UNIVERZITETNA KLINIKA
ZA PLJUČNE BOLEZNI IN
ALERGIJO
GOLNIK

Zbornik
Golniški simpozij 2015

Golnik, Bled
2 - 3 oktober 2015

Izdajatelj
Univerzitetna klinika za pljučne bolezni in alergijo, Golnik

Urednik zbornika
Mitja Košnik

Predsednik simpozija
Matjaž Fležar

Organizacija srečanja
Robert Marčun

Golnik, Bled
2 - 3 oktober 2015

Izvedbo 13. ‚Golniškega simpozija so omogočili:

Boehringer Ingelheim
Chiesi
Eli Lilly
Glaxo SmithKline
Roche

Astra Zeneca
Bayer
Boehringer Ingelheim
EL med
Ewopharma
Medis
IRIS
Jadran-galenski laboratorij d.o.o. Ljubljana
Krka
Lek
Novartis
Medicotehna
Pfizer
Providens
Pulmodata
Sanofi
Solpharm
Sonar

V zborniku so zbrani posterji, s katerimi so golničani v zadnjem letu dni predstavili rezultate svojega dela na strokovnih in znanstvenih srečanjih v Sloveniji in v tujini

1. **Varnost bolnikov (Košnik, Toni) 9:00-10:30** *(Slovenian language)*
   - Pasti zdravljenja z zdravili – P. Svetina, 15 minut
   - Kako pripomorejo k večji varnosti zdravljenja z zdravili:
     - Klinični farmacevti – L. Knez, 10 min
     - Zdravstvena nega – S. Kadivec, 10 min
     - Laboratorij za mikrobiologijo – V. Tomič, 10 min
   - Primer dobre prakse: celovit pristop k povečanju varnosti sistemskega zdravljenja raka – prof. T Čufer, asist L Knez, 15 min
   - Razprava 10 minut
   - Lunder: Pasti paliativne oskrbe: varnost ob spremembi ciljev obravnave 20 minut

Pasti zdravljenja z zdravili

Petra Svetina, dr.med., *Univerzitetna klinika za pljučne bolezni in alergijo, Golnik*

Cilj zdravljenja z zdravili je doseganje določenih terapevtskih rezultatov, ki izboljšajo kvaliteto bolnikovega življenja in sočasno predstavljajo čim manjše tveganjem za bolnika. Med tveganja zdravljenja z zdravili sodijo škodljivi učinki zdravil (neželeni učinki) in napake oz. neželeni dogodki, ki so posledica zdravljenju z zdravili. Za uspešno preprečevanje teh napak so potrebni učinkoviti sistemi kakovosti in osveščenost zdravstvenih delavcev za prepoznavanje medicinskih napak pri zdravljenju z zdravili in poročanje o njih.
Napake oz. neželeni dogodki pri zdravljenju z zdravili vodijo v nezaupanje bolnikov v zdravstveni sistem in povečujejo stroške zdravljenja. Razlogov za njihovo pojavljanja je več - pomanjkanje znanja, pomanjkanje motivacije, preobremenjenost zdravstvenih delavcev, neustrezni delovni pogoji, slabi sistemi kakovosti, slaba komunikacija, strah pred poročanjem, strah pred posledicami, …
Pogostost pojavljanja napak oz. neželenih dogodkov pri zdravljenju z zdravili ni natančno znana, saj je še vedno veliko napak neprepoznanih. Po podatkih iz literature naj bi se pojavljale pri več kot 50% vseh sprejemov v bolnišnico oz. pri 9 -15% vseh predpisov zdravil. Pogostost pojavljanja napak oz. neželenih dogodkov pri zdravljenju z zdravili je odvisna od učinkovitosti ukrepov za preprečevanje, odkrivanje in odpravljanje napak ter od osveščenosti zdravstvenih delavcev, med tem ko izobrazba, starost ter delovna doba zdravstvenih delavcev nimajo pomembnega vpliva na pogostost pojavljanja napak.

Napake pri zdravljenju z zdravili delimo na napake oz. neželene dogodke in skorajšnje napake oz. skorajšnje neželene dogodke.
Napaka oz. neželen dogodek pri zdravljenju z zdravili je dogodek, ki se zgodi zaradi nepravilne priprave, predpisa, izdaje ali dajanja zdravila.
Skorajšnja napaka oz. skorajšnji neželeni dogodek pri zdravljenju z zdravili je dogodek, ko se je med pripravo ali pri predpisu, izdaji ali dajanju zdravila ugotovila napaka, vendar se je napaka odkrila preden je bolnik prejel napačno zdravilo oziroma napačen odmerek zdravila.
Pri zdravljenju z zdravili v bolnišnici sodelujejo zdravnik, medicinska sestra in klinični farmacevt, zato lahko prihaja do napak ali skorajšnji napak pri zdravljenju z zdravili zaradi napačne izbire zdravila, napačne priprave zdravila, napak pri izdaji zdravila in napak pri dajanju zdravila.
Pogosti vzroki za napačno izbiro zdravila so neupoštevanje izbire zdravila glede na indikacije, kontraindikacije, neupoštevanje znane alergije na zdravila, neupoštevanje dosedanjega izida zdravljenja ali neupoštevanje možnih interakcij med sočasno predpisanimi zdravili. Zaradi nečitljivega zapis zdravila ali neupoštevanja »pravila 5P« pri razdeljevanju zdravil, lahko bolnik prejme napačni odmerek, napačno obliko, napačno koncentracijo zdravila ali prejme zdravilo po napačni pot ali v nepravilnih časovnih intervalih.

Ob ugotovitvi napake oz. neželenega dogodka je potrebno vedno oceniti klinično pomembnost napake oz. dogodka. Glede na posledice napake za bolnika in ukrepanje ločimo tri skupine napak oz. dogodkov:

a) napaka oz. dogodek, ki ima majhno klinično pomembnost – ni posledic za bolnika in ukrepanje ni bilo potrebno, razen opazovanja.
b) napaka oz. dogodek, ki ima srednjo klinično pomembnost – bolnik je utrpel začasno škodo, potrebno je bilo ukrepanje
c) napaka oz. dogodek, ki ima veliko klinično pomembnost – neželen dogodek je povzročil trajno škodo ali smrt, potrebni so bili ukrepi za ohranitev življenja

Napako oz. dogodek je dolžna prijaviti oseba (npr.: medicinska sestra, zdravnik, klinični farmacevt), ki je dogodek prepoznala (lahko je prijavitelj soudeležen pri tem dogodku ali ga je le prepoznal), zdravnik mora oceniti posledice napake oz. dogodka za bolnika in odrediti ukrepanje. Bolnišnice z dobrim sistemom kakovosti morajo imeti ustaljene ukrepe za prepoznavo in poročanje napak pri zdravljenju z zdravili. Poleg prepoznave napak ali skorajšnjih napak, je potrebno poleg poročanja o napakah oz. skorajšnjih napakah, pripraviti in upoštevati ukrepe, ki bodo preprečili pojavljanje iste napake v prihodnje.

Če je bilo v preteklosti zdravljenje z zdravili samo v rokah zdravnikov, je sedaj to multidisciplinarni proces, kjer imajo pomembno vlogo poleg zdravnikov tudi medicinske sestre, klinični farmacevti in lab. delavci. Pri prepoznavanju, poročanju in odpravljanju napak pri prepisovanju zdravil, so pomembni: stalen sistem kakovosti in nadzora, stalno izobraževanje in primerne obremenitve zdravstvenih

delavcev, ustrezna preskrba z zdravili, dostopnost določenim zdravstvenim delavcem do kliničnih podatkov o bolnikih, ustrezna komunikacija in primerno delovno okolje.
Preprečevanje napak oz. neželenih dogodkov pri predpisovanju zdravil je eden najuspešnejših ukrepov za zmanjšanje tveganja za bolnika in s tem doseganje dobrih terapevtskih rezultatov.

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Kako klinični farmacevti pripomoremo k večji varnosti zdravljenja z zdravili

asist. dr. Lea Knez, mag.farm. spec., *Univerzitetna klinika za pljučne bolezni in alergijo, Golnik*

Uvod

Zdravljenje z zdravili je neizogibno povezano tudi s tveganjem za neželene dogodke zdravljenja z zdravili (NDZ), ki zahteva razmislek o razmerju med pričakovano dobrobitjo in tveganji ob predpisu vsakega zdravila. Seveda se NDZ lahko pripetijo že ob zdravljenju z enim samim zdravilom, verjetnost pa je zagotovo večja pri zdravljenju z več zdravili, klinični pomen teh NDZ pa je zagotovo večji v primerih, ko so vpletena zdravila z ozkim terapevtskim oknom. Tudi nekatere značilnosti bolnika, npr. okrnjena ledvična funkcija ali aplikacija zdravil po nazogastrični sondi, lahko izpostavi bolnika dodatnemu tveganju za NDZ. V preteklih letih smo klinični farmacevti na Kliniki Golnik usmerili svoje aktivnosti ravno v to področje: preprečevanje NDZ pri tistih bolnikih, kjer so NDZ praviloma bolj verjetni, in pri tistih zdravilih, kjer so NDZ praviloma klinično bolj pomembni. Pri načrtovanju novih storitev smo si prizadevali zagotoviti njihovo dosledno in stalno izvajanje. Te aktivnosti so bolj podrobno opisane v nadaljevanju.

Zagotavljanje varnosti zdravljenja z zdravili pri skupinah bolnikov, ki se zdravijo z zdravili z velikim tveganjem za resne neželene dogodke

V bolnišnici smo izpostavili stalno in dobro usklajeno sodelovanje kliničnih farmacevtov tam, kjer uvajamo zdravila z velikim tveganjem za resne NDZ. Najbolj intenzivno je to sodelovanje pri bolnikih na sistemskem zdravljenju raka, na zdravljenju s protituberkuloznimi zdravili in tistimi bolniki, ki prejemajo zdravila za preprečevanje in zdravljenje epizod hereditarnega angioedema. Razmišljanja, ki so botrovala k izbiri teh skupin bolnikov so predstavljena v nadaljevanju.

Zdravila za sistemsko zdravljenje raka sodijo med zdravila z ozkim terapevtskim oknom, pri katerih so resni, življenje ogrožajoči NDZ možni že ob doslednem upoštevanju vseh preverjenih znanj, veljavnih navodil in priporočil za njihovo uporabo v vsakodnevni klinični praksi. Zato je pri zdravljenju s temi zdravili nujno na vseh korakih zmanjšati tveganje za napake pri zdravljenju z zdravili. Klinični farmacevti danes vsakodnevno sodelujemo na Enoti za internistično onkologijo, same aktivnosti, ki so bile na Enoti vpeljane v preteklih letih, pa so predstavljene v ločenem predavanju.

Režimi zdravljenja s protituberkuloznimi zdravili praviloma vedno vsebujejo rifampicin, ki je močan induktor jetrnih citokromov in kot tak pomembno zmanjša sistemsko izpostavljenost in posledično učinek številnim zdravilom, druga zdravila v protituberkuloznih režimih pa z inhibicijo citokromov še dodatno zapletejo zgodbo. Za ilustracijo implikacij tovrstnih interakcij naj povemo, da je potrebno ob uvedbi zdravljenja z rifampicinom odmerek npr. varfarina povečati za 2 do 5-krat, seveda z ustreznimi časovnimi zamiki in ponovno prilagoditvijo ob ukinitvi zdravljenja z rifampicinom. Posledic nepravočasnega ukrepanja se verjetno vsi zavedamo, zato je samoumevno, da je nujno vse tovrstne interakcije preprečiti in ravno to je ključna naloga kliničnega farmacevta na oddelku za tuberkulozo. Torej, klinični farmacevt pregleda interakcije ob uvedbi protituberkuloznih zdravil, predlaga prilagoditve terapije in smiselno spremljanje. Seveda pa sodelovanje presega te okvirje in vključuje tudi predlog ukrepov za zmanjšanje tveganja za neželene učinke zdravljenja ter svetovanje bolnikom o zdravljenju s protituberkuloznimi zdravili pred odpustom. Tako je sodelovanje kliničnega farmacevt dobro integrirano v vsakodnevno klinično prakso na oddelku za tuberkulozo.

Hereditarni angioedem je redka bolezen in kot taka večini zdravstvenim delavcem slabo poznana. Epizode hereditarnega angioedema se običajno pripetijo v domačem okolju in zahtevajo relativno hitro zdravljenje z zdravili, ki so bolj izjemoma dostopna v zunanjih ali bolnišničnih lekarnah. Zato je ključno, da i) bolnik ima vedno pri sebi zdravilo, seveda z veljavnim rokom uporabe, ii) da ima dovolj informacij za varno in smotrno uporabo zdravila, ne glede na to, ali zdravilo zahteva aplikacijo v zdravstveni ustanovi ali ne, in iii) da ima pri sebi tudi navodila za ukrepanje ob epizodah HAE, s katerimi lahko seznani zdravstvene delavce. V preteklih letih smo tudi s sodelovanjem kliničnega farmacevta pripravili informativno gradivo za bolnike in zdravstvene delavce, danes je svetovanje kliničnega farmacevta o pravilni uporabi zdravil s HAE sestavni del vsakodnevne klinične prakse. Istočasno smo v preteklih letih izpostavili tudi sistem za racionalno preskrbo bolnikov s HAE zdravili, ki je zagotavljal, da ima vsak bolnik vedno pri sebi zdravila za HAE z ustreznim rokom uporabe in da so zaloge teh zdravil najbolj smotrno razporejene po Sloveniji z minimiziranjem pretečenih zdravil. Sistem je zagotovo pripomogel k poenotenju in izboljšanju kakovosti oskrbe bolnike s HAE, verjetno tudi k zmanjšanju števila obiskov zdravstvenih ustanov, žal pa smo zaradi sprememb v omejitvah predpisovanja teh zdravil lahko bolniki in zdravstveni delavci koristili prednosti tega sistema le kratek čas.

Zagotavljanje varnosti zdravljenja z zdravili pri skupinah bolnikov z dejavniki tveganja za neželene dogodke zdravljenja z zdravili

Nujni predpogoj za dosledno izvajanje katerekoli storitve je to, da je sama storitev dobro definirana. To smo klinični farmacevti na pobudo zdravnikov tudi naredili, in sicer smo kot bolnike z dejavniki tveganja za neželene dogodke zdravljenja z zdravili prepoznali tiste bolnike:

i) pri katerih spremljamo plazemske koncentracije zdravil, ker je izvide plazemskih koncentracij nujno potrebno interpretirati glede na čas vzorčenja krvi, režim jemanja zdravila ter upoštevajoč druge vplive in ker gre v primeru učinkovin, kjer spremljamo plazemske koncentracije, praviloma za zdravila z ozkim terapevtskim oknom, npr. digoksina, teofilina, vankomicina. Neustrezna interpretacija izvida lahko vodi do napačnih terapevtskih odločitev, npr. znižanje odmerkov zdravil ob lažno prevelikih koncentracijah zaradi vzorčenja krvi kmalu po danem odmerku ali do neustrezne prilagoditve odmerkov ob vzorčenju krvi pred dosego stacionarnega stanja;
ii) ki se zdravijo z močnimi inhibitorji ali induktorji jetrnih citokromov ali prenašalnih proteinov, saj lahko stopajo v klinično pomembne interakcije med zdravili, ki vodijo bodisi v neučinkovitost ali v neželene učinke sočasno predpisanih zdravil;
iii) ki prejemajo zdravila preko nazogastrične sonde (NGS), saj nekatera zdravila niso primerna za aplikacijo po sondi in lahko, v kolikor zdravilo, farmacevtska oblika in režim odmerjanja niso ustrezno prilagojeni, aplikacija po NGS vodi do neželenih dogodkov zdravljenja z zdravili, npr. predoziranja ob drobljenju tablet s prirejenim sproščanjem;
iv) s slabo ledvično funkcijo (oGFR pod 30 ml/min), kjer so pogosto potrebne prilagoditve režimov zdravljenja z zdravili zaradi spremenjene farmakokinetike zdravil ali večjega tveganja za posamezne neželene učinke zdravil;
v) ki v terapiji prejemajo močne opioide, saj predpis pogosto zahteva tudi kompleksne izračune, upoštevajoč ekvianalgetičnih odmerkov opioidov in razlike v biološki uporabnosti različnih poti aplikacij, napake v teh izračunih pa lahko pripeljejo bodisi do tudi življenje ogrožajočih neželenih učinkov ali do odtegnitvenih sindromov.

