je predvidena anestezija s halogeniranimi anestetiki, je treba poskrbeti, da bolnik zdravila Foster ne dobi vsaj 12 ur pred začetkom anestezije, ker obstaja tveganje za motnje srčnega ritma. Tako kot pri drugi inhalacijski terapiji se lahko po uporabi pojavi paradoksen bronhospazem s takojšnjim poslabšanjem piskajočega in težkega dihanja. Bolnike morate redno kontrolirati in odmerek inhaliranega kortikosteroida zmanjšati do najnižjega odmerka, s katerim je mogoče astmo učinkovito obvladovati. Dolgotrajno zdravljenje z velikimi odmerki inhaliranih kortikosteroidov lahko zavre delovanje nadledvičnih žlez in povzroči akutno adrenalno krizo. Da bo tveganje za orofaringealne okužbe s kandido manjše, bolnikom svetujte, naj po inhalaciji predpisanega odmerka usta splaknejo, grgrajo vodo ali si umijejo zobe. **INTERAKCIJE**: Pri bolnikih z astmo se izogibajte uporabi blokatorjev beta (vključno s kapljicami za oko). Za ostale interakcije glej celotno navodilo. **NOSEČNOST IN DOJENJE:** Foster uporabite med nosečnostjo in dojenjem le, če pričakovane koristi odtehtajo možna tveganja. **GLAVNI NEŽELENI UČINKI: Pogosti:** faringitis, disfonija, glavobol. **Občasni:** Gripa, glivična okužba v ustih, kandidoza žrela in požiralnika, nožnična kandidoza, gastroenteritis, sinuzitis, granulocitopenija, alergijski dermatitis, hipokaliemija, hiperglikemija, nemir, tremor, omotica, otosalpingitis, palpitacije, podaljšanje korigiranega intervala QT na elektrokardiogramu, spremembe elektrokardiograma, tahikardija, tahiaritmija, hiperemija, zardevanje, rinitis, kašelj, produktiven kašelj, draženje žrela, astmatična kriza, driska, suhost ust, dispepsija, disfagija, pekoč občutek na ustnicah, navzeja, dizgevzija, srbenje, osip, hiperhidroza, mišični spazmi, mialgija, zvišanje C-reaktivnega proteina, povečano število trombocitov, zvišanje prostih maščobnih kislin, zvišanje insulina v krvi, zvišanje ketonskih teles v krvi. **NACIN IZDAJANJA ZDRAVILA:** Zdravilo se izdaja le na recept.

Pred predpisovanjem, prosimo, preberite celotni povzetek glavnih značilnosti zdravila!

Dodatne informacije so na voljo pri Torrex Chiesi Slovenija, d.o.o., Trdinova 4, Ljubljana. Datum priprave informacije: avgust 2008

Torrex PHARMA Chiesi

041-734 399
pokličite 24ur/7dni

SAPIO LIFE HELIOS
TEKOČI KISIK

Če so vas zadnja leta spraševali , kako bodo bolniki s KOPB zalivali rože okrog hiše, poslušali ptičje petje v parku in uživali ob žuborečem potočku ob mlinu, ker vas je KOPB privezal na koncentrator, si preberite sledeči prospekt

Do danes s koncentratorjem in prenosnimi jeklenkami

Do danes so bili prisiljeni uporabljati edini razpoložljiv vir kisika. Bili so priklenjeni na koncentrator, ki je električna naprava in oddaja koncentriran zračni kisik. Poleg omejitve koncentracije kisika, so vezani na vir elektrike, naprava oddaja veliko toplote in je glasna, predvsem pa se ne morejo gibati na prostem in bodo za zdravje porabili kar nekaj denarja. Zato :

- se jim poviša nevarnost tromboze globokih ven
- nimajo osebnega stika s prijatelji
- ne morejo v naravo, negibljivim se povečuje število obiskov pri zdravniku
- če želijo na prosto, morajo imeti jeklenke s kisikom, ki jim jih polnijo v pooblaščeni polnilnici in za to potrebujejo osebo, da za njih hodi polniti jeklenke
- imajo stroške z električno energijo za koncentrator , za jeklenke bodo mesečno plačevali kar nekaj denarja, prave svobode pa ne bodo občutili, saj jim mora jeklenke polniti pooblaščena organizacija in za to bolnik potrebuje osebo, ki gre zanj v polnilnico plinov

Od danes naprej s Sapio Life Helios tekočim kisikom

Sapio Life Helios tekoči kisik z rezervoarjem in prenosno enoto, odpravi težave opisane pri koncentratorju in prenosnih jeklenkah. Res je, za sistem bodo plačali mesečno najemnino, vendar lahko zato odštejejo stroške elektrike za koncentator in najem jeklenk, torej bo strošek za novi sistem tako le za malenkost dražji. Kaj bodo dobili v zameno za najemnino?

- prostost in možnost gibanja v naravi, neodvisnost, družbo, kvalitetnejše življenje
- naravo, zrak, sonce
- nabrali si bodo fizično kondicijo. Gibanje zvišuje splošno pljučno rehabilitacijo, zato se jim bo najverjetneje zmanjšalo število obiskov pri zdravniku

Kako ste s Sapio Life Helios tekočim kisikom lahko neodvisni - svobodni v gibanju - vedno samos

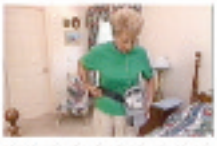
Sapio Life Helios tekoči kisik

Omogoča bolniku novo svobodo gibanja in nov pozitiven pogled na življenje, ker je enostaven in lahek za nošnjo, ker vam omogoča opasanje, obešanje in nošnjo kot nahrbtnik. Z njim se boste sprehajali v naravi kolikor vam srce poželi. Izboljšuje rehabilitacijo, povečuje aktivnost bolnika...
Sapio Life Helios tekoči kisik sprošča iz rezervoarja popolnoma čist kisik skoraj neslišno, ne potrebuje elektrike, ni se vam treba bati električnih mrkov, ne boste občutili vročine v stanovanju v poletnih mesecih, lahko se boste družili s svojimi znanci, šli boste na dopuste, v zdravilišča, življenje su vam bo izboljšalo in sproščeni boste in krepkejši, ker se boste gibali in še veliko več.
Sapio Life Helios tekoči kisik je vir kisika, ki je prenosljiv in omogoča bolj normalno socialno življenje, obenem pa tudi lažjo skrb za telesno kondicijo, ki je pri bolezni KOPB nujno potrebna! Nikakor se ne sme začeti zmanjševati mišična moč in vzdržljivost mišic tisti trenutek, ko bolnik dobi predpisan kisik. S prenosno enoto si je možno omogočiti redno gibanje, kar vpliva tudi na apetit, preprečevanje izgube kostne mase in normalno delovanje mišis ter srca. Posebej če je med telesno aktivnostjo kisika v krvi premalo (kar se da izmeriti z pulznim oksimetrom - aparatom, ki se natakne na prst in izmeri saturacijo krvi s kisikom) boste z dodanim kisikom zmogli več in ob tem manj obremenjevali vaše srce.