Pri teh skupinah bolnikov smo ocenili, da bodo naša specifična znanja s področja klinične farmacije najbolj koristna pri preprečevanju NDZ. Dosledno izvajanje farmakoterapijskih pregledov seveda zahteva aktivno iskanje teh skupin bolnikov s pregledom laboratorijskih izvidov in terapevtskih list. Kljub številnim optimizacijam, to iskanje ni še avtomatizirano, ostaja časovno potratno in kot tako šibka točka pri izvajanju storitev. Po identifikaciji bolnikov farmacevti terapijo usmerjeno pregledamo in mnenje zapišemo v obliki farmakoterapijskega izvida v naš bolnišnični informacijski sistem. Seveda se trudimo mnenje tudi ustno predati odgovornemu zdravniku, kar pa v trenutnem izvajanju je še daleč od optimalnega. Osebno sodelovanje je zagotovo boljše, saj nudi možnost diskusije, in zato smo si, v želji po njegovem izboljšanju, zadali kot bližnji cilj vzpostavitev rednega, najmanj enkrat tedenskega sodelovanja kliničnega farmacevta na oddelčnem raportu.

V želji po izboljšanju izvajanja farmakoterapijskih pregledov pri izbranih skupinah bolnikov smo izvedli retrospektivno analizo, v katero smo vključili 500 naključno izbranih bolnikov, hospitaliziranih med 1.1. in 15.5. 2014. V celotni skupini bolnikov jih je 40 % (198/500) imelo vsaj en dejavnik tveganja za NDZ, ki zahteva farmakoterapijski pregled, in sicer skoraj polovica pregledov (122/254) bi bilo potrebnih zaradi inhibitorjev ali induktorjev jetrnih citokromov, četrtina (66/254) zaradi slabe ledvične funkcije, 15 % (39/254) zaradi meritev plazemskih koncentracij zdravil, ostali dejavniki so bili prisotni v manjšem deležu. Od 254 pričakovanih farmakoterapijskih pregledov smo farmacevti v bolnišnični informacijski sistem vnesli le tretjino (86), in sicer smo najslabše opravili, ko je bil farmakoterapijskih pregled potreben zaradi zdravljenja z močnimi opioidi ali inhibitorji/induktorji jetrnih citokromov (pri obeh opravljenih manj kot petina pričakovanih), k čemu je po eni strani pripomogla slaba identifikacija težav, po drugi strani pa, verjetno odsotnost potencialnih težav v zdravljenju z zdravili, predvsem v primeru zmernih inhibitorjev citokromov. Smiselnost predlaganih ukrepov potrjuje dejstvo, da je bilo sprejetih in udejanjenih več kot polovica (39/70), veliko število neizdelanih farmakoterapijskih pregledov pa zagotovo zahteva izboljšanje. V slabem je vedno tudi nekaj dobrega in tako nam neizdelani farmakoterapijski pregledi nudijo možnost za oceno klinične pomembnosti izvajane storitve, in sicer za oceno prisotnosti ne samo potencialnih ampak tudi dejanskih težav v zdravljenju z zdravili pri bolnikih s prisotnimi dejavniki tveganja za NDZ. In ravno to je namen specialistične naloge Tine Morgan.

Zaključek

V preteklih letih smo klinični farmacevti na Univerzitetni kliniki Golnik usmerili svoje aktivnosti v dosledno izvajanje farmakoterapijskih pregledov pri skupinah bolnikov z večjim tveganjem za neželene dogodke zdravljenja z zdravili in tako pripomogli k preprečevanju varnostnih zapletov tam, kjer so ti

bolj verjetni. Na sedanji obseg aktivnosti smo zelo ponosni, zagotovo nas čaka še veliko dela pri njegovem izboljšanju, kjer nas kot naslednji korak čaka redno sodelovanje na oddelčnih sestankih, nekje v prihodnosti pa uresničitev principov usklajevanja zdravljenja z zdravili v redni klinični praksi. Slednjega pa zagotovo ne bomo mogli uresničiti le s tiskanjem zapisov zdravil na Kartici zdravstvenega zavarovanja ali z retrospektivnim pregledovanjem odpustnic, temveč samo z zavzetim sodelovanjem zdravnikov, medicinskih sester in farmacevt skupaj z zelo premišljeno in logistično izvedljivo sistemsko rešitvijo. V duhu optimizma si nadejamo, da jo bomo lahko prestavili na enem izmed prihodnih Golniških simpozijih!

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Kako pripomorejo k večji varnosti zdravljenja z zdravili – področje zdravstvene nege

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Za kakovostno in varno ravnanje z zdravili v zdravstveni negi potrebujemo:

- Kompetentno osebje
- Jasna pravila in navodila s strani zdravnikov in kliničnih farmacevtov
- Ustrezno delovno okolje

Kako uspešno in učinkovito izvajamo vse potrebne aktivnosti, moramo izpolniti nekaj pogojev:

- Ustrezna dokumentacija – na področju ravnanja z zdravili imamo v zdravstveni negi na voljo dva temeljna dokumenta: SOP 111-SZO-SC-24 Dajanje zdravil skozi usta, v usta, pod jezik, v oko, v uho, v nos, na kožo, v danko, v vagino in SOP Navodila za ravnanje s prepovedanimi drogami na oddelkih.
- Izobraževanje – za medicinske sestre izvajamo učne delavnice (zdravila, ki vplivajo na vrednost krvnega tlaka, …)
- Spremljanje kazalnikov kakovosti – (napake pri razdeljevanju zdravil, spremljanje števila naročil po telefonu)
- Izvajanje notranjih nadzorov in notranjih presoj. V Kliniki Golnik notranje nadzore in presoje uporabljamo kot orodje ki pokaže kako in v kakšni meri izpolnjujemo sprejete standarde zdravstvene oskrbe. Spremljamo kako se naloge in cilji, ki jih določi vodstvo klinike prenese do izvajalcev osnovnih izvedbenih procesov in kakšne ukrepe izvajajo z namenom doseganja skupno določenih ciljev. Sistem vodenja kakovosti z notranjimi nadzori in presojami po standardih DIAS in ISO 9001: 2008 nam pomaga, da ohranjamo našo usmeritev v uspešno, učinkovito in varno skrb za pacienta. Zato je ob ugotovljenih neskladnostih z zahtevami standarda jasno in razumljivo, kako je potrebno dopolniti ali spremeniti obstoječi način dela, da bo zagotavljal večjo kakovost in varnost pri obravnavi bolnikov.

Glavne dileme, s katerimi smo se srečevali:

- **Kaj v primeru, ko bolnik prinese svoja zdravila.**
  Dogovor je, da bolnik, četudi s seboj prinese svoja zdravila, le te jemlje pod nadzorom. V ta namen je treba pripraviti dokument, ki bo služil kot dokumentiran dogovor med zdravnikom in bolnikom, da jemlje terapijo sam. Naloga medicinskih sester je v nadzoru preverjanja ustreznosti uporabe posebno vdihovalnikov in v sprotnem jasnem dajanju navodil glede pravilne tehnike jemanja zdravil.

- **Kakšno odgovornost prevzame medicinska sestra z dano parafo na terapevtsko listo.**
  Beleženje dajanja danega zdravila mora narediti oseba, ki zdravilo bolniku da in to po tistem, ko je bolnik zdravilo prejel. Medicinska sestra tako s podpisom jamči, da je bolnik dobil ustrezno zdravilo.

- **Merjenje RR pred dajanjem antihipertenzivne terapije.**
  Dogovor v kliniki je, da je potrebo izmeriti vitalne znake pred deljenjem terapije. Na ta način se izognemo temu, da bi bolniki, ki prejemajo zdravila, ki vplivajo na krvni tlak, prejemali zdravila pred določitvijo RR. V ta namen smo pripravili delavnice za medicinske sestre katera zdravila vplivajo na krvni tlak in kako naj ukrepajo. Pomemben je dogovor z zdravniki, katera meja krvnega tlaka je tista, pri kateri še da zdravilo.

Reševanje in uvajanje sistemskih ukrepov v Kliniki Golnik je potekalo na več nivojih:

- Poročanje o ugotovitvah na komisiji za kakovost
- Sprejetje ukrepov in spremljanje realizacije
- Večdisciplinarno reševanje problema je med drugim dalo naslednje rezultate:
  - Stališče do jemanja zdravil, ki jih bolniki prinesejo od doma.
  - Ravnanje MS v primeru, ko se ji zdi, da je predpis zdravila sporen.
  - Plakat, ki bolnika seznanja z namenom dvojne identifikacije.
  - Seznam zdravil, ki nižajo RR in postavitev referenčne meje, kdaj MS razmisli o dajanju zdravil za nižanje RR.
  - Zagotavljanje navodil o pripravi zdravil v slovenskem jeziku.
  - Navodila za pripravo zdravil i.v.

- Vzpostavitev komunikacije med zdravnikom in DMS, ki zagotavlja prenos informacij na način, ki zmanjša možnost napake v zvezi z ravnanji z zdravili.
- Vidno označevanje sprememb predpisa zdravil na T listi.

- Pogovori o varnosti. Na pogovorih o varnosti smo v letih 2013-15 poročali o napakah, ki nastajajo na relaciji:
  - Predpisovanje zdravil
  - Naročanje po telefonu
  - Napake pri razdeljevanju zdravil
  - Napake pri dajanju morfija
  - Naročilo nestandardne oblike naročila v dežurstvu

Zaključek:
Skrb za varno ravnanje z zdravili je večdisciplinarna. Medicinska sestra skupaj z zdravniki in kliničnimi farmacevti sodeluje v tem procesu. Za zagotavljanje kakovostne in varne obravnave bolnika moramo upoštevati določila stroke, zakonodaje in interna določila posamezne zdravstvene organizacije. Z ustreznim izvajanjem korektivnih in preventivnih ukrepov zagotavljamo izboljševanje dela na področju ravnanja z zdravili. Učinkovitost dogovorjenih ukrepov preverjamo v postopku strokovnih nadzorov in notranjih presoj.
Na tak način je možen stalen razvoj zaposlenih, učenje na konkretnih primerih in iskanje rešitev. Pri tem sledimo krogu PDCA in vrednotimo uspešnost uvedenih sprememb. Zaposleni tako dobijo tudi možnost biti aktivni pri uvajanju potrebnih sprememb.

Kako pripomore k večji varnosti zdravljenja mikrobiološki laboratorij?

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Glede na poročilo Komisije za okolje, javno zdravje in varno hrano o varnejši zdravstveni oskrbi v Evropi, se pri 8% do 12% bolnikov med bolnišnično oskrbo zgodi neželen dogodek in skoraj polovico teh dogodkov bi lahko preprečili (1). Najpogostejši neželeni dogodki so bolnišnične okužbe (pribl. 25%), napake pri predpisovanju zdravil, kirurške napake, napake pri medicinskih pripomočkih, diagnostične napake, neustrezna obravnava glede na izide preiskav (2). Delo mikrobiološkega laboratorija pomembno prispeva k varni obravnavi posameznega bolnika kot tudi varnemu delovanju v primeru epidemij oz. pandemij.

Hitra in zanesljiva diagnostika povzročitelja okužbe je osnovni element kakovostne obravnave posameznega bolnika. Klinična mikrobiologija je znanost interpretativne presoje, ki postaja vedno bolj kompleksna (3). Ko govorimo o kakovostni in varni obravnavi posameznega bolnika, mora mikrobiološki laboratorij priskrbeti kliniku odgovore na tri osnovna vprašanja in sicer:

- ali bolezen povzroča mikroorganizem?
- kateri mikroorganizem?
- kakšna je njegova občutljivost za protimikrobna zdravila, da bi lahko predpisali ciljano terapijo

Te odgovore moramo pridobiti hitro, iz ustrezne in kakovostne kužnine ter jih nedvoumno sporočiti klinikom. Kliniki pa morajo zaupati, da so rezultati preiskav mikrobiološkega laboratorija točni in klinično relevantni (3). V celotnem procesu se prepletajo vloge različnih subjektov (zdravnik, medicinska sestra, laboratorijski tehnik, klinični mikrobiolog), zato so dobra povezanost, komunikacija in stalen prenos znanja nujni za kakovostno in varno diagnostiko. Zavedati se moramo, da so napake možne v predanalitski, analitski in postanalitski fazi preiskave in neprepoznane, spregledane ali zamolčane napake imajo lahko resne neželene posledice. Z rednim izobraževanjem vseh strokovnih skupin, ki so vpletene v proces mikrobiološke diagnostike (od odvzema kužnine do končnega izvida in zdravljenja bolnika) ter z vzpodbujanjem odkrivanja in javljanja napak brez kaznovanja, razvijamo in vzdržujemo visoko raven kakovosti.

Mikrobiološki laboratorij lahko pomembno prispeva k preudarni rabi protimikrobnih zdravil. S hitrim odkrivanjem povzročitelja okužbe in testiranjem občutljivosti za antibiotike v primeru bakterijske okužbe, omogočimo ciljano zdravljenje, ožanje spektra delovanja empirično izbranega antibiotika in celo ukinitev antibiotičnega zdravljenja, če ugotovimo, da gre pri bolniku za virusno okužbo. Med hospitalizacijo do 55% bolnikov prejme antibiotik in 30% do 50% teh zdravljenj ni potrebnih ali so neustrezna, kar vodi v zaplete in neželene posledice, ki bi jih lahko preprečili (4). Glede na podatke ameriškega nacionalnega registra za neželene dogodke (ang. National Electronic Injury Surveillance System) je 142.505 bolnikov obiskalo urgentne ambulante zaradi neželenih učinkov antibiotičnega zdravljenja. Antibiotiki so bili vzrok 20% vseh obiskov urgentnih ambulant zaradi z zdravili pogojenih neželenih dogodkov. Morda ena najočitnejših povezav preudarne rabe antibiotikov in varnosti bolnikov, je zmanjšanje števila okužb s *Clostridium difficile*, kjer številne strokovne objave dokazujejo pozitiven vpliv antibiotičnega nadzora (ang. antimicrobial stewardship).

Če pogledamo širše mikrobiološki laboratorij s hitro in zanesljivo diagnostiko omogoča pravočasno ukrepanje pri zamejevanju in obvladovanju izbruhov bolnišničnih okužb (npr. virusne črevesne okužbe, gripa), preprečevanju širjenja večkratno odpornih mikroorganizmov kot so proti meticilinu odporen *Staphylococcus aureus* (MRSA), enterobakterije, ki izločajo beta-laktamaze razširjenega spectra (ESBL-enterobakterije) in mnogi drugi. S stalnim spremljanjem gibanja odpornosti mikroorganizmov proti antibiotikom, mikrobiološki laboratorij omogoča prilagajanje priporočil za empirično zdravljenje, kar pripomore h kakovostnejši in varnejši obravnavi posameznega bolnika, saj zgodnje zdravljenje z ustreznim antibiotikom zmanjša možnost neugodnega izida zdravljenja.

Prispevek mikrobiološkega laboratorija k večji varnosti zdravljenja bolnikov je večplasten. V kolikšni meri bo mikrobiološki laboratorij izkoriščen v dobro bolnika pa je odvisno od različnih dejavnikov kot so umeščenost laboratorija, povezanost med kliniki in kliničnimi mikrobiologi, povezanost med negovalnim osebjem in laboratorijskimi tehniki, zaupanje, dvosmerno sodelovanje, redno komuniciranje, svetovanje in poučevanje, vzpodbujanje odkrivanja in javljanja napak brez kaznovanja, svetovanje za preudarno rabo antibiotikov, spremljanje epidemioloških razmer in upoštevanje priporočil za antibiotično zdravljenje, upoštevanje priporočil za preprečevanje in obvladovanje bolnišničnih okužb in izbruhov.

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Pristop k povečanju varnosti sistemskega zdravljenja raka

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Uvod

Na Enoti za internistično onkologijo Univerzitetne klinike Golnik se zdravijo rakavi bolniki s sistemskim zdravljenjem, bodisi s kemoterapijo, tarčnimi zdravili, hormonskimi zdravili ali imunoterapijo. Dolgoletna preživetja bolnikov z rakom so se v zadnjih desetletjih prav na račun učinkovitega sistemskega zdravljenja močno dvignila. Tako danes v ZDA po podatki SEER ozdravi kar 70% vseh obolelih od raka, v Evropi pa okoli 60%. Seveda pa je za doseganje teh rezultatov potrebna ustrezen izbor in izvedba zdravljenja pri vsakem posameznem bolniku. Najpomembnješa dejavnika za dobro in ustrezno sistemsko zdravljenje rakavih bolnikov sta gotovo ustrezno znanje in usposobljenost celotnega tima, ki sodeluje pri tem zdravljenju. Zaradi obsežnih novih znanj in nuje po visoko specializirani oskrbi bolnikov na sistemskem zdravljenju raka je bila internistična onkologija razpoznana kot samostojna stroka in danes sistemsko zdravljenje raka v razvitem svetu izvajajo specialisti internisti onkologi. Enako pomembno pa je tudi poglobljeno onkološko znanje celotnega tima, od medicinskih sester do farmacevtov in drugih. Svetovna onkološka združenja so poleg visoke specializiranosti in usposobljenosti vseh sodelujočih zdravstvenih delavcev izpostavila kot ključno točko pri zagotavljanju varnosti sistemskega zdravljenja raka in izboljšanju oskrbe bolnikov z rakom tudi standardizacijo vseh postopkov v procesu sistemskega zdravljenja raka, od predpisovanja do priprave in dajanja protitumorskih zdravil.

Samo sistemsko zdravljenje raka je kompleksno, saj običajno zahteva predpis več zdravil z zapletenimi režimi odmerjanja. Bolj kompleksni režimi zdravljenja povečujejo tveganje za neželene dogodke zdravljenja z zdravili. Zdravljenje z zdravili v sistemski terapiji raka (ST) zahteva v primerjavi z ostalimi zdravili še dodatno previdnost. Protitumorska zdravila namreč uvrščamo med zdravila, pri katerih je razmerje med tveganjem in koristjo zelo majhno: premajhen odmerek lahko ogrozi učinkovitost zdravljenja in posledično vodi do napredovanja osnovne bolezni, prevelik odmerek pa lahko vodi do neželenih učinkov, ki ogrozijo bolnikovo življenje. Zato so napake v predpisovanju, pripravi in uporabi protitumorskih zdravil povezane z veliko verjetnostjo resnih neželenih dogodkov, ki lahko pripeljejo tudi do smrtnega izida. Dodatno kompleksnost predpisovanja poveča podporno zdravljenje, ki je pomemben del oskrbe bolnika na sistemski terapiji. Nepravilni predpisi sistemske terapije raka so povezani s hudimi zapleti. Tragičnost teh dogodkov običajno doseže veliko medijsko odmevnost, hkrati pa služi kot vzvod za izboljšanje sistema v njihovo preprečevanje v prihodnosti.

Zavzetost zdravstvenih delavcev k obvladovanju tveganj za napake v sistemskem zdravljenju raka mora biti zelo visoka, kar je ob zavedanju večje možnosti za napake ob uporabi kompleksnih režimov zdravljenja in katastrofalnih posledic, ki jih napake v zdravljenju z zdravili z ozkim terapevtskim oknom lahko imajo za bolnika, pričakovano. To zavedanje se izraža v vsakodnevni praksi Enote za internistično onkologijo Univerzitetne klinike Golnik (EIO) kot skupek aktivnosti in praks, ki so usmerjene k zagotovitvi varnosti sistemskega zdravljenja raka.

Sistem zagotavljanja sistemskega zdravljenja raka na Enoti za internistično onkologijo UK Golnik

Urejeno in enotno dokumentiranje zdravljenja ter jasno postavljeni standardi kakovosti dokumentacije so predpogoj za zagotavljanje kakovosti dela in varnosti bolnikov, zato smo v preteklih letih vložili veliko truda v njihovo pripravo. Vsi dokumenti so bili pripravljeni v tesnem sodelovanju zdravnikov onkologov, farmacevtov, medicinskih sester in drugih. Z multiprofesionalnim sodelovanjem smo med različnimi profili zdravstvenih delavcev osmislili potrebo po predlaganih spremembah in jih spodbudili k prevzemu odgovornosti. V samem poteku priprave dokumentov se nam zdi pomembno izpostaviti nekatere ključne točke. Pri izdelavi dokumentov smo si prizadevali, da bodo v pomoč v vsakodnevni praksi in ne v nekoristno administrativno breme, zato smo vključili le tiste podatke, ki so pomembni za bolnikovo obravnavo. Po vpeljavi dokumentov v klinično prakso smo načrtno zbirali vse pripombe na dokumente in jih na redne razmike, pričakovano, večkrat dopolnili. V nadaljevanju opisujemo ključne dokumente, ki seveda še vedno izboljšujemo in stalno posodabljamo z novimi učinkovinami, ki vstopajo v sistemsko zdravljenje pljučnega raka.

Dokumenti, ki se vežejo na predpis zdravil v sistemskem zdravljenju raka

List sistemske terapije

List sistemske terapije je enoten obrazec za predpis in spremljanje sistemskega zdravljenja raka. Na njem so zbrani vsi ključni podatki, potrebni za predpis ST, podatki o neželenih učinkih in učinku

zdravljenja. List sistemske terapije zmanjša možnost za napake, saj so vsi podatki zabeleženi na enem mestu. Ob vsakem bolnikovem obisku zabeležimo osnovne klinične in laboratorijske podatke, neželene učinke in učinek zdravljenja, kar je vse potrebno za strokovno utemeljeno in racionalno odločitev o nadaljnjem zdravljenju. Načrt zdravljenja potrdi odgovorni onkolog s svojim podpisom, pregled predpisa zdravil pa farmacevt s svojim in tako omogoča dvojno kontrolo predpisanega zdravljenja. Na hrbtni strani Lista ST je predviden prostor za natančno oceno (klinično, radiološko in laboratorijsko) uspeha zdravljenja, ki ga izpolni zdravnik. Za vsako novo linijo ST uporabimo nov list, ki ga vpnemo v bolnikovo mapo sistemskega zdravljenja raka. Ta mapa je opremljena z naslovno stranjo, ki vsebuje podatke o bolniku in tumorju, pregled bolnikovega dosedanjega zdravljenja (npr. operacija ali obsevanje) in sistemskega zdravljenja.

Protokoli zdravljenja s posameznimi shemami sistemske terapije

Protokoli združujejo vse bistvene podatke o posamezni shemi zdravljenja. Vsebujejo podatke o odmerjanju in režimu odmerjanja protitumorskih zdravil, volumnu nosilnih raztopin, vrstnemu redu in času dajanja zdravil, natančnim predlogom premedikacije z antiemetiki in drugim podpornim zdravljenjem, potrebne prilagoditve odmerkov glede na krvno sliko, ledvično in jetrno funkcijo, najpogostejše neželene učinke in potrebne ukrepe za njihovo preprečevanje ter najpogostejše interakcije z ostalimi zdravili. Protokoli so osnovani na povzetkih glavnih značilnosti zdravil, navodil za posamezno shemo kemoterapije svetovnih terciarnih centrov za zdravljenje onkoloških bolnikov in strokovne literature. Protokoli so v pomoč tako zdravnikom pri predpisu terapije, farmacevtom pri pregledu predpisa in rekonstituciji zdravil ter medicinskim sestram pri aplikaciji zdravil. Seveda pa se vsi vpleteni zavedamo, da so odstopanja od veljavnih priporočil pogosto potrebna za dobro obravnavo bolnika, ki zahteva prilagajanje zdravljenja glede na potrebe in značilnosti posameznega bolnika. In ravno zaradi tega lahko protokoli služijo zgolj kot opomnik in nikakor ne morejo nadomestiti poglobljenega osebnega znanja in izkušenj s posameznim sistemskim zdravljenjem, niti intelektualnega razmisleka o tem, kaj je za bolnika najboljša odločitev glede zdravljenja. Hkrati pa se moramo vsi vpleteni tudi zavedati, da lahko vsako nenamerno odstopanje v zdravljenju s protitumorskimi zdravili ogrozi bolnikovo varnost in je zato pomembno taka odstopanja prepoznati in preprečiti. In ravno zaradi tega smo v vseh korakih zdravljenja s ST uvedli dvojno kontrolo s strani dveh neodvisnih zdravstvenih delavcev.

Protokoli aplikacije sistemske terapije

Protokoli aplikacije ST so namenjeni predpisu in aplikaciji zdravil v sistemskem zdravljenju in tako, skupaj z Listom sistemskega zdravljenja, v celoti nadomeščajo običajni terapevtski list. Protokoli zdravljenja so za večino ST zapleteni, vključujejo več zdravil, s točno določenim zaporedjem in posebnimi zahtevami glede aplikacije zdravil. Protokole aplikacije ST smo izdelali, da bi olajšali predpisovanje in aplikacijo ST, zmanjšali možnost za napake pri tem in tako povečali varnost zdravljenja s ST. Osrednji del protokola aplikacije ST je preglednica zdravil v posamezni shemi. Zdravila so zapisana za vsak dan zdravljenja ločeno v predvidenem vrstnem redu aplikacije, ob tem so navedeni tudi podatki o primerni rekonstituciji in hitrosti aplikacije zdravila. Za vsako zdravilo zdravnik predpiše želeni odmerek in veljavnost predpisa potrdi s parafo. Ob aplikaciji zdravila medicinska sestra zapiše uro aplikacije in se parafira. Predpis zdravil pregleda tudi farmacevt, ki ustreznost potrdi s podpisom.

List sočasne terapije med sistemskim zdravljenjem raka

Kot vsa ostala zdravila, tudi zdravila v ST lahko stopajo v interakcije, ki lahko pomembno vplivajo na potek zdravljenja. V želji, da vse možne interakcije prepoznamo že pred uvedbo ST in se jim izognemo, klinični farmacevt naredi pregled interakcij med zdravili v ST in bolnikovo kronično terapijo že pred samo uvedbo ST. O prepoznanih klinično pomembnih interakcijah se farmacevt pogovori z zdravnikom onkologom. Tako bolnikovo sočasno terapijo kakor prisotnost klinično pomembnih interakcij zapišemo na obrazec List sočasne terapije med sistemskim zdravljenjem raka, ki je v pomoč tudi pri nadaljnjih obiskih.

Izobraževalno gradivo za bolnike

Eden izmed osnovnih predpogojev za varnost ST je tudi ozaveščen bolnik, ki razume svoje zdravljenje, ukrepe za preprečevanje neželenih učinkov in navodila za ukrepanje ob njihovem pojavu. To je pomembno za ST, ki jo apliciramo v bolnišnici, morda pa še bolj pomembno pri peroralni ST, ki jo bolnik jemlje v domačem okolju. Ker se tega zavedamo, se ob uvedbi zdravljenja o teh točkah z bolnikom in svojci pogovori tako zdravnik kakor medicinska sestra, vsak bolnik pa dobi tudi pisna navodila. Splošne informacije in priporočila o ST so zbrana v zloženki Sistemska terapija pljučnega raka in v informativnem filmu, za posamezna zdravila in izbrane neželene učinke pa smo pripravili tudi bolj natančna navodila na eni A4 strani. Slednja so še posebej pomembna pri zdravilih, ki so v splošni

strokovni javnosti manj poznana, saj vsebujejo bistvene informacije, ki so lahko v pomoč zdravniku družinske medicine ali drugim zdravstvenim delavcem.

Evalvacija lastnega dela

Evalvacija lastnega dela je osnova za njegovo izboljšanje. Ker se tega zavedamo, smo kmalu po pripravi Protokolov zdravljenja s posameznimi shemami ST v 5-mesečni retrospektivni študiji pregledali odstope med predpisano kemoterapijo in priporočili v protokolih (za podroben opis glej Knez in sodelavci, 2011). Rezultati raziskave so nam pomagali pri izboljšanju našega dela in so potrdila nujnost dvojne kontrole pri vsakem koraku zdravljenja s ST. Veliko intervencij je bilo potrebnih zaradi neskladij v predpisu podporne terapije, ki je nujna za varnost ST, in, da bi število tovrstnih neskladij zmanjšali, smo v Protokole aplikacije ST že vključili predloge zdravil v podporni terapiji, specifično za posamezno shemo. Nezanemarljivo število klinično pomembnih intervencij je bilo potrebnih zaradi nepravilnega odmerka zdravila glede na ledvično funkcijo ali celo prisotne kontraindikacije za predpis protitumorskega zdravila ob slabi ledvični funkciji. Zagotovo smo na tem področju naredili pomemben korak s podajanjem ocene glomerulne filtracije, upoštevajoč tudi bolnikovo telesno težo in višino, na vsakem izvidu serumskega kreatinina. Prepričani smo, da smo s temi ukrepi še dodatno povečali varnost ST.

Ne nazadnje pa so glavni in najpomembnejši dokazi kakovostne oskrbe onkoloških bolnikov podatki o njihovim preživetju. Trud, ki smo ga in ga še vedno vnašamo v vzdrževanje Registra pljučnega raka, nam od leta 2010 omogoča, da preverimo naše delo tudi z analizo preživetja pri nas zdravljenih bolnikov (za pregled glej www.klinika-golnik.si/dejavnost-bolnisnice/klinicna-dejavnost/onkoloska-dejavnost/register-raka-pljuc.php) . In rezultati so dobri in primerljivi z izidi zdravljenja v okviru kliničnih študij (Slika 1), s povprečnim 22,0 mesečnim preživetjem za bolnike, zdravljenje s tarčnimi zdravili, 12,6 mesecev za bolnike zdravljenje s kemoterapijo vsebujoč pemetreksed in 10,3 mesecev za ostale bolnike zdravljenje s kemoterapijo. Zagotovo so ti rezultati spodbuda za nadaljnje delo.