Prenosno enoto polnite v svojem stanovanju iz rezervoarja, ki vam ga pripelje Sapio Life k vam domov. Polnjenje prenosne enote traja vsega 40 - 60 sekund.

Prenosna enota ima tehtnico, s katero izmerite polnost. Polna enota H300 je zelo lahka (1,5 kg)

Nastavite pretok na željeno vrednost pri enoti H300 0,12 D4 litra/min , pri enoti H850 1 D6 litrov/min



Preverite, če je prenosna enota polna, si jo obesite na rame, oblečete plašč in že se na avtobusu na poti k znancu, se sprehajate po parku, opazujete labode na ribniku, kupite časopis v trafiki in še več.

*Sistem **SAPIO LIFE HELIOS TEKOČI KISIK** je popolnoma varen, skladišča kisika niso pod visokim tlakom, tekoči kisik ne more eksplodirati. Ker je temperatura tekočega kisika nizka, je potrebno paziti na opekline- zmrzline pri polnjenju prenosne enote. Zanesljivost sistema je primerljiva koncentratorju kisika, s tem, da so dejanske koncentracije kisika v zraku, ki ga proizvaja koncentrator za kisik pogosto nižje, kot pa deklarirane na merilcu tega aparata. V tem je tekoči kisik natančnejši. Za polnjenje prenosne enote tekočega kisika lahko prosite drugo osebo, je pa možno, da si prenosne enote popolnoma sami napolnite. Zdravstvene težave, ki bi nastopile zaradi tekočega kisika in ne bi nastopile tudi pri kisikovem koncentratorju niso poznane.*

Doc.dr.Matjaž FLEŽAR dr.med.

Sapio Life ima 24 urno tehnično pomoč in zagotavlja telefonski odziv 8 ur na pomoč za tehnične težave ter 24 urni tehnični servis v primeru kvara.

Sapio Life team servis vam 24 ur na dan/7dni na teden vam vedno v oporo.

ZA POLNJENJE PRENOSNE ENOTE POSKRBITE VI

za vse ostalo poskrbi SAPIO LIFE

Pokličite za več informacij in za predstavitev Sapio Life Helios tekoči kisik naprave pri vas.

OSTALA PONUDBA PODJETJA

Ventilator terapija na domu

Zahvaljujoč ventilator terapiji na domu so pacienti, ki so jih včasih lahko zdravili le v bolnišnicah in ki so kazali neprestane težave zaradi težav pri dihanju, ki je posledica pomanjkanja zraku, danes lahko zdravijo v svojem hišnem okolišu ter si na tak način izboljšajo življenjske pogoje ter obenem zmanjšajo stroške bolnišnične oskrbe.

Sindrom sleep-apnea (zastoj dihanja v spanju)

Zaporednje zbujanja in ponovnega vračanja v spanje, ki je značilen za tovrstni sindrom, je posebno rizično stanje zaradi pomanjkanja dihanja (s posledičnim zmanjšanjem koncentracije in težnje po spanju), ki samo zase povzroča v organizmu spremembe in težave.

Sapio Life nudi najsodobnejšo in najnaprednejšo tehnologijo za hišni in bolnišnični monitoring sindroma OSAS ter daja na razpolago ustrezne sisteme CPAP (naprave za kontinuirni pozitivni tlak) v dihalnem sistemu, s katerim lahko uspešno blažimo ta sindrom.

Terapevtski pripomočki

Terapevtski pripomočki, kot so naprimer vozički , specialne postelje ali opornice ter drugi proizvodi, pripomorejo pacientu da se laže in uspešneje vključujejo v vsakdanje okolje.

Sapio Life ponuja širok izbor pripomočkov, ki jih daja svojim pacientom na razpolago.

Aerosolna terapija

Pri zdravljenju mnogih bolezni je aerosolna terapija primeren način vnašanja zdravila v bolnikovo telo, saj se z inhaliranjem zdravila slednje bolje razporedi in prej pride na kraj, kjer ga bolnik nujno potrebuje , t.j. v bolnikove dihalne poti in na tak način z manj zdravila povzroči manj stranskih učinkov na pacientu.

Sapio Life je na tem področju zelo dejaven in lahko svojim pacientom ponudi širok in učinkovit spekter proizvodov in ustrezne opreme.

Druge dejavnosti : bolnišnični servis, monitoring, integrirana oskrba, enteralna prehrana

SAPIO PLINI d.o.o. - PE SAPIO LIFE

Ulica Tolminskih puntarjev 012 , 5000 NOVA GORICA , tel.05-3330 230 , fax.05-3330 231

tel.:03-6202 403 , 03-6202 404 , fax. 03-6202 405 , gsm 041-734 399 , **www.sapio.si** , *life@sapio.si*

Topljivo in učinkovito.
Na zdravje!

novo

Amoksiklav®

SOLVO

Se topi!

POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Amoksiklav® SOLVO 1000 mg tablete za peroralno suspenzijo, Amoksiklav® SOLVO 625 mg tablete za peroralno suspenzijo