Zaključek

Na Enoti za internistično onkologijo UK Golnik smo v preteklih letih naredili velik korak v standardizaciji postopkov v procesu predpisa, priprave in aplikacije sistemske terapije raka. Gotovo pa nas čaka še veliko dela na področju visoke specializiranosti in usposobljenosti vseh zdravstvenih delavcev, ki sodelujejo v procesu sistemskega zdravljenja bolnikov z rakom. Dosedanje delo je zahtevalo in še vedno zahteva veliko ur potrpežljivega in konstruktivnega multiprofesionalnega sodelovanja, za nadaljnje izboljšave pa bo potrebno izoblikovati in izvajati jasno vizijo razvoja internistične onkologije v naši ustanovi.

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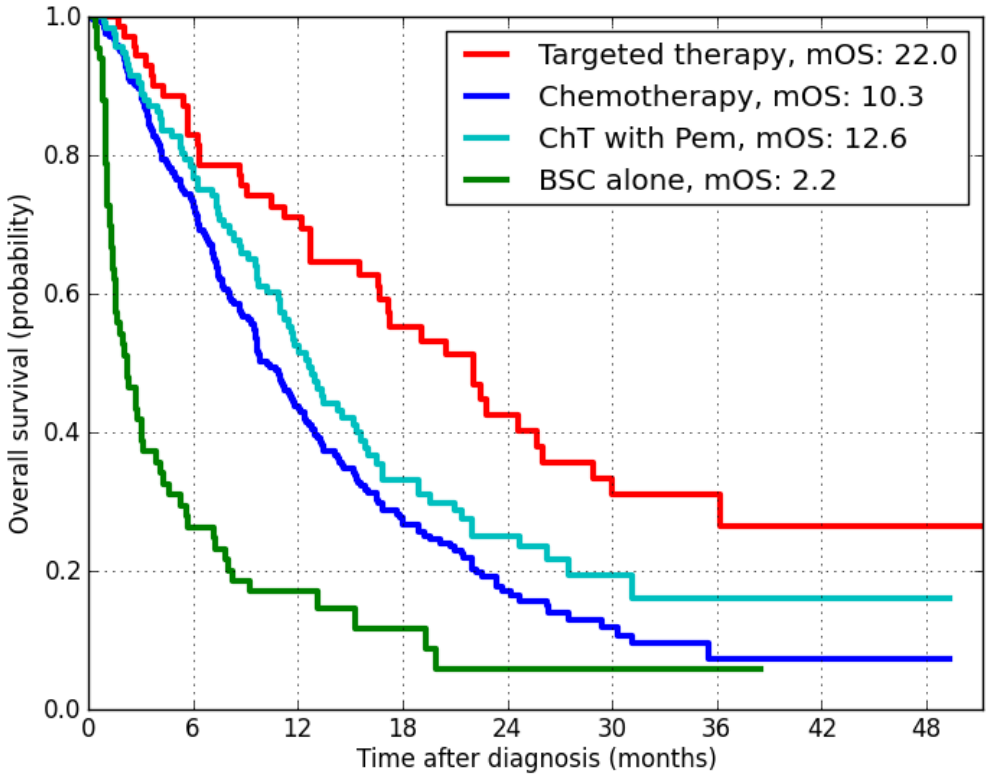

Slika 1. Preživetja bolnikov z razsejanim nedrobnoceličnim rakom pljuč (Register pljučnega raka Klinike Golnik 2010-2013). Graf prikazuje celokupno preživetje (overall survival), izražen kot verjetnost (probability), v odvisnosti od časa od diagnoze (time after diagnosis), ki je izražen v mesecih (months). Rdeča krivulja prikazuje preživetje bolnikov, zdravljenjih s tarčnimi zdravili (targeted therapy), svetlo modra krivulja preživetja bolnikov, zdravljenih s kemoterapijo s pemetreksedom (Cht with Pem), modra krivulja preživetja bolnikov, zdravljenih s kemoterapijo (Chemotherapy), zelena krivulja pa preživetja bolnikov samo na paliativnem zdravljenju (BSC alone).

Pasti paliativne oskrbe: varnost ob spremembi ciljev obravnave

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Uvod

Paliativna oskrba se v zadnjih dveh desetletjih razvija tudi v Sloveniji z vedno več enotami paliativne oskrbe v bolnišnicah in s paliativni timi in ambulantami paliativne oskrbe za boljšo paliativno oskrbo tudi na primarni ravni (Lunder, 2011). Razvoj je očiten, če ga primerjamo le s posamičnimi iniciativami v prvih opisih slovenske paliativne oskrbe (Lunder, Červ, 2002).
Sočasno ob napredku in širjenju paliativne oskrbe pa se zaznavajo tudi pogostejše napake in nedoslednosti pri predpisovanju in aplikaciji zdravil, največkrat pri predpisovanju morfinov. Slaba izobraženost glede paliativne oskrbe med zdravstvenimi delavci in pomanjkljivo razumevanje pomena cilja obravnave v različnih obdobjih paliativne obravnave je velikokrat prisotno v klinični praksi.
V prispevku sta predstavljeni dve tematiki. V prvi so opisane razlage ob težavah zdravstvenih delavcev glede spreminjanja ciljev paliativne obravnave, v drugi pa nekateri primeri posledic nenatančnega predpisovanja in apliciranja morfinov kot priložnosti za izboljšanje klinične prakse.

Spremembe ciljev zdravstvene obravnave pri neozdravljivo bolnem

Vedno pogosteje se tudi v Sloveniji prepoznava vrednost paliativne oskrbe za bolnika z napredovalo neozdravljivo boleznijo in njegove bližnje na vseh ravneh zdravstvene obravnave. Predpisovanje tipičnih zdravil za lajšanje motečih simptomov je pogostejše (Poročilo Agencije za zdravila - na povpraševanje). Javnost se vedno bolj zaveda, kaj je paliativna oskrba in kakšne so njihove pravice do paliativne oskrbe, vendar je prisotno enačenje hospic oskrbe nevladnih organizacij, s paliativno oskrbo podobno kot v tujini (2011 Public opinion research on palliative care). Hospic oskrba se prične ob zaključevanju življenja bolnika, ko so vse možnosti zdravljenja kronične bolezni izčrpane. Paliativna oskrba pa se lahko vključi že zgodaj ob postavitvi diagnoze napredovale neozdravljive bolezni in je tesno vpletena v zdravstveni sistem.
V študijah je vedno več dokazov, da je paliativna oskrba učinkovitejša, če je vključena v bolnikovo obravnavo dovolj zgodaj, vzporedno z aktivnostmi zdravljenja kronične neozdravljive bolezni, ne le pri raku (Temel, 2011, Greer et al, 2013), temveč tudi pri drugih kroničnih neozdravljivih boleznih, kot sta srčno popuščanje (Highet et al, 2014) in multipla skleroza (Higginson et al, 2011). Tako lahko govorimo o različnih obdobjih paliativne oskrbe, ki imajo različne cilje obravnave.
Za zgodnjo paliativno oskrbo je značilno, da je bolnik s svojimi bližnjimi vključen v ambulantno paliativno oskrbo po postavitvi diagnoze napredovale neozdravljive bolezni ob sočasnem aktivnem zdravljenju kronične bolezni in so njegove potrebe po lajšanju telesnih simptomov še neizrazite. Za to obdobje je značilno, da v paliativni oskrbi ponudimo celostno oceno potreb in prihodnjih možnih težav in je v oskrbo vključeno načrtovanje oskrbe v prihodnosti ter koordinirano spremljanje (Highet et al, 2014). Zgodnja paliativna oskrba vse od dokazane učinkovitosti z izboljšanjem kakovosti življenja bolnikov in njihovih družin in celo podaljšanja življenja bolnika (Temel, 2010) omogoča drugačno razumevanje umestitve paliativne oskrbe v bolnikovo obravnavo ob napredovali neozdravljivi bolezni. Bolnikom in svojcem omogoča večjo pripravljenost in sprejetje za zadnje obdobje in avtonomijo v odločitvah pri skupnih procesih odločanja z zdravstvenimi delavci.
Raziskave kažejo, da je že v implementaciji paliativne oskrbe ob koncu življenja, ko bolniki v prvi vrsti potrebujejo lajšanje težavnih simptomov, podporo pri psiho-socialnih in duhovnih problemih, običajno v zdravstvenih institucijah na voljo premalo finančnih sredstev in izobraženega osebja (Ravi et al, 2013). Toliko bolj so te pomanjkljivosti izražene za vpeljavo zgodnje paliativne oskrbe, ki se jim poleg finančnih in kadrovskih primanjkljajev pridružujejo še težave v neutemeljenih stališčih zdravstvenih delavcev, da bodo morda s prezgodnjim vpeljevanjem paliativne oskrbe bolnikom odvzeli upanje.

Pasti pri predpisovanju morfinov

Čeprav so morfine uporabljali že zelo dolgo v zgodovini medicine in je moderna medicina bistveno doprinesla k sintezi mnogih novih oblik morfinov, ko njihove farmakološke lastnosti poznamo do potankosti, ostaja predpisovanje morfinov za lajšanje bolečin, težke sape in kašlja še vedno občutljivo področje s številnimi možnimi tveganji (Dunn et al, 2010). Zdravnikovo temeljito znanje glede mehanizma delovanja različnih oblik opioidov in praktičnega znanja o pravilnih aplikacijah sta temelja varnosti v predpisovanju.
V prvem delu so predstavljeni trije primeri nenatančnega predpisovanja oksikodonskih tablet s podaljšanim sproščanjem z neželenimi posledicami.

1. **Primer:** 76-letna bolnica z razsejanim rakom črevesja z nezadostno lajšano kronično bolečino v predelu desnega kolka, kjer je slikovno dokazana osteolitična metastaza, ob sprejemu v

kliniko navaja, da morfinov ne bo več jemala. V anamnezi ugotovimo, da je gospa pred nekaj dnevi odpuščena iz psihiatrične bolnišnice, kamor so jo sprejeli po več dneh zmedenosti, ko je klicala policijo, »da so ji vdrli tatovi in jo neprestano ogrožajo tuji ljudje«. Bolničina hči je nekajkrat kontaktirala zdravnico, ki je bolnici pred tem dogajanjem predpisala Oxycontin 10mg tablete, z navodilom, da naj jih razpolovi in tako vzame 5mg Oxycontina na 12 ur. Uro ali dve po zaužitju polovico tablete, zjutraj in zvečer je gospa postala nemirna, imela je halucinacije, bila je prestrašena in je vpila, bila je nevodljiva. Popoldne je bila spet jasnih misli, a imela je močne bolečine, prav tako tudi ponoči proti jutru. Po zdravničinem mnenju je imela gospa znake demence. V psihiatrični kliniki so ukinili morfin, bolnica je postala popolnoma bistra in orientirana kot pred tem dogajanjem, imela pa je močne bolečine, ki jih s kombinacijo nesteroidnih analgetikov in paracetamola ni bilo mogoče učinkovito lajšati.

2. **Primer:** Sin stanovalke v domu starejših občanov v obmejnem kraju kliče za nasvet na našo 24-urno telefonsko številko za podporo v paliativni oskrbi: od kar je njegova mama za težko sapo ob napredovali cistični fibrozi dobila nova zdravila pri specialistu v njihovem kraju, je postala dopoldne zaspana, zmedena in nesposobna jasnega komuniciranja. Nekaj ur ni prav »dostopna«, nato pa se zbistri in je povsem jasnih misli. Predpisano zdravilo so Oxycontin tablete 10mg na 12 ur. Že več let se hrani preko perkutane gastro-stome (PEG), zato so medicinske sestre tablete zdrobile.

3. **Primer:** V ambulanto zgodnje paliativne oskrbe je napoten gospod z razsejanim rakom prostate, ki je za poslabšane bolečine zaradi rasti kostnih metastaz pri svojem zdravniku prejel povečan odmerek tablet Oxycontina: iz prejšnjega odmerka 20mg na 12 ur, sedaj 30mg na 12 ur. Gospod opaža zelo motečo zmedenost dopoldne, ko vzame zdravila, da ničesar normalnega ne zmore početi vse do časa kosila in nato pozno zvečer preden zaspi enako. Zdravnik je zatrdil, da bo ta občutek po nekaj dneh minil, vendar se po enem tednu to ni spremenilo. Pri tem bolečina še vedno ni učinkovito lajšana. Ker ni prejel dodatnega recepta za Oxycontin tablete po 10mg, je vzel eno tableto Oxycontina 20mg in dodatno je eno tableto Oxycontina še razpolovil, da se je držal navodil svojega zdravnika in tako vzel skupno 30mg Oxycontina.

V vseh treh primerih je vzrok težav v nepravilnem predpisu Oxycontin tablet. Gre za tablete s podaljšanim ali tako imenovanim kontroliranim sproščanjem, ki zagotavlja 12-urno enakomerno koncentracijo zdravila v serumu. Tehnologija za kontrolirano sproščanje učinkovin takšne tablete je v sestavi dveh različnih učinkovin zdravila v sredici in v zunanjem sloju tablete, to sta čisti morfinski agonist in delni agonist za bolečinske receptorje v centralnem živčnem sistemu (Gregory, 2013). Kadar tableto zdrobimo, ali razpolovimo, vse učinkovine delujejo nemudoma v nekaj prvih urah po zaužitju v celotnem odmerku, ki bi sicer zadoščal za enakomerno sproščanje v 12 urah. prelamljanjem ali drobljenjem spremenimo tableto s podaljšanim sproščanjem v običajno tableto takojšnjega delovanja (Gregory, 2013). Tudi najmanjši odmerki Oxycontina na ta način lahko bistveno vplivajo na bolnikovo kognicijo do te mere, da lahko celo pristane v psihiatrični bolnišnici, ob tem pa ni učinkovitega lajšanja bolečine za preostale ure.
Podobne posledice so možne tudi pri lomljenju ali drobljenju tablet drugih morfinov s podaljšanim sproščanjem: morfinijev sulfat (MST Contin), hidromorfon (Jurnista). Le hidromorfon Palladone je izdelan v obliki zrnc s podaljšanim sproščanjem, ki so vložene v kapsule. Te se med zdravili s podaljšanim sproščanjem edine lahko odprejo in razdelijo v manjše odmerke ali varno uporabijo pri dovajanju zdravil preko sonde (nazogastrične sonde ali perkutane gastrostome).
Rešitve zgornjih primerov:

1. **Primer - rešitev:** V kliniki s titriranjem kratko delujočega morfina v dveh dneh ugotovimo učinkoviti dnevni odmerek morfina in skupaj s ko-analgetiki zaradi nevropatskega karakterja bolečine zelo učinkovito lajšamo bolečino pri bolnici. Prejemala je MST Contin tablete 30mg na 12 uro, Lyrica tablete 75mg dvakrat na dan in glukokortikoid. Za prebijajočo bolečino je prejemala morfinsko raztopino (20mg/ml) 10 mg po potrebi. Pri tem ni imela nobenih znakov zmedenosti, njene funkcijske sposobnosti so se znatno izboljšale, prav tako njeno psihično stanje.
2. **Primer - rešitev:** Domski zdravnici svetujemo, da stanovalki za moteči simptom težke sape predpiše kapsule Palladone (hidromorfon) in lekarni sporoči navodilo za natančno deljenje odmerkov iz kapsul za dovajanje po PEG. Odmerek hidromorfona, ki je ekvivalenten 10mg oksikontin tabletam, je polovica 4 mg kapsule Palladone po ekvianalgezični tabeli. Za rešilni odmerek prebijajočega simptoma dispneje naj ima osebje za stanovalko na voljo tudi morfinsko raztopino (20mg/ml) z navodilom, da po potrebi ali pred predvidenim naporom

vzame 10-15% dnevnega odmerka morfina (oksikontin 10mg/12 ur = 20mg; kar je ekvivalentno 40mg morfinijevega sulfata ali klorida; 10% dnevnega odmerka morfinske raztopine je torej 4mg). Ob takem predpisu je pomembno upoštevati tudi učinek morfina na zaprtje in je potrebno predpisati tudi odvajala po potrebi, ki imajo stimulativen učinek na peristaltiko (sena praparati). Osebje v domu starejših občanov potrebuje dodatno izobraževanje o lastnostih in pravilni aplikaciji morfinov.

3. **Primer – rešitev:** gospodu je potrebno predpisati dodatni recept za Oxycontin 10mg tablete, kljub temu da še ima zalogo 20mg tablet Oxycontina in ga poučiti, da vzame 1 tableto po 20mg in eno tableto po 10 mg na 12 ur ter tablet nikoli ne razpolavlja ali drobi. Gospodu predpišemo tudi kratko delujoči morfin (Sevredol tablete ali morfinsko raztopino) v 10-15% odmerku celotnega dnevnega odmerka oksikontina. Za prevod glede na ekvianalgezično tabelo na drugi morfin in izračun je možen vir: Lahajnar Čavlovič s sodelavci, 2008.

Pasti predpisovanja fentanila (obliž in transmukozni kratko delujoči fentanil)

Fentanil je sintetični morfin, ki se od vseh morfinov v tablirani obliki, so torej vodotopni, topi v maščobah. Po svoji potentnosti je najmočnejši morfin med vsemi morfini v klinični uporabi za lajšanje bolečin. Fentanil v obliki transdermalnega obliža po aplikaciji obliža na kožo doseže maksimalno koncentracijo v serumu šele v 13-24 urah. Če bolnik ni poučen o tem in nima predpisanega hitro delujočega morfina za prebijajočo bolečino (Sevredol tablete, morfinska raztopina, transmukozni fentanil) za premoščanje tega časa, si ob močni kronični bolečini najpogosteje pomaga tako, da v nekaj urah, ko bolečina še vedno ni lajšana, nalepi drugi obliž. V najhujših situacijah so pripeljani bolniki v urgentno ambulanto s štirimi obliži, ki so bili nameščeni zaporedoma v enem dnevu in bolečina je res učinkovito lajšana čez 13-24 ur, a bolnik je lahko pri tem nezavesten in življenjsko ogrožen zaradi depresije dihanja.

Novejša oblika kratko delujočega fentanila je v obliki transmukoznega zdravila: kot pršilo v nosno sluznico ali tableta za bukalno aplikacijo. Namenjen je kot rešilni odmerek za prebijajočo bolečino ob sočasnem jemanju bazičnega morfina s podaljšanim sproščanjem. Predpis tega zdravila ne sme slediti enostavni logiki kot pri predpisovanju vodotopnih morfinov (kodeinijev sulfat, morfinijev sulfat, oksikontin, hidromorfon), kjer je rešilni odmerek praviloma varen odmerek 10-15% dnevnega odmerka morfina s podaljšanim sproščanjem. Pri fentanilu, ki je topen v maščobi, se razporeditev v serumu in drugih telesnih tekočinah ter tkivih vrši po farmakokinetiki drugega reda, ki ni enostavna soodvisnost, ko je koncentracija zdravila v serumu premo sorazmerno odvisna od koncentracije vnosa zdravila. Razporejanje fentanila v serumu se vrši po prvem vrhu koncentracije polnjenja v krvnem obtoku, nato pa se po določenem času zgodi drugi vrh višje koncentracije v serumu, kot sproščanje zdravila iz depojev maščobnih tkiv v telesu. Zato je pomembno, da se kratko delujoči transmukozni fentanil predpisuje le bolnikom s kronično bolečino, ki jim je že dokazana toleranca za morfine (že nekaj tednov prejemajo druge morfine, ki dokazano učinkujejo in ne povzročajo motečih stranskih učinkov) in se to zdravilo predpiše le, če drugi kratko delujoči morfini niso učinkoviti, oziroma gre za zelo močno prebijajočo bolečino. Pri določanju odmerka zdravnik uporabi postopke titracije pravega rešilnega odmerka kratko delujočega fentanila, saj ne gre za enostavno primerjavo in izračun glede na mikrograme dolgo delujočega fentanilskega obliža v mikrograme kratko delujočega transmukoznega fentanila.

Za pravilno in učinkovito lajšanje bolečin so v pomoč domača Priporočila za lajšanje bolečin pri odraslem rakavem bolniku (Lahajner Čavlovič et la, 2008) ter z dokazi podprte smernice za lajšanje kronične bolečine pri onkološkem bolniku Evropskega združenja paliativne oskrbe (Caraceni et al, 2012), v pomoč pa je predvsem stalno dodatno izobraževanje o novostih na tem področju. V zapletenejših primerih je pomembno vključiti tudi specialiste, ki delajo na področju paliativne oskrbe.

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2. **Systemic therapy of lung cancer 1** (Čufer, Kern, Mohorčič) 11:00-13:00
    - Basic pathology and molecular diagnostics in NSCLC – I.Kern, 30min
    - Update on systemic treatment of advanced NSCLC- T.Čufer, 30min
    - Diagnostic and treatment algorithms in N2 NSCLC – S. Popević, Beograd, 30min
    - Advances in combined chemotherapy and radiotherapy in NSCLC- K Stanič, M.Vrankar, 30min

3. **Systemic therapy of lung cancer 2** (Čufer, Kern, Mohorčič) 14:30-16:30
    - Anti EGFR directed therapy – Slovenian experience, N.Turnšek Hitij, 20min
    - Anti EGFR directed therapy – Croatian experience, M. Jakopović, Zagreb, 20min
    - Anti-EML 4-ALK-directed therapy – K.Mohorčič, 20min
    - Imunotherapy of NSCLC- U.Janžič, 20min
    - Supportive and palliative care of NSCLC patients – M.Globočnik, 20min
    - Discussion, 20min

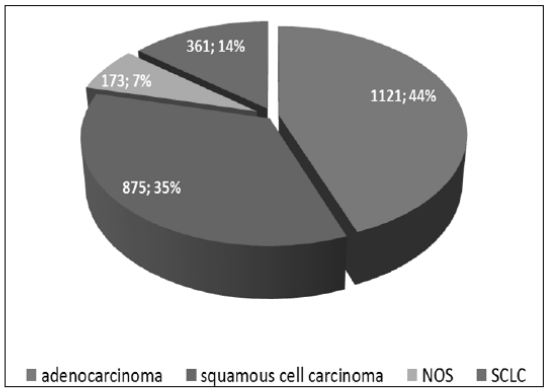
Basic pathology and molecular diagnostics in NSCLC

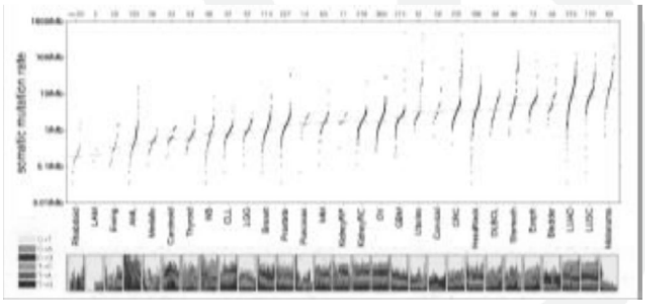
Prim. Izidor Kern, dr. med, *University Clinic Golnik*

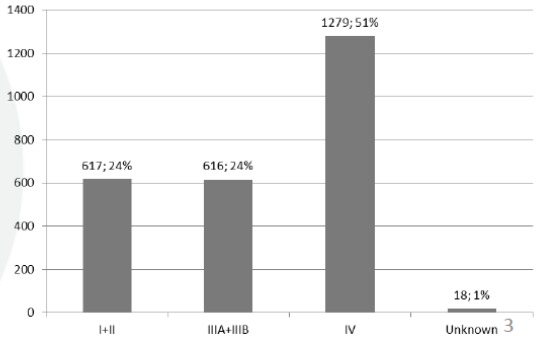
Case:
•male, ex-smoker, 72 y/o
•tumor LUL, clinical stage IV
•bronchoscopy, broncial biopsy
IHC: CK5, CK7, CK14, CK18, CK20, AE1/AE3, MNF116 chromogranin, CD56, TTF1, CEA, EMA, calretinin, LCA, CD31
Dg: adenocarcinoma, poorly diferentiated, most likely primary lung
•type?, no tumor tissue left for EGFR testing

Lung cancer facts

- NSCLC 85% of all lung ca
- adenocarcinoma predominant type
- Advanced stage 75%
- Heavily mutated cancer







Conflicting goals?
> 70% of cases only biopsy and or cytology

accurate typing	**tissue sparing**
•crucial for patient treatment •relevant for prognosis	•molecular testing •research •clinical studies

Use the minimum of specimen necessary for an accurate diagnosis to preserve as much tumor as possible for potential molecular and other studies

Clinical information
•influence the specimen processing and diagnostic approach
•communication with the clinician, radiologist, endoscopist, surgeon,... MDT meetings
•ever lasting learning process
•expanding knowledge
•continous improvements in work-up

Obtaining tumor sample
•paradigm shift; ↑ requirements & ↓ sample size
•tissue
–BB, TBB – 4-5x, 2 mm
–cryobiopsies, TBNB
–TTNB – 2-3x
–VATS
•cytology
–bronchial lavates, washings, brushings, imprints of biopsies, BAL
–sputum
–TBNA (3-4x), transthoracic FNAB
–pleural fluid
–FNAB of peripheral lymph nodes, liver metastasis,...
•combined approach to get the most of the procedure

Lung cancer & sample size
•one person or one lab (cytology + histology), more centralized approach, organized logistics
•continous collaboration with the "providers"
–ROSE
•management of the sample, choose the best sample for ancillary methods and molecular staff maximize the patients eligible for testings, prioritization of tests
    •various specimens
    •various quantity of tumor tissue in specimens
    •ICC/IHC – typing, origin
    •special stains
    •ISH (FISH/CISH/SISH)
    •PCR

Specimen processing
•sine qua non condition = immediate & time-controlled fixation (6-48h)
•standardized protocols
    •sampling (cells, tissue)
    •transport
    •fixation
    •lab acquisition and processing (for suspected cancer)
•determine how specific a diagnosis is needed
•anticipation of IHC and molecular studies
•prevent unnecessary usage of tumor sample

Quantity is essential: fate of one biopsy:
1.H&E 5x
2.IHC 2x (basic histotyping)
3.H&E first control
4.DNA extraction min 3x10µm (EGFR, KRAS,… testing)
5.IHC (additional if needed) 2x
6.ISH & IHC 2x (ALK & ROS1 testing)
7.IHC (PD-L1?)
8.H&E last control

Morphology = HE ± AB
•establish malignancy and subtype it
•stepwise thougt process
1.specimen quality
2.tumor vs nonneoplastic vs tumor-like changes vs artefacts
3.malignant vs benign neoplasm
4.carcinoma vs other lung tumors
5.primary vs secondary
6.NSCLC vs SCLC
7.NSCLC type, SCC vs AC

Morphology is fundamental
•male, 61 y/o, smoker
•CT: RUL tumor
•subcutaneous mass in abdominal wall
•needle biopsy
•IHC
–positive CK7, EMA
–negative PSA, CK20, TTF1, CHR
•sent for EGFR testing
•no need for IHC, morphology is essential, no EGFR testing

IHC/ICC
•in up to 40% NSCLC morphological subtyping is not possible/accurate
•kappa value 0,25-0,39 for NSCLC (poor interobserver agreement)
•squamoid or adenoid appearance!
•no NSCLC NOS (?) – goal <10%
•WHO 2015 morphological criteria can be applied to cytology and biopsies

A panel of 2 (4) Ab for NSCLC subtyping:

SCC vs AC	AC	SCC
p40	-	+
TTF1	+	-
napsin A	+	-
CK5/6	-	+

AC: SPA+, CK7+, CK20-
SCC: p63, 34betaE12+, SOX2+, desmocollin+

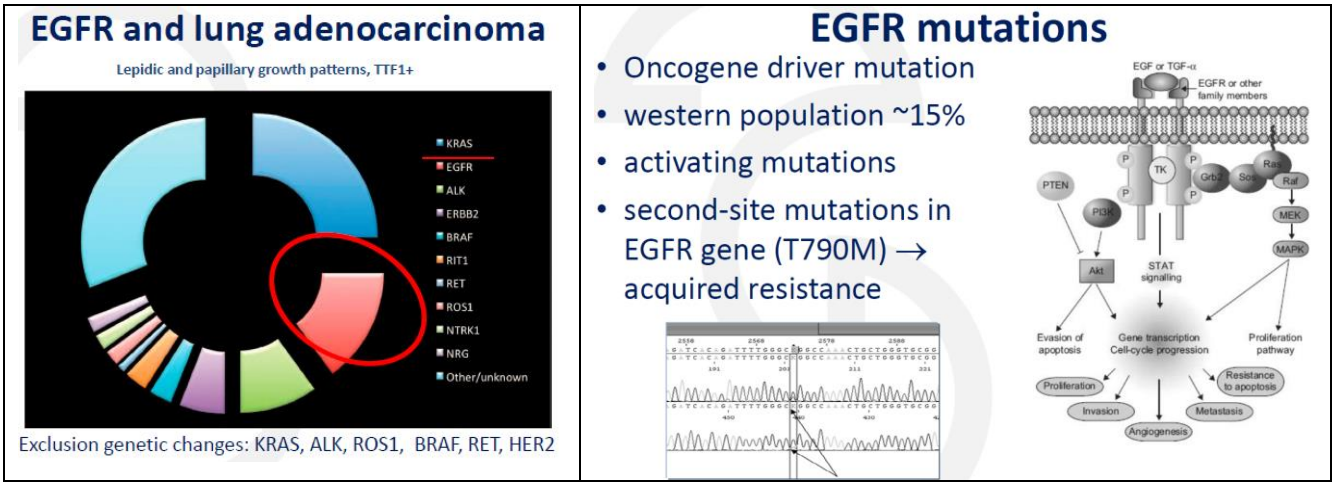
WHO classification 2015
•NSCLC (> 80%)
–SCC
–AC
–LCC
–ASCC
•SCLC (15%)
•other lung malignant tumours (< 5%)
–lymphomas, soft tissue tumours,...
–sarcomatoid carcinomas
–carcinoids

Adenocarcinoma
•the most common type of NSCLC
•the most histologically variable, heterogeneous form of NSCLC (mixture of patterns)
•Grading by predominant pattern