SESTAVA: 1 tableta vsebuje 875 ali 500 mg amoksicilina v obliki trihidrata in 125 mg klavulanske kisline v obliki kalijevega klavulanata. **INDIKACIJE:** Okužbe zgornjega dela dihal (akutni in kronični sinusitis, akutno in kronično vnetje srednjega ušesa – otitis media, ponavljajoči se tonzilitis, peritonzilarni absces), okužbe spodnjega dela dihal (akutni bronhitis z bakterijsko superinfekcijo, akutne eksacerbacije kroničnega bronhitisa, pljučnica), okužbe sečil, ginekološke okužbe, gonoreja, ugrizi živali in človeka, okužbe kože in mehkih tkiv, okužbe kosti in sklepov, holangitis, holecistitis, kankroid, odontogene okužbe, abdominalne okužbe in pooperacijski intraabdominalni zapleti, mešane okužbe, ki jih povzročajo po Gramu negativni in po Gramu pozitivni mikroorganizmi ter anaerobni mikroorganizmi. **ODMERJANJE IN NAČIN UPORABE:** Običajni dnevni odmerek za odrasle in otroke, ki tehtajo več kot 40 kg, je ena tableta po 1000 mg vsakih 12 ur ali ena tableta po 625 mg vsakih 8 ali 12 ur. Trajanje zdravljenja mora ustrezati indikaciji in ne sme trajati dlje kot 14 dni brez ponovnega zdravniškega pregleda. Amoksiklav® SOLVO v tabletah po 1000 mg in 625 mg ni primeren za otroke, mlajše od 12 let, ali posameznike, ki tehtajo manj kot 40 kg. NAČIN UPORABE: Bolnik mora tableto raztopiti v pol kozarca vode (najmanj 30 ml) in vsebino pred zaužitjem temeljito premešati ali tableto raztopiti v ustih, preden jo pogoltne. Da bi zmanjšali možnost nastanka gastrointestinalne intolerance, mora bolnik zdravilo zaužiti na začetku obroka. **KONTRAINDIKACIJE:** Preobčutljivost za zdravilne učinkovine (amoksicilin in klavulansko kislino), katerokoli pomožno snov ali druge penicilinske antibiotike. Bolniki s holestatsko zlatenico ali zmanjšanim jetrnim delovanjem v anamnezi, povezanim z jemanjem penicilina ali amoksicilina in klavulanske kisline. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Amoksiklav® SOLVO predpisujemo previdno bolnikom z alergijo ali okvaro jeter v anamnezi. Pri hujših okvarah ledvic je treba prilagoditi odmerek oziroma podaljšati presledek med dvema odmerkoma. Uporaba Amoksiklava® SOLVO ni priporočena pri bolnikih z infekcijsko mononukleozo in limfocitno levkemijo. Upoštevati je treba možnost nastanka psevdomembranoznega kolitisa. V primeru superinfekcije z odpornimi bakterijami in glivicami je treba zdravljenje prekiniti ter pričeti z nadomestnim zdravljenjem. Pri jemanju velikih odmerkov amoksicilina je priporočljivo vzdrževati zadosten vnos tekočin in izločanja urina, da se zmanjša možnost nastanka kristalurije. **NOSEČNOST IN DOJENJE:** Nimamo podatkov o teratogenih učinkih na plod. Amoksiklav® SOLVO lahko uporabljamo v nosečnosti, kadar pričakovana korist za mater upravičuje tveganje za plod. Ker se amoksicilin in klavulanska kislina izločata v materino mleko, morajo doječe matere zdravilo uporabljati previdno. **MEDSEBOJNO DELOVANJE Z DRUGIMI ZDRAVILI IN DRUGE OBLIKE INTERAKCIJ:** Pri hkratnem zdravljenju z Amoksiklavom® SOLVO in metotreksatom se zveča toksičnost metotreksata. V kombinaciji z alopurinolom je pogostejši eksantem. Amoksiklav® SOLVO je fizikalno in kemično nekompatibilen z aminoglikozidi. V posameznih primerih lahko zdravilo vpliva na podaljšanje protrombinskega časa, zato je potreben premislek pred sočasnim zdravljenjem s peroralnimi antikoagulanti. Kombinacija amoksicilina in klavulanske kisline zmanjša učinkovitost peroralnih kontracepcijskih sredstev. Zaradi vpliva na gastrointestinalno floro penicilini lahko spremenijo enterohepatični obtok glikozidov digitalisa in se zaradi tega njihova absorpcija lahko poveča. **NEŽELENI ŠKODLJIVI UČINKI:** Najpogostejše so poročali o driski, navzeji, bruhanju in slabi prebavi. Nastanejo lahko kandidozni vaginitis, psevdomembranozni kolitis, preobčutljivostne reakcije (srbenje, makulopapulozni izpuščaj, koprivnica, angionevrotični edem, bronhospazem, anafilaktični šok), holestazna zlatenica, hepatitis in intersticijski nefritis, povečane vrednosti jetrnih encimov, anemija, levkopenija, agranulocitoza, trombocitopenija in eozinofilija. **NAČIN IZDAJANJA ZDRAVILA:** Samo na zdravniški recept. **OPREMA:** Škatlice z 10 tabletami za peroralno suspenzijo po 625 mg, škatlice z 10 tabletami za peroralno suspenzijo po 1000 mg.
IMETNIK DOVOLJENJA ZA PROMET: Lek farmacevtska družba d.d., Verovškova 57, Ljubljana, Slovenija. **DATUM ZADNJE REVIZIJE BESEDILA:** december 2006.

lek

član skupine Sandoz | let razvoja

Lek farmacevtska družba d.d. Verovškova 57, 1526 Ljubljana, Slovenija • www.lek.si

NEW

IN SLOVENIA!

INEGY®†

(ezetimibe/simvastatin)

DUAL POWER!

For your patients in secondary prevention with LDL- cholesterol > 2,5 mmol/l despite statin therapy![1,2]