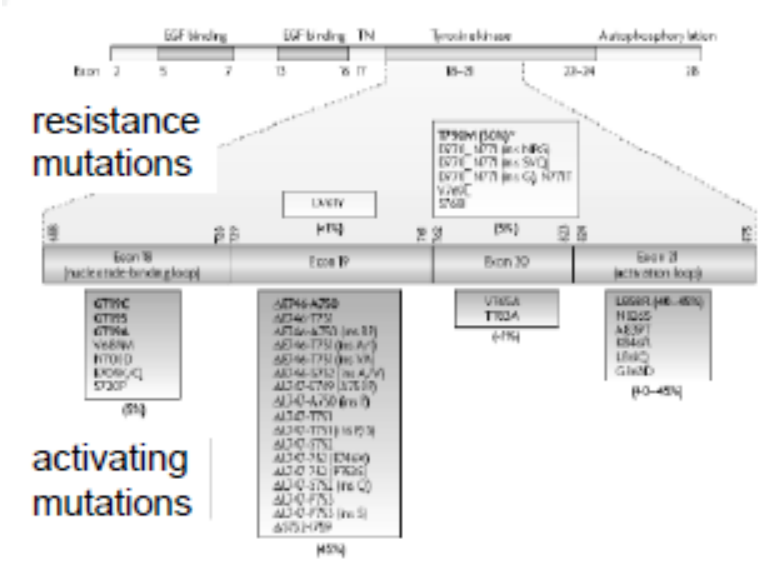
Lepidic growth pattern
•AAH, AIS, MIA, A with lepidic pattern
•Mucinous adenocarcinoma
•Preserved baseline architecture of lung
•Unreliable diagnosis in small biopsies
•Diagnosis not possible in cytology

Molecular pathology & histology

mucinous A, TTF1 negative	KRAS mutations	TKI resistance
peripheral nonmucinous A TTF1 positive	EGFR mutations	TKI sensitivity
mucinous solid A, TTF1 positive	ALK translocation	crizotinib



somatic mutation constant activation
•overexpression in various cancers
•activity (non-ligand dependant) could be inhibited by small molecules
•Best predictor of TKI treatment



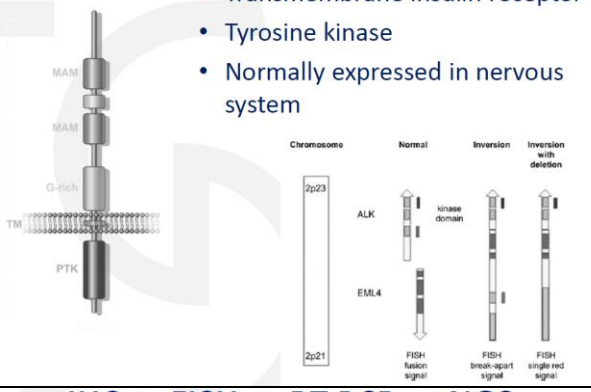
EGFR tissue testing at UCG

•From 11/2009 in routine practice
•2009 to 2014
–2412 patients tested
–363 EGFRmu+ patients (15%)
–M 125, F 238
•International guidelines implemented
–Not all patients tested

Year	Unknown %	Positive %
2010	34.5	14.2
2011	26.3	23.5
2012	20.7	13.0
2013	16.0	13.6
2014	13.1	15.1

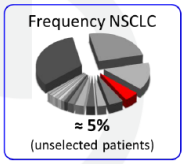
ALK

- Transmembrane insulin receptor
- Tyrosine kinase
- Normally expressed in nervous system

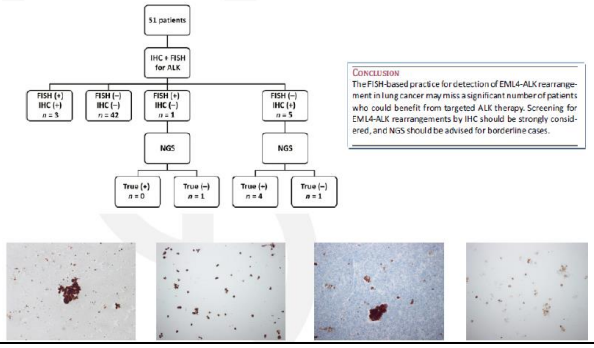


ALK gene rearrangement

- KRAS and EGFR wild type cancers
- Paracentric inversion within ALK gene in chromosome 2 → fusion with EML4 gene (or others) → expression of oncogenic ALK protein
- IHC screening method: available, routine method, time



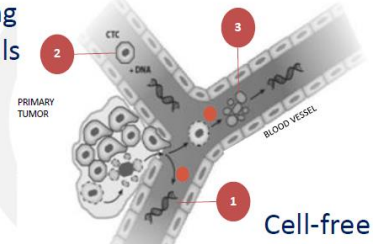
IHC or FISH or RT PCR or NGS



Tumor biomarkers in blood

Exosomes & micro vesicles

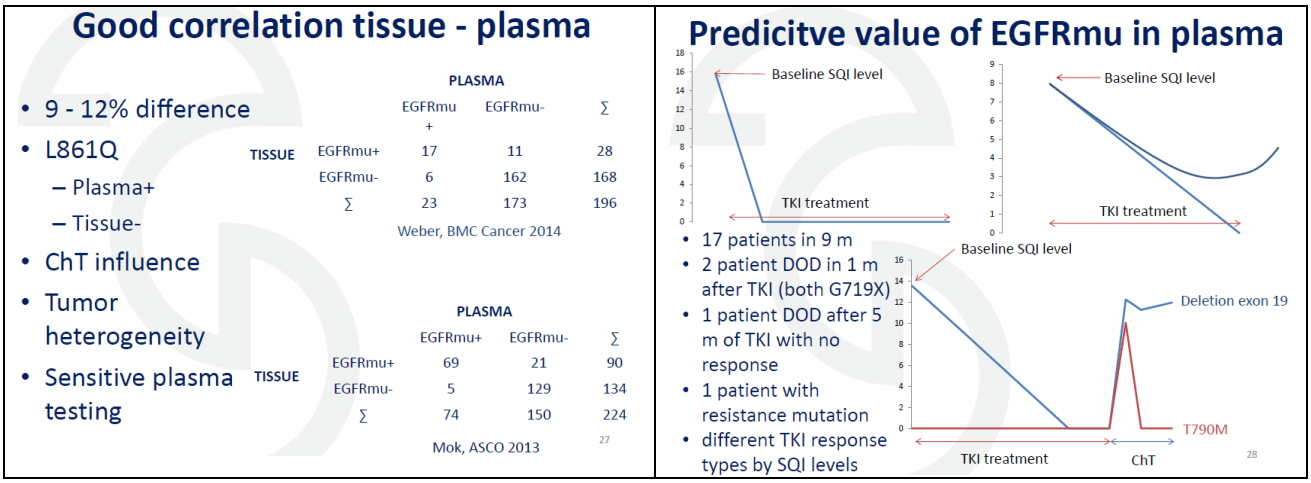
Circulating tumor cells (CTCs)



Cell-free DNA (cfDNA)

Plasma based EGFR testing

•Quality and or quantity limitations of cytology and tissue biopsy samples for tissue based testing
•Blood is an alternative sample, rich source of circulating free tumor DNA
•Plasma EGFRmu is a potential biomarker for monitoring tumor response



PD-L1

•PD-1 (programmed cell death) co-inhibitory receptor expressed on lymphoid and other cells
•Negatively regulates T-cell response
•PDL-1 major PD-1 ligand expressed on tumour cells
•Predicitve marker???
•IHC – 4 antibodies, different platforms
•Tresholds ?
•Tumour heterogeneity
•Response in negative cases
•Higher expression in SCC

Distinct NSCLC groups by PD-L1+

•TC3 tumors have lower lower immune cell infiltration and are characterized by sclerotic, desmoplastic stroma
•IC3 tumors represent CD8+ rich infiltration
•IC0 and TC0 means non-functional immune infiltration

More questions than answers

•Which assay and expression level?
•Is PD-L1 a correct biomarker?
•Does archival tumor tissue testing reflect the PD-L1 expression in tumor at the time of immunotherapy?
•What about the sample size?
•Does the oncology community trust IHC result?

Advances in combined chemotherapy and radiotherapy in NSCLC

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Key words: inoperable locally advanced non-small cell lung cancer, LA-NSCLC, chemoradiotherapy, concurrent chemoradiotherapy

Treatment of inoperable locally advanced non-small cell lung cancer (LA-NSCLC) remains one of the biggest health care challenges worldwide in spite of many scientific and technological advances. Patients with LA-NSCLC comprise a heterogeneous group, some of whom have curable disease. Radical chemoradiotherapy with 60 to 66 Gy in 30-33 fractions represent a backbone of treatment in inoperable LA-NSCLC. In fit patients, radiation is administered concurrently with chemotherapy leading to improved survival compared to radiotherapy alone or the sequence of both. Meta-analysis published in 2010 demonstrated moderate 4.5% survival benefit and reduced loco-regional failure by 6.1% at 5 years.[1] The most commonly used chemotherapy regimens given in combination with radiotherapy are cisplatin/etoposid or carboplatin/paclitaxel. Unfortunately, due to co-morbidities, advanced age and poor performance status only about 60% of patients are eligible for concomitant therapy. For unfit patients, the treatment of choice is sequential chemoradiotherapy or merely radiotherapy. Long term survival rates with these approaches are only in the order of 15%.[2] Therefore, different strategies to improve outcomes are being explored.

Advances in radiotherapy techniques allow more precise targeting and delivering higher doses to the tumor whilst minimizing the dose to organs at risk. The routine use of PET imaging within the last years has aided in staging and radiation planning. However, higher doses are currently not recommended due to the results of the recent phase III RTOG 0617 trial comparing standard dose radiotherapy with high dose (74 Gy) conformal radiotherapy demonstrating a significant increase in the risk of death in the high dose arm.[3] Altered fractionation schedules, hyperfractionation and hypofractionation as well as boosts targeting the high PET or hypoxic areas have been reported to be successful, but logistics limits its use in routine practice.

The best systemic regimen to be used concurrently with radiation has yet to be defined. Whilst histological and molecular testing drives specific oncological therapy in advanced disease it plays no major role in LA-NSCLC. Platinum based chemoradiotherapy with combination of etoposid and paclitaxel has been the standard of care for past decades with no proven difference in efficacy between them. Furthermore, recent results of the phase III study of the novel anti-folate pemetrexed in combination with cisplatin compared to standard etoposide/cisplatin did not show efficacy difference between the schedules with slightly less toxicity reported in pemetrexed arm.[4]

In recent years, there were several attempts to improve results in the treatment of LA-NSCLC patients with delivering additional chemotherapy before (induction) or following (consolidation) concurrent chemoradiation. A recent pooled analysis of 41 phase II/III trials has confirmed that there remains no evidence to suggest that consolidation chemotherapy after concurrent radiochemotherapy improves survival for patients with stage III NSCLC.[5] Other recent reports on the treatment of locally advanced NSCLC include new drugs such as pemetrexed and cetuximab either during radiotherapy and/or sequentially. In a randomized phase II trial of 4 cycles of carboplatin-pemetrexed and concurrent radiotherapy folowed by pemetrexed with or without addition of cetuximab (101 patients), 18-months OS of 54% in the arm with and 58% without cetuximab and median OS of 25.2 months with and 21.2 months without cetuximab were reported.[6]

Initial attempts to incorporate moleculary targeted therapies into chemoradiation have been also disappointing thus far. A phase III randomized trial of maintenance gefitinib vs. placebo in patients with stage III NSCLC, unselected for EGFR status, who had responded to concurrent radiochemotherapy and consolidation docetaxel demonstrated worse survival in the gefitinib arm.[7] Median survival of 35 months in the control arm compares favorably with results from other phase III studies, although a selection bias must be stressed as patients were randomized following a response to concurrent radiochemotherapy and consolidation chemotherapy.

Encouraging results have been achieved with trimodality treatment. A multicenter phase II trial (CISTAXOL) showed long-term survival of induction chemotherapy with three cycles cisplatin/paclitaxel followed by concurrent chemoradiation cisplatin/etoposide and surgery in locally advanced NSCLC.[8] The median survival was 25 months with 5 and 10-year survival rates of 30.2% and 26%, respectively. In spite of the fact that nearly two thirds of the 64 patients in the trial had stage IIIB, the R0-resection rate was 50%.

Targeting immune regulatory pathways has proven to be a successful strategy in NSCLC. A phase III randomized trial, consolidating chemoradiation with an immunotherapy has been studied in stage III NSCLC.[9] Tecemotide, a MUC1 antigen-specific cancer immunotherapy, was evaluated as consolidation therapy after chemoradiation. Although overall survival did not statistically differ between the two groups, a subset analysis favored the tecemotide arm (median survival, 30.8 vs. 20.6 months). In conclusion, treatment of LA-NSCLC has not significantly progressed in the last decade, in spite of major changes and improvement in treatment of advanced NSCLC. Combined concurrent chemoradiotherapy with cisplatin-based combinations remains the standard of care for patients in good performance status and no major comorbidities. The role of targeted agents in molecularly selected subgroups and immunotherapy in LA-NSCLC and the optimal treatment approaches in unfit and elderly patients has yet to be defined and are the subject of ongoing clinical trials.

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Treatment of ALK positive NSLC

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TARGETABLE ONCOGENES IN NSCLC:

No mutation detected: 36.4%
KRAS 25%
EGFR 23%
ALK 6%
BRAF 3%
PIK3CA 3%
MET 2%
HER2 1%

ALK REARRANGEMENTS

- *EML4-ALK* frequency:~ 4% (64/1709)
- Primarily in adenocarcinoma
- More common in younger patients, never-smokers
- Higher rate of pericardial and pleural disease, more sites of metastases at presentation

CRIZOTINIB STUDIES IN ALK-POSITIVE NSCLC

Study (Phase) Author	Study Arms	No. of pts	RR (%)	PFS Median (mo)	OS Median (mo)
PROFILE 1001 (Phase I) [1]	Crizotinib	149	61	9.7 **18.7 FL**	NYR 74% at 1y
PROFILE 1005 (Phase 2)[2]	Crizotinib	261	60	8.1	NR
PROFILE 1007 (Phase 3)[3]	Crizotinib Cht Pem Doce	347	*65 20 29 7	*7.7 3.0 4.2 2.6	20.3 22.8 70% at 1y
PROFILE 1014 (Phase 3)[4]	Crizotinib Cis/Pem	343	*74 45	*10.9 7.0	NYR 65% at 1y

1.Camidge DR et al., Lancet Oncol 2012; 2. Kim D-W et al., J Clin Oncol 2012,
3. Shaw A et al., N Engl J med 2013, 4. Mok T et al., ASCO Abstract 2014.

RAMDOMIZED PHASE 3 TRIALS OF CRIZOTINIB IN ALK-FISH POSITIVE NSCLC

PROFILE 1007: 2ND LINE CRIZOTINIB VS. CHEMOTHERAPY (347pts)

- mPFS crizotinib vs ChT 7.73m vs 3.0m, HR 0.49(0.37-0.64),(p<0.001)

PROFILE 1014: 1st LINE CRIZOTINIB VS. CHEMOTHERAPY (343pts)

- mPFS crizotinib vs ChT 10.9m (8.3-13.9) vs 7.0m (6.8-8.2). p<0.001
- oRR crizotinib vs ChT: 74% vs 45%

CRIZOTINIB: ACQUIRED RESISTANCE

- ORR to crizotinib 60%
- Median PFS 8-10m
- Most patients develop resistance to crizotinib, ususally within 7-11months
- CNS relapses are common
- Mechanisms of resistance are diverse
- ALK resistance mutations or
- Alternative signaling pathways

CNS PROGRESSION

- CNS is the first site of progression in 46% of *ALK*+ crizotinib treated patients
- TREATMENT OF ASYMPTOMATIC BRAIN METASTASES: ESMO guidelInes for METASTATIC NSCLC;"Asymptomatic brain metastases should not be treated with radiotherapy. Deferred irradiation in case of progression is valuable option (II,B)".