MSD Schering-Plough

SHORT SUMMARY OF PRODUCT CHARATERISTICS Before prescribing please read the complete Summary of Product Characteristics, available at our sales representatives or at the company's seat! • **Composition:** Each tablet contains 10 mg ezetimibe and 10, 20, 40 or 80 mg of simvastatin. • **Indications:** ***Hypercholesterolaemia*** - adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate. ***Homozygous Familial Hypercholesterolaemia (HoFH)*** INEGY is indicated as adjunctive therapy to diet for use in patients with HoFH. • **Posology and method of administration:** ***Hypercholesterolaemia*** INEGY can be administered orally with or without food, in range of 10/10 mg/day through 10/80 mg/day in the evening. The typical dose is 10/20 mg/day or 10/40 mg/day given as a single dose in the evening. The 10/80-mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks. Not all pack sizes may be marketed. Homozygous ***Familial Hypercholesterolaemia*** INEGY 10/40 mg/day or 10/80 mg/day in the evening, may be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. ***Coadministration with other medicines*** ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant. In patients taking amiodarone or verapamil concomitantly with INEGY, the dose should not exceed 10/20 mg/day. In patients taking ciclosporin, danazol, or lipid-lowering doses (≥ 1 g/day) of niacin concomitantly with INEGY, the dose should not exceed 10/10 mg/day. ***Use in special population of patients:*** No dosage adjustment is required for elderly patients, in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) and in patients with moderate renal insufficiency. If treatment in patients with severe renal insufficiency (creatinine clearance ≤ 30 ml/min) is deemed necessary, dosages above 10/10 mg/day should be implemented cautiously. Treatment with INEGY is not recommended in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score > 9) liver dysfunction. INEGY is not recommended for use in children due to a lack of data on safety and efficacy. • **Contraindications** Hypersensitivity to ezetimibe, simvastatin, or to any of the excipients, pregnancy and lactation, active liver disease or unexplained persistent elevations in serum transaminases, Concomitant administration of potent CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors and nefazodone). • **Special warnings and precautions for use** ***Myopathy/Rhabdomyolysis*** manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10 X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. If myopathy is suspected for any other reason, treatment should be discontinued.Therapy with INEGY should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes. Concomitant intake of grapefruit juice and INEGY should be avoided. ***Liver Enzymes*** In controlled coadministration trials in patients receiving ezetimibe with simvastatin, consecutive transaminase elevations (≥3 X ULN) have been observed. It is recommended that liver function tests be performed before treatment with INEGY begins and thereafter when clinically indicated. Patients titrated to the 10/80 mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80 mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment. If the transaminase levels show evidence of progression, particularly if they rise to 3 X ULN and are persistent, the drug should be discontinued. INEGY should be used with caution in patients who consume substantial quantities of alcohol. ***Excipient*** Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. • **Interaction with other medicinal products and other forms of interaction:** Strong CYP3A4 inhibitors are contraindicated with INEGY; coadministration of INEGY with fibrates is not recommended; with ciclosporin, danazol, or niacin (≥ 1 g/day) don't exceed 10 mg/10 mg daily; with amidaron and verapamil don't exceed 10mg/20mg daily; with diltiazem don't exceed 10/40 mg daily; fusidic acid - patients should be closely monitored, temporary suspension of INEGY treatment may be considered; cholestyramine - concomitant cholestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental LDL C reduction due to adding INEGY to cholestyramine may be lessened by this interaction. • In patients taking coumarin anticoagulants, prothrombin time should be determined before starting INEGY and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. If the dose of INEGY is changed or discontinued, the same procedure should be repeated. • **Undesirable effects** In more than 3800 patients in clinical trials they reported concerning next common (≥ 1/100, < 1/10) undesirable effects: headache, flatulence, myalgia. In coadministration trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) was 1.7%. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. Clinically important elevations of CK (≥10 X ULN) were seen in 0.2% of the patients treated with INEGY. ***Post-marketing experience:*** The adverse reactions reported for INEGY are consistent with those previously reported with ezetimibe and/or simvastatin. ***Common:*** (≥ /100, < 1/10) abdominal pain, diarrhoea, fatigue; Rare: (≥ 1/10,000, < 1/1000) nausea, hepatitis, hypersensitivity reactions, including rash, urticaria, and very rarely, anaphylaxis, angio-oedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopaenia, eosinophilia, red blood cell sedimentation rate increased, arthritis and arthralgia, urticaria, photosensitivity reaction, pyrexia, flushing, dyspnoea and malaise arthralgia, anaemia, dizziness, paresthaesia, peripheral neuropathy, constipation, abdominal pain, dyspepsia, diarrhoea, nausea, vomiting, pancreatitis, hepatitis/jaundice, rash, pruritus, alopaecia, myopathy, rhabdomyolysis, muscle cramps, aesthenia; ***Very rare*** (≤1/10.000) thrombocytopaenia, pancreatitis, cholelithiasis, cholecystitis, myopathy/rhabdomyolysis; ***Laboratory Values*** Rare: increased transaminases; increased CK, increases in γ-glutamyl transpeptidase, elevated alkaline phosphatase. • **Nature and contents of container on Slovenian market** Packs of 30 tablets. • **Method and regimen of dispensing:** Medical prescription only. • **Marketing authorisation holder** MSD-SP Ltd. Hertford Road UK-Hoddesdon, Hertfordshire EN11 9BU United Kingdom. • **Date of revision of the text:** 18.03.2007

References: 1. Povzetek Glavnih značilnosti zdravila. **2.** Graham I. et al European guidelines on cardiovascular disease prevention in clinical practice: Fourth joint task force of the European society of Cardiology and other societies on cardiovascular disease prevention in clinical practice. European Journal of Cardiovascular Prevention and Rehabilitation; 2007; 14 (Supp 2): E1-E40.

Merck Sharp & Dohme, inovativna zdravila d.o.o.
Šmartinska cesta 140, 1000 Ljubljana; Phone: 01/ 5204 201, fax: 01/ 5204 349
Schering-Plough CE AG • Dunajska 22, 1000 Ljubljana
Phone: 01/ 300 10 70, fax: 01/ 300 10 80

Information prepared: Slovenia, March 2008

Before prescribing please read the complete Summary of Product Characteristics, available at our sales representatives or at the company's seat! Medical prescription only.

CODE_??????????????????

BISTVENI PODATKI IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA

REVATIO 20 mg filmsko obložene tablete

Sestava in oblika zdravila: Ena filmsko obložena tableta vsebuje 20 mg sildenafila (v obliki citrata). Tablete vsebujejo tudi laktozo. **Indikacije:** Pljučna arterijska hipertenzija v III. funkcijskem razredu po razvrstitvi Svetovne zdravstvene organizacije (SZO) za izboljšanje sposobnosti za telesno obremenitev. Primarna pljučna hipertenzija in pljučna hipertenzija, ki spremlja bolezni vezivnega tkiva. **Odmerjanje in način uporabe:** Zdravljenje sme uvesti in nadzorovati le zdravnik, ki ima izkušnje z zdravljenjem pljučne arterijske hipertenzije. Pri odraslih je priporočeni odmerek 20 mg trikrat na dan v presledku približno 6 do 8 ur, s hrano ali brez nje. Pri starejših bolnikih odmerka ni potrebno prilagajati. Če bolnik z okvaro ledvic in/ali jeter (razred A in B po Child-Pughu) terapije ne prenaša dobro, je treba po natančni oceni koristi in tveganj razmisliti o zmanjšanju odmerka na 20 mg dvakrat na dan. Sildenafila pri otrocih in mladostnikih ni priporočljivo uporabljati. V primeru prekinitve zdravljenja je odmerek treba zmanjševati postopoma. V primeru sočasne uporabe sildenafila in drugih zdravil za pljučno arterijsko hipertenzijo je potrebna previdnost. **Kontraindikacije:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Donorji dušikovega oksida ali nitrati. Močni zaviralci CYP3A4. Bolniki, ki so izgubili vid na enem očesu zaradi nearteritične anteriorne ishemične optične nevropatije (NAION), tudi če ta dogodek ni bil povezan s predhodnim jemanjem zaviralcev PDE5. Huda okvara jeter, anamneza nedavne možganske kapi ali miokardnega infarkta, huda hipotenzija ob uvedbi. Doječe matere. Če ni nujno potrebno, se pri nosečnicah ne sme uporabljati. **Posebna opozorila in previdnostni ukrepi:** Funkcijski razred I in IV. Znane dedne degenerativne bolezni mrežnice. Zaviralci in/ali induktorji CYP3A4. Določene že obstoječe bolezni. Resni kardiovaskularni dogodki. Anatomske deformacije penisa in bolezni, ki povzročajo nagnjenost k priapizmu. Okvara vida in primeri nearteritične anteriorne ishemične optične nevropatije. Bolnika je treba opozoriti, da naj v primeru nenadne okvare vida preneha jemati Revatio in o tem nemudoma obvesti svojega zdravnika. Zaviralci alfa. Bolniki z motnjami strjevanja krvi ali z aktivno peptično razjedo. Antagonisti vitamina K. Znaki pljučnega edema. Bolniki z redkimi prirojenimi motnjami, kot so galaktozna intoleranca, laponska oblika zmanjšane aktivnosti laktaze ali malabsorbcija laktoze, ne smejo jemati tega zdravila. **Medsebojno delovanje z drugimi zdravili:** Substrati CYP3A4 ali kombinacija le-teh in zaviralcev beta, induktorji in/ali zaviralci CYP3A4, bosentan, zaviralci citokroma P450, zaviralci beta, sok grenivke, nikorandil, zaviralci alfa, donorji dušikovega oksida ali nitrati. **Vpliv na sposobnost vožnje in upravljanja s stroji:** Poročali so o omotici in spremembah vida, zato morajo biti bolniki, preden vozijo ali upravljajo s stroji, seznanjeni, kako lahko Revatio nanje vpliva. **Neželeni učinki:** Najpogosteje opisani neželeni učinki so glavobol, zardevanje, dispepsija, driska in bolečine v okončinah. **Način in režim izdajanja:** Izdaja zdravila je le na recept, uporablja pa se po navodilu in pod posebnim nadzorom zdravnika specialista ali od njega pooblaščenega zdravnika. **Imetnik dovoljenja za promet:** Pfizer Limited, Sandwich, Kent CT13 9NJ, Velika Britanija. **Datum zadnje revizije besedila:** 03/2008

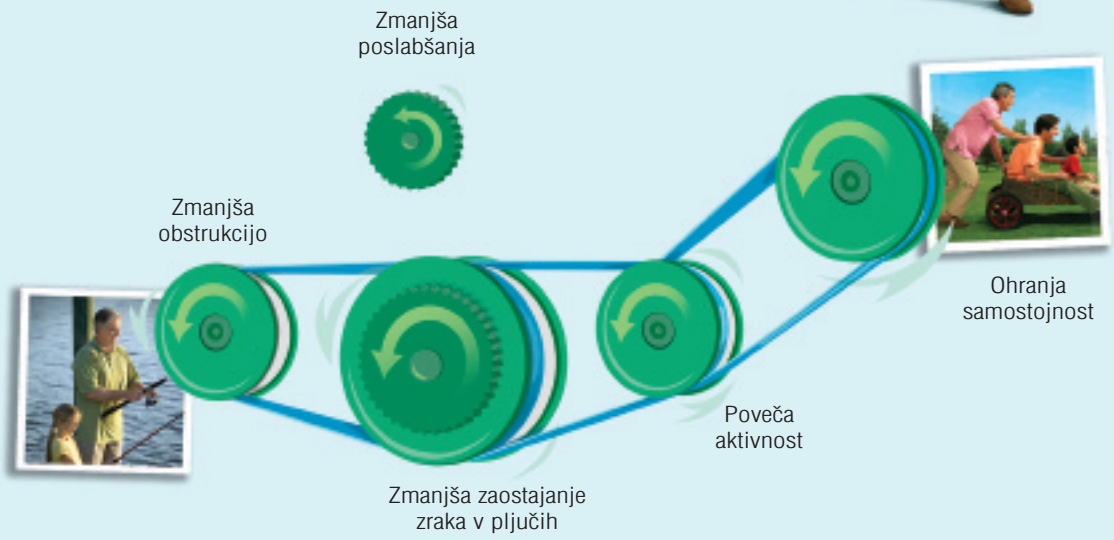
Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

REV-01-08

Pfizer Luxembourg SARL, GRAND DUCHY OF LUXEMBOURG,
51, Avenue J. F. Kennedy, L-1855
Pfizer, podružnica Ljubljana, Letališka cesta 3c, Ljubljana

“Vplivajte na klinični potek KOPB . . . ”

Zgodnja uporaba SPIRIVE omogoča bolnikom s KOPB, da dlje živijo aktivno in samostojno življenje[1-4]



- SPIRIVA zmanjša obstrukcijo[5]
- SPIRIVA zmanjša zaostajanje zraka v pljučih[5]
- SPIRIVA poveča bolnikovo zmogljivost[6]
- SPIRIVA zmanjša število poslabšanj[2,7]

SPIRIVA LAHKO IZBOLJŠA ŽIVLJENJE BOLNIKOV S KOPB[6,7]

Živeti bolje. Vsak dan...

SPIRIVA® (tiotropium)

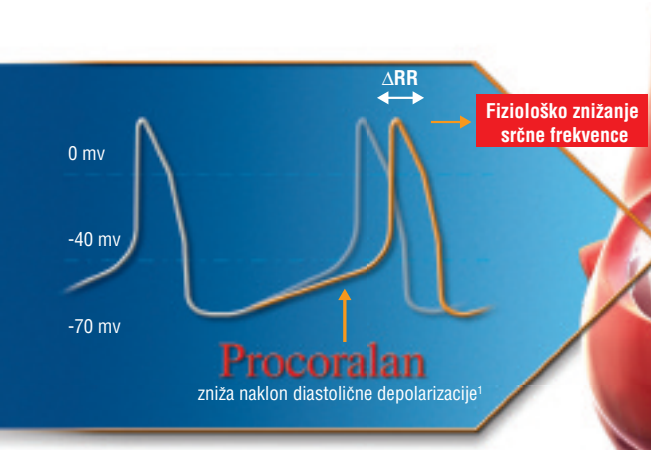
Literatura:
1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: executive summary. Posodobljeno 2006. Dostopno na: www.goldcopd.com. 2. Niewohner DE s sod. Ann Inter Med. 2005;143: 317-326. 3. Petty TL s sod. Chest. 2000;117(soppl):326S-331S. 4. Sewell L s sod. Chest. 2005;128:1194-1200. 5. Celli B s sod. Chest. 2003;124:1743-1748. 6. Casaburi R s sod. Chest. 2005;127:809-817. 7. Vincken W s sod. Eur Respir J. 2002;19:209-216.