ASCEND 1 TRIAL- 2nd GENERATION ALK INHIBITOR CERITINIB (ZYKDIA®) in ALK Rearranged NSCLC

ASCEND 1- CERITINIB EFFICACY OUTCOMES

- HIGH AND DURABLE RESPONSES IN ALK INHIBITOR NAIVE AND PTS WHO HAVE RECEIVED PRIOR THERAPY
- ORR ALK +: **61.8%** (95% CI 55.4-67.9), **median PFS 9.0m** (95% CI 6.9-11), **18.4m for ALK inhibitors naive pts .**Median time to response **6.1** weeks (3-42)*
- **Active in CNS** (50% of pts in the study had brain mets!),
- Overall intracranial RR; 36% (prior ALK inhibitor) vs 63% (ALK inh. naive)**
- ACCELERATED FDA APROVAL APRIL 2014 after progresion on crizotinib

OTHER ALK INHIBITORS: ALECTINB, BRIGATINIB

CONCLUSIONS

- ALK rearangements are present in 3-5% of NSCLC (women, younger, light smokers, more metastatic sites at presentation)
- All non squamous NSCLC should be tested for ALK mutations (effort to get enough tissue)
- PROFILE 1014 demonstrated superiority of CROZITINIB vs ChT in 1st line treatment and ALK + pts should receive ALK inhibitors in 1st line systemic treatment
- Impresive response: ORR to crizotinib 60.5%, PFS 9.7m
- Despite good and durable response, progression on 1st generation anti ALK therapy due to ACQUIRED RESISTANCE develops inevitably
- CNS progression is common
- Newer generations of ALK inhibitors like CERITINIB and ALECTINIB are effective in tumors resistance to crizotinib, they also penetrate into CNS

Supportive and symptomatic care for lung cancer patients on systemic therapy

Tanja Čufer, MD, PhD, Katja Mohorčič, MD, Marta G. Kukovica, MD; *University Clinic Golnik, Slovenia*

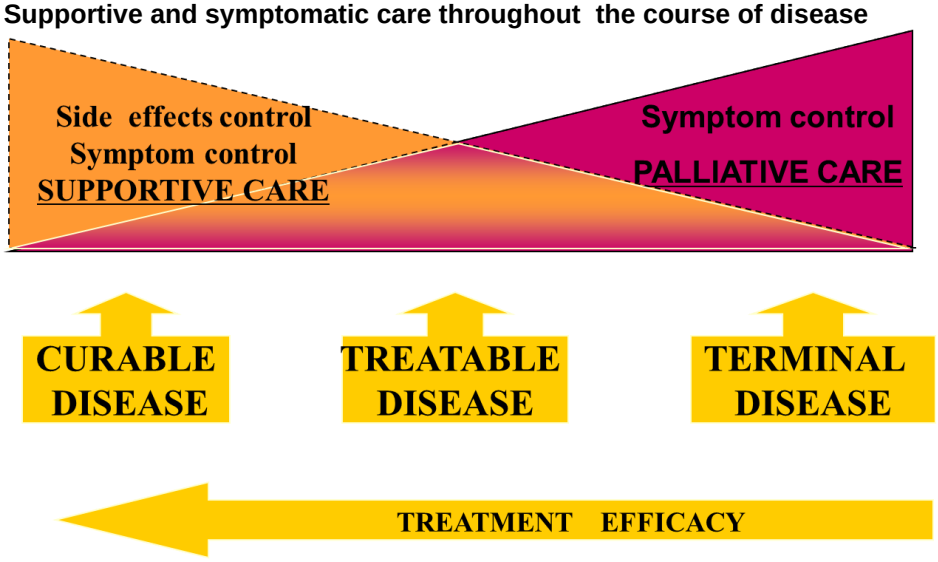
Burden of lung cancer (LC)

LC is a leading cause of death due to cancer, with 1.6 million deaths worldwide .and also the most frequently diagnosed cancer worldwide (yearly more than 1.8 milion new cases=13% of total). Approx. 50% of LC patients are diagnosed in advanced disease, with high burden of symptoms and poor QoL. Median survival rate of advanced LC is only 8- 10 months, with 12 % of pts alive at 5 years.

Advanced lung cancer

Cure is not an realistic option. In selected patients with EGFR- or ALK-driven NSCLC long lasting remissions (median OS around 30 months) could already be achieved . The goals of treatment are palliation of symptoms and prolongation of life.

Supportive and symptomatic care throughout the course of disease



Supportive care is treatment given to prevent, control, or relieve complications and side effects and to improve the patient's comfort and quality of life. Supportive care is the care given at the time of specific oncologic treatment (chemotherapy, biologic treatment, radiation).
The most common side effects of currently used systemic agents are Emesis/nausea, Myelotoxicity, Fatigue, Neurotoxicity , Renal toxicity, Mucositis, Skin toxicity.

Emesis and antemetics ,

Acute	Occurs within a few minutes to several hours after ChT, ususally resolves withihn 24 hours
Delayed	Occurs more than 24 hours after ChT
Anticipatory	Occurs before a cycle of ChT.
Breaktrough	Occurs despite prophylactic treatment and/or requires rescue antiemetic agent
Refractory	Occurs during subsequent treatmen cycles when antiemetic prophylaxis and/or rescue have failed in earlier cycles

ANTIEMETICS:

- Corticosteroids
- 5HT3 antagonists (palonosetron)
- Cannaboids (dronabidol)
- Dopamine antagonists
- NK1 antagonists (aprepitant)

- Benzodiazepines

ASCO Emetic risk groups and treatment guidelines, 2011

Emetic risk group with representative agents	Treatment Acute - Day 1	Algorithm Delayed Day 2 - 4
High (≥90% pts at rosk) **Cisplatin**	**5-HT3 (palonosetron prefered)+ NK1 (aprepitant) + steroid**	**NK1 (aprepitant)+ steroid**
Intermediate anthracyclines carboplatin cyclophosphamide	**5HT3 (palonosetron)** + steroid	Steroid alone or 5-HT3 (palonosetron) alone
Low: taxanes etoposide gemcitabin cetuximab	Steroid alone	No routine profilaxis
Very low**:** vincas methotrexat gefitinib, erlotinib bevacizumab	No routine profilaxis	No routine profilaxis

Controlling emesis: Major developments and major obstacles

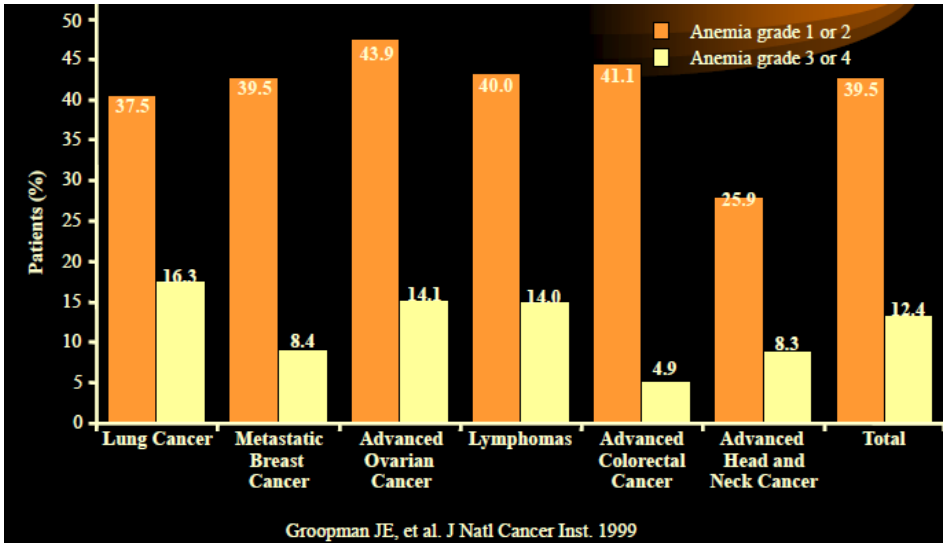
Developments	**Obstacles**
Introduction of 5-HT3 and NK1 antagonists Control of delayed emesis Establishing the guidelines	Bad control especially of delayed emesis Cost of NK1 Bad compliance Lack of individualized therapy

How to optimize antiemetic therapy?

- Optimal use of available drugs
- Regular assessment of patient's response to treatment with individualized antiemetic schedules and treatment modification
- Use of sedatives and/or haloperidol in refractory nausea/vomiting
- Delayed emesis remains a management challenge

Prevention is the key!

Anemia in Cancer Patients



Anemia consequences

- Anemia correlates with worse prognosis in cancer patients [1]
- It could result in the delay/ termination or reduced dose of ChT [2]
- QoL is reduced at low Hb values[3]
- Anemic patients have fatigue[4]

Anemia correction on the systemic treatment

Pros:	**Cons**:
Better QoL ↓ tumor hypoxia and ↑ efficacy of systemic treatment	Transfusion and /or ESA side effects

Meta-analyses of ESAs in cancer : 13.933 patients, 53 phase 3 trials. atients treated with ESA had 6% ↓ overall survival, 17% ↑ risk of death during treatment and Significantly ↑ risk of VTE.

Guidelines for the use of ESA

Cautious use ESAs in a potentialy curable disease! (Aapro MS, et al. The oncologist. 2008;13:33-36. 2. Schrijvers D, et al. Ann Oncol. 2010;21(5):v244-v247. 3. Rizzo DJ, et al. J Clin Oncol. 2010;28(33):4996-5010. 4. NCCN Clinical Practice Guidelines in Oncology – v. 2.2014. www.nccn.org.)

Smernice	EORTC 2008[1]	ESMO 2010[2]	ASCO 2010[3]	NCCN 2013[4]
Purpose of ESA use	Avoid transfusions, better QoL	Avoid transfusions, better QoL	Avoid transfusions	
Start Hb	Symptomatic anemia atChT/RT (Hb 90-110 g/L)	Symptomatic anemia at ChT (Hb ≤ 100 g/L)	Anemia at ChT(Hb ≤ 100 g/L)	
Targetet Hb	Cca. 120 g/L and less symptoms	Cca. 120 g/L	Lowest Hb value to avoid transfusions	
Fe	Parenteral application at Fe defficit	i.v. At functional Fe deficit(feritin >100 ng/ml + sat. transferina <20 %)	Npt enough data for a routine use	i.v. At functional Fe deficit (feritin ≤800 µg/l + sat. transferin <20 %)
TE	1.6x higher risk	↑ risk: reduce the use in high risk patients		↑ risk independent of Hb value
Purpose of ChT	Palliative ChT	Use it with caution in a curable disease	Palliative ChT	Palliative ChT,symptomatic anemia

Febrile neutropenia & use of GCSF
Is an oncologic EMERGENCY, life threatening side effect of systemic therapy and/or irradiation.
Deffinition: absolute neutrophil count < 0,5 x 10^9/L (or if expected drop under 0,5) AND temperature above 38,5 C measured once or if the temperature does not drop below 38° C more than 2hours (1.Freifeld et al. CDI. 2011;52(4):56-93; Flowers et al. J Clin Oncol. 2013;31:794-810; de Naurois et al. Ann Oncol. 2010;21(5):252-6). Bacteriaemia in 20% of pts, threat of septic shock with ARDS. Mortality is high: 5% in solid cancers and 11% in hematologic malignancies.

Chemotherapeutic schemas with high to moderate risk of FN in lung cancer

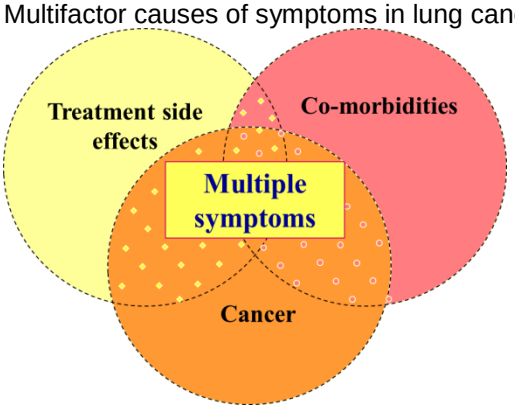
Cancer Hystology	Risk of FN	Cht schema	FN (% of pts)
SCLC	High > 20	**ACE** 45 – 50/1.000/100 – 120^{d1-3} Q3W **ICE** 5.000/300/180^{d1+2} Q4W **Topotekan** 1,5^{d1-5} Q3W **TopT (topotektan/paklitaksel)** 1^{d1-5}/135^{d5} Q4W **VICE** 1 mg^{d15}/5.000/300/120^{d1+2} + 240^{d3} Q2W-6W	24 – 57 24 28 > 20 70
	Intermediate 10 – 20	**Etopozid/karboplatin** 100^{d1-3}/300 Q3W **Topotekan/cisplatin** 0.75^{d1-5}/60 Q3W **CAV** 750/40/1,3 Q3W **CODE** 25/1$^{(week\ 3,5,7-9)}$ /40$^{(week\ 2,4,6,8)}$ /80 $^{d1-3\ (week\ 2,4,6,8)}$ QW + G-CSF	10 – 20 19 **14** 19
NSCLC	High > 20	**DP (docetaksel/karboplatin)** 75/AUC6 Q3W **Etopozid/cisplatin** (200/35)$^{d1-3}$ Q4W **VIG** (25^{d1} + 20-25^{d4})/3.000/(1.00^{d1} + 800-1.000^{d4}) Q3W	26 54 25
	Intermediate 10 - 20	**Paklitaksel/cisplatin** 135/75^{d2} Q3W **Docetaksel/cisplatin** 75/75 Q3W	**16** 5 - 11

Recommendations for the use of hematopoietic CSF (EORTC 2011)
WHICH G-SCF?: filgrastim, lenograstim, pegfilgrastim
PRIMARY PROPHYLAXIS:
- expected incidence of febrile neutropenia (FN) >20% according to ChT regimens
- Paitient related risk factor has to be considered in regimens with intermediate risk of FN (10-20%) (age, poor PS…)

SECONDARY PROPHYLAXIS:
- pts with history of FN

G-CSF GENERALLY NOT RECOMMENDED as therapy during FN

Symptomatic care:
Multifactor causes of symptoms in lung cancer



Prevalence of 10 most common symptoms in advanced cancer patients (Walsh D et al, Support Care Cancer 2000)

Symptom	Female (n= 450) %	Male (n= 550) %	All (n=1000)%
Pain	83	82	**82**
Easy fatigue	69	67	**67**
>10% Weight loss	69 *	60	**60**
Anorexia	63	64	64
Lack of energy	61	59	59
Dry mouth	59	53	55
Constipation	51	50	51
Dyspnea	51	49	**51**
Sleep problems	44	50	47
Nausea	43 *	31	36
* p<0.01			