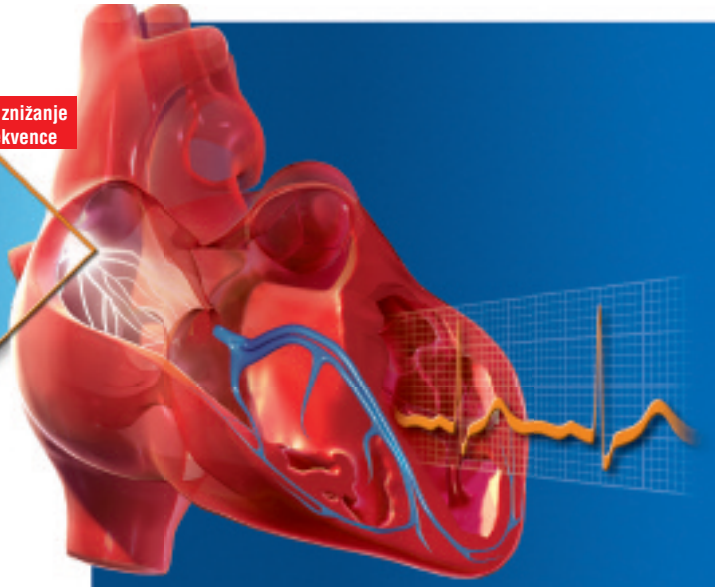
Inovacija v kardiologiji

Procoralan® 7,5 mg

Ivabradin

Prvi selektivni in specifični zaviralec I_f kanalov





Življenje je boljše **pod 60** utripi/min.

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Procoralan® 5 mg: filmsko obložena tableta, Procoralan® 7.5 mg: filmsko obložena tableta. **Sestava:** Procoralan® 5 mg - filmsko obložena tableta vsebuje 5 mg ivabradina (kar ustreza 5,390 mg ivabradinijevega klorida). Procoralan® 7.5 mg - filmsko obložena tableta vsebuje 7,5 mg ivabradina (kar ustreza 8,085 mg ivabradinijevega klorida). *Pomožne snovi:* laktoza monohidrat, magnezijev stearat (E 470 B), koruzni škrob, maltodekstrin, brezvoden koloidni silicijev dioksid (E 551), hipromeloza (E 464), titanov dioksid (E 171), makrogol 6000, glicerol (E 422), magnezijev stearat (E 470 B), rumeni železov oksid (E 172), rdeči železov oksid (E 172). **Delovanje:** Procoralan je specifično zdravilo za zniževanje srčne frekvence. Procoralan selektivno in specifično zavira tok I_f v srcu, ki ureja spontano diastolično depolarizacijo v sinusnem vozlu in srčno frekvenco. Učinki v srcu so specifični za sinusni vozel, brez delovanja na čase intraatrijskega, atrioventrikularnega ali intraventrikualrnega prevajanja, ali na kontraktilnost miokarda ali repolarizacijo prekatov. **Indikacija:** Simptomatično zdravljenje kronične stabilne angine pektoris pri bolnikih z normalnim sinusnim ritmom, pri katerih so blokatorji receptorjev beta kontraindicirani ali jih ne prenašajo. **Odmerjanje in način uporabe:** Za različna odmerjanja so na voljo filmsko obložene tablete, ki vsebujejo 5 in 7,5 mg Procoralan-a. Običajni priporočeni začetni odmerek Procoralan-a je po 5 mg dvakrat na dan, med obroki. Po treh do štirih tednih zdravljenja lahko odmerek povečate na 7,5 mg dvakrat na dan glede na terapevtski odziv. Če se med zdravljenjem srčna frekvenca vztrajno znižuje pod 50 utripov na minuto med mirovanjem ali če bolniki doživljajo simptome, povezane z bradikardijo, kot so omotica, utrujenost ali hipotenzija, morate odmerek titrirati navzdol, vključno do možnega odmerka po 2,5 mg dvakrat na dan (po eno polovico 5-mg tablete dvakrat na dan). Zdravljenje morate prekiniti, če srčna frekvenca pod 50 utripov na minuto ali simptomi bradikardije vztrajajo. **Kontraindikacije:** preobčutljivost za Procoralan ali katerokoli pomožno snov, srčna frekvenca med mirovanjem pod 60 utripov na minuto pred zdravljenjem, kardiogeni šok, akutni miokardni infarkt, huda hipotenzija (< 90/50 mm Hg), hudo jetrno popuščanje, sindrom bolnega sinusa, sinoatrijski blok, bolniki s srčnim popuščanjem III. do IV. razreda po funkcijski razvrstitvi Newyoreškega društva za srce (NYHA), potreba po srčnem spodbujevalniku, nestabilna angina pektoris, atrioventrikularni blok 3. stopnje, kombinacija z močnimi zaviralci citokroma P450 3A4, kot so azolski antimikotiki (ketokonazol, itrakonazol), makrolidnimi antibiotiki (klaritromicin, eritromicin peroralno, josamicin, telitromicin), zaviralci proteaze virusa HIV (nelfinavir, ritonavir) in nefazodon, nosečnost in dojenje. **Interakcije:** *Sočasno jemanje ni priporočljivo:* zdravila, ki podaljšujejo interval QT: na primer kinidin, dizopiramid, bepridil, sotalol, ibutilid, amiodaron ali na primer pimozid, ziprazidon, sertindol, meflokin, halofantrin, pentamidin, cisaprid, eritromicin intravensko. Sočasni uporabi srčnožilnih in nesrčnožilnih zdravil, ki podaljšujejo interval QT, se morate ob ivabradinu izogibati, saj se podaljšanje intervala QT lahko poslabša z zniževanjem srčne frekvence. Sočasno jemanje močnih zaviralcev citokroma P450 3A4, kot so azolski antimikotiki (ketokonazol, itrakonazol), makrolidnimi antibiotiki (klaritromicin, eritromicin peroralno, josamicin, telitromicin), zaviralci proteaze virusa HIV (nelfinavir, ritonavir) in nefazodon, je kontraindicirano. **Previdnostni ukrepi:** *Bolniki s hipotenzijo.* Podatki pri bolnikih z blago do zmerno hipotenzijo so omejeni, zato morate pri njih ivabradin uporabljati previdno. *Atrijska fibrilacija* - srčne aritmije, ni dokazov o tveganju (prevelike) bradikardije ob vrnitvi na sinusni ritem pri sprožanju farmakološke kardioverzije pri bolnikih, ki jemljejo ivabradin. Toda ker ni obsežnejših podatkov, razmislite o neurgentni kardioverziji z enosmernim tokom v 24 urah po zadnjem odmerku ivabradina. Uporabi ivabradina se moramo izogibati pri bolnikih, ki imajo prirojeni sindrom podaljšanega intervala QT ali jemljejo zdravila, ki ga podaljšujejo. *Uporaba pri bolnikih z zmernim jetrnim popuščanjem;* pri uporabi ivabradina pri bolnikih z zmernim jetrnim popuščanjem morate biti previdni. *Uporaba pri bolnikih s hudim ledvičnim popuščanjem;* pri uporabi ivabradina pri bolnikih s hudim ledvičnim popuščanjem (očistkom kreatinina < 15 ml/min) morate biti previdni. **Neželeni učinki:** *Očesne bolezni:* pojavi svetlikanja (fosfeni): opaža jih 14,5 % bolnikov in opisujejo jih kot prehodno povečanje svetlosti na omejenem področju vidnega polja. Običajno jih sprožajo nenadna nihanja jakosti svetlobe. Fosfeni se večinoma pojavljajo v prvih dveh mesecih zdravljenja in nato se lahko večkrat ponovijo. Fosfeni so bili na splošno blage do zmerne jakosti. Vsi fosfeni so ponehali med zdravljenjem ali po njem, in sicer večina med zdravljenjem (77,5 %). Manj kot 1 % bolnikov je zaradi fosfenov spremenilo svojo vsakdanjo rutino ali prekinilo zdravljenje. *Zamegljen vid. Srčne bolezni:* bradikardija: 3,3 % bolnikov, zlasti v prvih 2 do 3 mesecih po uvedbi zdravljenja. 0,5 % bolnikov je doživelo hudo bradikardijo s 40 utripov na minuto ali manj, atrioventrikularni blok 1. stopnje, ventrikularne ekstrasistole, palpitacije, supraventrikularne ekstrasistole. Bolezni prebavil: slabost, zaprtje, diareja. *Splošne težave:* glavobol, večinoma v prvem mesecu zdravljenja, omotica, vrtoglavica, dispneja, mišični krči. *Preiskave:* hiperurikemija, eozinofilija, povečanje kreatinina v krvi. **Način izdajanja:** Samo na zdravniški recept. **Oprema:** Zloženka z 28, 56 tabletami zdravila Procoralan 5 mg in zloženka z 28, 56 tabletami zdravila Procoralan 7,5 mg. **Rok uporabnosti:** 3 leta. **Izdeluje:** Les Laboratoires Servier Industrie, Francija. **Podrobnejše informacije so na voljo pri imetniku dovoljenja za promet z zdravilom:** Servier Pharma d.o.o., Pot k sejmišču 33, 1231 Ljubljana-Črnuče, tel.: 01/563 48 11, faks: 01/563 48 29.

www.procoralan.com

SERVIER

po 4 tednih,
če je SF nad 60 utripi/min

SF - srčna frekvenca

1. Borer JS et al. *Circulation.* 2003;107:817-823.

5 do 7.5 mg, dvakrat dnevno

▲ *ALIMTA je v kombinaciji s cisplatinom indicirana za zdravljenje bolnikov z neresektabilnim malignim plevralnim mezoteliomom, ki jih še nismo zdravili s kemoterapijo.*[1,2]

▲ *ALIMTA je indicirana kot monoterapija za zdravljenje bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim pljučnim karcinomom po predhodni kemoterapiji.*[1,3]

ALIMTA®
pemetreksed

▲

Moj cilj je preživetje

SI-AL-Ad-07-feb-001
Marec 2007

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

ALIMTA 500 mg prašek za koncentrat za raztopino za infundiranje **Sestava** Vsaka viala vsebuje 500 mg pemetrekseda (v obliki dinatrijevega pemetrekseda). Pomožne snovi: manitol, klorovodikova kislina, natrijev hidroksid. **Indikacije** ALIMTA je v kombinaciji s cisplatinom indicirana za zdravljenje bolnikov z neresektabilnim malignim plevralnim mezoteliomom, ki jih še nismo zdravili s kemoterapijo. ALIMTA je indicirana kot monoterapija za zdravljenje bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim pljučnim karcinomom po predhodni kemoterapiji. **Odmerjanje in način uporabe** ALIMTO smemo dajati le pod nadzorom zdravnika, usposobljenega za uporabo kemoterapije za zdravljenje raka. Maligni plevralni mezoteliom Priporočeni odmerek ALIMTE je 500 mg/m² telesne površine (TP), dan kot intravenska infuzija v 10 minutah prvi dan vsakega 21-dnevnega ciklusa. Nedrobnocelični pljučni karcinom Priporočeni odmerek ALIMTE je 500 mg/m² TP, dan kot intravenska infuzija v 10 minutah prvi dan vsakega 21 dnevnega ciklusa. **Kontraindikacije** Preobčutljivost za pemetreksed ali katerokoli pomožno snov. Med zdravljenjem s pemetreksedom je treba dojenje prekiniti. Sočasno cepljenje proti rumeni mrzlici. **Opozorila** Pri bolnikih moramo biti med zdravljenjem pozorni na morebiten pojav mielosupresije, pemetrekseda pa bolnikom ne smemo dajati, dokler se absolutno število nevtrofilcev (ANC) ne povme na ≥ 1500 celic/mm³ ter število trombocitov na ≥ 100.000 celic/mm³. Bolnikom, zdravljenim s pemetreksedom, moramo naročiti, naj jemljejo folno kislino in vitamin B12 kot preprečevalni ukrep za zmanjšanje toksičnosti, povezane z zdravljenjem. Predhodno zdravljenje z deksametazonom (ali drugim ustreznim kortikosteroidom) lahko zmanjša incidenco in resnost kožnih reakcij. Uporabe pemetrekseda pri bolnikih z očistkom kreatinina < 45 ml/min ne priporočamo. Bolniki z blagim do zmernim popuščanjem delovanja ledvic (očistek kreatinina od 45 do 79 ml/min) naj se izogibajo jemanju nesteroidnih protivnetnih zdravil (NSAID), denimo, ibuprofena in acetilsalicilne kisline (> 1,3 g dnevno) 2 dni pred dajanjem pemetrekseda, na dan dajanja in še 2 dni po dajanju pemetrekseda. Vsi bolniki, ki jih lahko zdravimo s pemetreksedom, naj se izogibajo jemanju NSAID-ov z dolgimi razpolovnimi časi izločanja vsaj 5 dni pred dajanjem pemetrekseda, na dan dajanja in še vsaj 2 dni po dajanju pemetrekseda. Pri bolnikih s klinično pomembno tekočino tretjega prostora moramo razmisliti o drenaži izliva pred dajanjem pemetrekseda. Bolnike moramo pred prejemanjem terapije in/ali po njej ustrezno hidrirati ter prejeti zadostno antiemetično zdravljenje. Občasno so v kliničnih študijah pemetrekseda, običajno ob sočasnem dajanju z drugo citotoksično učinkovino, poročali o resnih srčnožilnih dogodkih, vključno z miokardnim infarktom in možganskožilnimi dogodki. Odsvetujemo uporabo živih oslabljenih cepiv (razen za rumeno mrzlico). Spolno zrelim moškim odsvetujemo zaploditev otroka v času zdravljenja in še 6 mesecev zatem. Zaradi možnosti, da zdravljenje s pemetreksedom povzroči trajno neplodnost, naj se moški pred začetkom zdravljenja posvetujejo o shranjevanju semena. Ženske v rodni dobi morajo v času zdravljenja s pemetreksedom uporabljati učinkovito kontracepcijo. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij** Sočasno dajanje nefrotoksičnih zdravil (denimo, aminoglikozidov, diuretikov zanke, spojin platine, ciklosporina) lahko potencialno povzroči zakasnjeni očistek pemetrekseda. Sočasno dajanje snovi, ki se tudi izločajo s tubulno sekrecijo (denimo, probenecid, penicilin), lahko potencialno povzroči zakasnjeni očistek pemetrekseda. Pri bolnikih z normalnim delovanjem ledvic (očistek kreatinina ≥ 80 ml/min) lahko visoki odmerki nesteroidnih protivnetnih zdravil (NSAID-i, denimo, ibuprofen > 1600 mg dnevno) in acetilsalicilna kislina v visokih odmerkih (≥ 1,3 g dnevno) zmanjšajo eliminacijo pemetrekseda in tako lahko povečajo pojavnost neželenih učinkov pemetrekseda. Pri bolnikih z blagim do zmernim popuščanjem delovanja ledvic (očistek kreatinina 45 - 79 ml/min) se moramo izogibati sočasnemu dajanju pemetrekseda z NSAID-i (denimo, ibuprofenom) ali acetilsalicilno kislino v visokih odmerkih 2 dni pred dajanjem pemetrekseda, na dan dajanja in še 2 dni po dajanju pemetrekseda. Sočasnemu dajanju NSAID-ov z daljšimi razpolovnimi časi s pemetreksedom se moramo izogibati vsaj 5 dni pred dajanjem pemetrekseda, na dan dajanja in še vsaj 2 dni po dajanju pemetrekseda. Velika različnost med posamezniki v koagulacijskem statusu v času bolezni ter možnost medsebojnega delovanja med peroralnimi antikoagulacijskimi učinkovinami ter kemoterapijo proti raku zahtevata povečano pogostnost spremljanja INR. Kontraindicirana sočasna uporaba: Cepivo proti rumeni mrzlici: tveganje za smrtno generalizirano bolezen po cepljenju. Odsvetovana sočasna uporaba: Živa oslabljena cepiva (razen proti rumeni mrzlici): tveganje za sistemsko, potencialno smrtno bolezen. **Neželeni učinki** Klinične študije malignega plevralnega mezotelioma Zelo pogosti: znižani nevtrofilci/granulociti, znižani levkociti, znižan hemoglobin, znižani trombociti, slabost, bruhanje, stomatitis/faringitis, anoreksija, diareja, zaprtje, utrujenost, nevropatija-senzorična, povišan kreatinin, znižan očistek kreatinina, izpuščaj, alopecija Pogosti: konjuktivitis, dispepsija, dehidracija, disgevzija Klinične študije nedrobnoceličnega pljučnega karcinoma Zelo pogosti: znižan hemoglobin, znižani levkociti, znižani nevtrofilci/granulociti, slabost, anoreksija, bruhanje, stomatitis/faringitis, diareja, utrujenost, izpuščaj/luščenje Pogosti: znižani trombociti, zaprtje, povišana telesna temperatura, povišanje SGPT (ALT), povišanje SGOT (AST), srbenje, alopecija Občasni: resni srčnožilni in možganskožilni dogodki, vključno z miokardnim infarktom, angino pektoris, cerebrovaskularnim insultom in prehodnimi ishemičnimi atakami Redki: primeri potencialno resnega hepatitisa, pancitopenija Po uvedbi zdravila na trg so pri bolnikih poročali o redkih primerih kolitisa. **Imetnik dovoljenja za promet** Eli Lilly Nederland B.V., Grootslag 1 5, NL 3991 RA, Houten, Nizozemska **Datum zadnje revizije besedila** 30.01.2006 Podrobnejše informacije o zdravilu Alimta, so na voljo na lokalnem predstavništvu:

1. Povzetek glavnih znacilnosti zdravila ALIMTA; 2. Hanna N et al. J Clin Oncol 2004;221589-1597, 3. Vogelzang NJ et al. J Clin Oncol 2003;21:2636-2644

Eli Lilly farmacevtska družba, d.o.o.
Dunajska 156, 1000 Ljubljana, Slovenija
Tel.: (01) 5800 010,
Faks: (01) 569 1705

Lilly

Symbicort SMART®

Symbicort **M**aintenance **A**nd **R**eliever **T**herapy
pomeni vzdrževalno in olajševalno zdravljenje v enem vdihovalniku.

SMART

Enostavneje ne gre.

Symbicort®
budezonid/formoterol