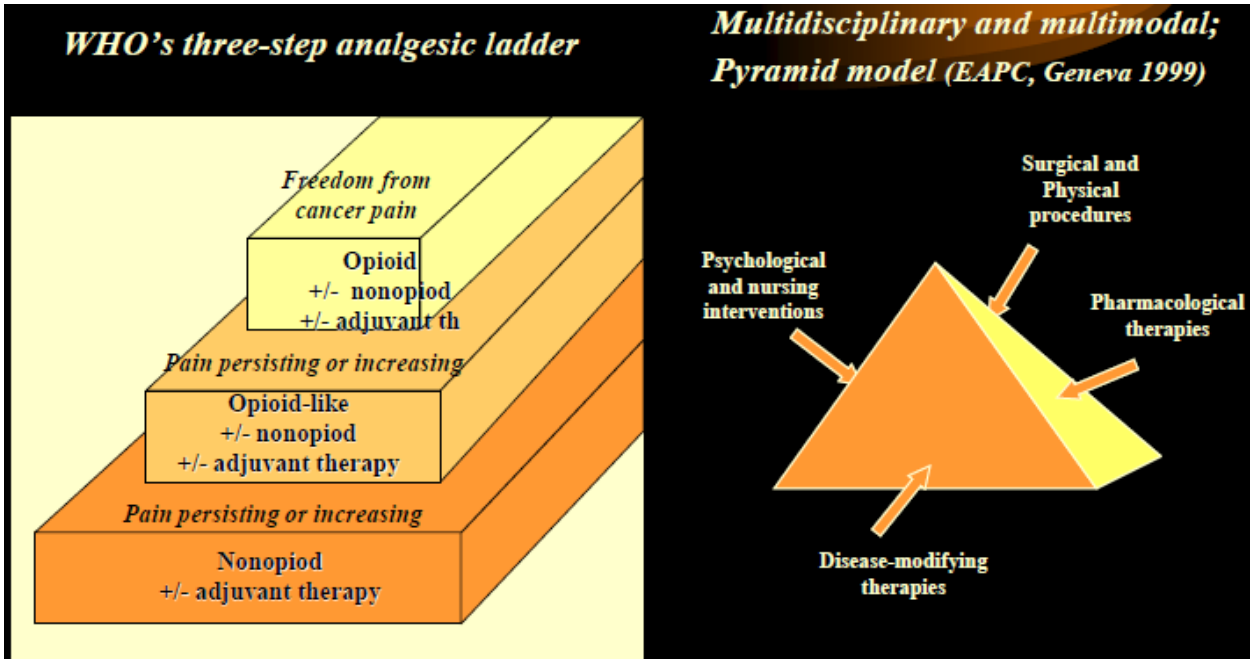
Symptom characteristics in 1000 patients with advanced cancer

- Symptom prevalence differs with age, gender and cancer site
- The median number of symptoms per patient was 11 (range 1-27)
- The most common symptoms were generally the most severe, clinically important in 60% to 80% occurrences

Cancer pain

Prevalence: at time of diagnosis 30-40%, advanced disease 65-85%, neuropatic pain 40%.
Pain and its therapies interact with other common cancer symptoms (fatigue, weakness, dyspnea, constipation) and anticancer therapy.

Pain control in cancer



Barriers to effective cancer pain management

Patient-related issues

- Bad complience with analgesic regimens
- Lack of knowledge about pain and pain management
- Fear of addiction, side-effects and tolerance

Professional-related issues

- Lack of familarity with WHO analgetic ladder
- Poor pain assesment
- Ignoring the principle of combined use of long-acting and short-acting opiod

Systems-related issues

- Lack of available opioids
- Restrictions in the use of opioids

Coanalgesic drugs for bone metastases are Bisphosphonates, Denosumab (RANKL inhibitor), Strontium 89, Samarium 153

- Bisphosphonates in patients with lung cancer and bone metastases desreases time to first SRE, pathologic fracture and palliative radiation.
- Survival improvement in NSCLC patients treated with denosumab vs. zoledronic acid is significant

Cancer-related weight loss

- Etiology is a multifactor (tumor-derived products, host-derived cytokines, other tumor or treatment related symptoms)
- 15% - 40% at presentation
- 80% or more with advanced disease
- Adverse prognostic factor
- Results in reduced quality of life

Management of cancer-related weight loss

Aggressive symptom management

- Delayed gastric emptying, early satiety (metoclopramide)
- Taste/Food aversions
- Constipation

Nutritional support

- Nutritional counseling
- Enteral nutrition (useful in pts with swallowing problems)
- Parenteral nutrition (only in selected patients, tumor obstruction, pre-operatively)

Pharmacologic interventions

- Megestrol acetate
- Corticosteroids
- Other (anamorelin ...)

Cancer-Related Fatigue

Fatigue affects patients everyday life the most. Prevalence is higher in special tumor types (breast cancer 6%, prostate cancer16%, NSCLC 50%), with the highest incidence (78%) in advanced disease. 47% of pts felt that fatigue was something they have to live with. 52% of pts with fatigue had never raised this issue with doctor. Only 14% of pts with fatigue had been prescribed or recommended any treatment. Only 4% of them were advised to take exercise

Management of fatigue

Patient	**Oncology team**
Structured aerobic exercise Energy conservation	Consider psychosocial issues Pharmacologic treatment **?** Antidepressants (paroxetine) Psychostimulants (methylphenidate)

Dyspnea

- Prevalence in advanced cancer: 21% -90%
- Contribution from non-cancer related illnesses (COPD,CHF, infection, etc.)
- The only reliable measure of breathlessness is patient self-report
- Respiratory rate, pO2, and pulse oximetry DO NOT correlate with feeling of breathlessness

Most common causes of dyspnea: Airway obstruction, Anxiety, Hypoxemia, Pericardial tamponade, Pleural effusion, Pneumonia, Pulmonary edema, Radiation pneumonitis, Anemia, Metabolic

Management of dyspnea

Treat the underlying cause

- Treat malignancy, if possible
- Identify the reversible causes (bronchospasm, effusion, emboli, hypoxemia, anemia, pneumonia)

Symptomatic management

- Opioids!
- Anxiolytics (dyspnea secondary to anxiety)
- Nonpharmacologic interventions (reassurance, education, environment)
- Oxygen ?
- End-of-life measures (control of secretions, positioning)

The systemic review of the litterature failed to demonstrate a consistent beneficial effect of oxygen inhalation over air inhalation for study participants with dyspnoea due to end stage cancer or cardiac failure. Some cancer study participants appeared to feel better during oxygen inhalation.

- Pulse oximetry not helpful in assesing response – ask the patient!
- Fan/cold air may do just as well
- Therapeutic trial of supplemental oxygen may be benefitial

Cranston JM et al. Oxygen therapy for dyspnoea in adults. Cochrane Database Syst Rev 2008 16;(3).

Major principles of symptom control

- Written instructions are helpful
- Regular assesment of symptoms and modification of treatment is mandatory
- Symptom and QoL assessment tools (FACT-L, LCS scale , QoL questionnaires) are valuable
- Treat all symptoms rather than focus on one !
- Avoid polypharmacy !
- Integrate palliative care into into standard care at initial diagnosis

Early palliative care for patients with metastatic NSCLC resulted in:

- Improved QoL (better FACT-L, LCS scores)
- Improved mood
- Less aggressive end-of-life care
- Longer survival

The Provisional Clinical Opinion

Based on strong evidence from a phase III randomized clinical trial (RCT), patients with metastatic non-small cell lung cancer should be offered concurrent palliative care and standard oncologic care at initial diagnosis. While a survival benefit from early involvement of palliative care has not yet been demonstrated in other oncology settings, substantial evidence demonstrates that palliative care – when combined with standard cancer care or as the main focus of care – leads to better patient and caregiver outcomes. These include improvement in symptoms, quality of life (QOL), and patient satisfaction, with reduced caregiver burden. Earlier involvement of palliative care also leads to more appropriate referral to and use of hospice, and reduced utilization of futile intensive care.

ASCO Guidelines

Clinical Tools and Resources

4. **What's new in pulmology** (Fležar) 17:30-19:00
    - What's new in the diagnosis of lung cancer (Rozman A)
    - mRNA and the Pathogenesis of airway diseases (Petrek M)
    - Hot topics in allergy research (in Slovenia) (P Korošec)
    - Long term systemic glucocorticoid therapy: endocrinologist's concerns (Kocjan T)

Hot topics in allergy research in Slovenia

Prof. Peter Korošec, PhD, CLG, *University Clinic of Respiratory and Allergic Diseases, Laboratory for Clinical Immunology & Molecular Genetics*,
E-mail: peter.korosec@klinika-golnik.si

Venom immunotherapy: side effects and build-up failure

Adverse systemic reactions (SRs) are more common in honeybee venom immunotherapy (VIT) than in wasp VIT. Factors that might be associated with SRs during the honeybee VIT are poorly understood. For that reason we compared the adverse SRs and their severity to various immunological (sIgE, tIgE, basophil CD63 response, baseline tryptase, and skin tests), patient-specific (age, sex, cardiovascular conditions and medications, and other allergic diseases), and sting–specific factors (anaphylaxis severity, time interval to onset of symptoms, and absence of cutaneous symptoms) in patients treated with honeybee VIT. High basophil allergen sensitivity, evaluated as dose-response curve metrics of EC15, EC50, CD-sens, AUC, or the response to submaximal 0.1 or 0.01 µg/ml of venom concentration, was the most significant risk factor and only independent predictor of severe SRs and/or build-up stop (1). There was no important difference in other immunological, patient-specific or sting–specific factors, including the baseline tryptase. None of the studied factors was associated with mild SRs. Overall, high basophil allergen CD63 sensitivity phenotype was a major indicator of severe adverse SRs during the build-up phase of honeybee VIT.

Before honeybee VIT, a cut-off threshold for increased basophil allergen sensitivity should be developed and clinically used to identify patients with a high risk for severe side effects (2). In these high sensitive patients the treatment should started with modified schemes of VIT and in the case of the most severe SR those patients should be co-treated with anti-IgE therapy. The importance of basophil allergen sensitivity was also recently confirmed in other anaphylactic models like peanut allergy (3). Further mechanistic studies are under way, both on the basophils and mast cells, together with colleges from UK (Imperial College London and University of Manchester), to find out what is the currently unknown cellular, genetic or molecular background for this increase allergen sensitivity.

Molecular allergology : improvement of recombinant allergens

We previously showed that routinely used major honeybee venom recombinant allergen rApi m 1 has low diagnostic sensitivity (approximately 70%)(4). This value is much lower than the sensitivities of native or custom recombinant Api m 1 allergen preparations, which have been reported to reach 90%. We demonstrated that the novel commercially available rApi m 1 (Immulite) have a significantly increased diagnostic sensitivity in comparison to currently routinely used rApi m 1 (ImmunoCAP) (5). The use of this novel recombinant allergen would enhanced diagnostic utility of venom recombinants and should improve the dissection of bee and yellow-jacket venom allergy.

Recently, Der p 23 a novel major Dermatophagoides pteronyssinus allergen associated with the peritrophic matrix of mite fecal pellets was identified (6). Together with colleges from Medical University in Vienna, we showed that this novel allergen has the highest allergenic activity of all house dudust mite allergens including Der p 1 and Der p 2. Publications are under way.

The mechanism of long-term pollen immunotherapy protection

An important advantage of allergen immunotherapy as compared to pharmacotherapy for allergic rhinitis is the long-term effect that persists after completing immunotherapy. The mechanism of the sustained effect of allergen immunotherapy is not completely understood. For that reason we conducted a 7-year study of monitoring allergen-specific basophil response and serological markers in subjects with moderate-to-severe grass pollen-allergic rhinitis just before beginning and after up-dosing of subcutaneous grass pollen immunotherapy, before the first pollen season, and 1-2 years after completion of 3-5 years of treatment. We showed that grass pollen immunotherapy induces sustained suppression of the allergen-specific basophil response that persists after completion of treatment and could account for long-term clinical tolerance (7). We also showed that this cellular suppression seems to be associated with persistent blocking activity of IgG antibodies.

Filaggrin mutations in early- and late-onset atopic dermatitis

Atopic dermatitis (AD) is a multifactorial immune-mediated inflammation of the skin that is driven by interactions of genetic and environmental factors. Besides over-reactive adaptive and dysregulated innate immune responses, the most important alterations that lead to the initiation and maintenance of the disease are impaired skin barrier functions. One basic component of the physicochemical barrier is filaggrin (FLG), which may show genetic loss (e.g. FLG loss-of-function

mutations) or decreased expression due to the local cytokine milieu produced by Th2 and Th22 cell subtypes in the skin of patients with AD. Patients who carry FLG mutations have more persistent disease, a higher incidence of skin infections with herpesvirus and a greater risk of multiple allergies and asthma than patients without such mutations. Another distinction between these two groups (FLG mutant and wild-type) can be the different ratio of genetic and acquired factors in the development of AD. Presumably those who carry detectable major genetic risk factors develop clinical signs earlier, but in those patients whose genetic susceptibility is not prominent, and need more environmental exposure. This proposed difference in the pathogenesis between patients with FLG mutant and wild-type AD is strongly supported by our recent study (8), who detected that FLG mutations are associated only with the early-onset form of AD, and not with the late-onset form.

According to our results the development of late-onset AD is not associated with FLG loss-of-function mutations, and therefore other susceptibility genes or acquired factors are more likely involved in the manifestation of skin lesions. These results underline the importance of detailed stratification for age at disease onset in further genetic studies. Another important issue for future investigations will be the precise definition of early- vs. late-onset AD, taking into account the clinical appearance, allergic sensitization, comorbidities and therapeutic approaches. In early-onset AD, specific barrier repair therapies should be emphasized and developed, while in late-onset forms the barrier alterations are more likely the consequences of acquired exposures, such as frequent usage of detergents, increased skin pH, allergens, infections and inflammatory skin microenvironment. In this case anti-inflammatory and nonspecific barrier protective therapies together may be effective.

Hereditary angioedema due to C1 inhibitor deficiency in Slovenia, Croatia and Serbia: novel mutations and genotype-phenotype associations

Hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) is a rare autosomal dominant disease characterized by recurrent life-threatening oedemas and/or abdominal pain, caused by mutations affecting the C1 inhibitor gene, *SERPING1*. We investigate the spectrum of SERPING1 mutations in HAE patients in Slovenia, Croatia and Serbia, together with our colleges from Croatia and Serbia, and further investigate the possible genotype-phenotype association.

A Slovenia nationwide survey identified nine unrelated families with HAE, among whom 17 individuals from eight families were recruited for genetic analyses. Our study identified four novel mutations in the Slovenian HAE population, highlighting the heterogeneity of mutations in the SERPING1 gene causing C1 inhibitor deficiency and HAE (9). In a single patient with HAE a homozygous variant g.566T>C (c.-21T>C) might be responsible for the disease.

In Serbia C1-INH-HAE was diagnosed in 40 patients from 27 families. Disease-causing mutation in SERPING1 was identified in all patients (10). In C1-INH-HAE type I we have identified 19 different mutations. Two mutations were reported for the first time. All C1-INH-HAE type II patients from three families harboured the same mutation. Furthermore, it appears that nonsense, frameshift, large deletions/insertions, splicing defect, and mutations at Arg444, might be responsible for a more severe disease phenotype in comparison to missense mutations, excluding mutations at Arg444.

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5. **Clinical use of biomarkers in asthma** (Škrgat) 9:00-10:30
    - How close / far we are in phenotyping of patients with asthma and what does it mean in clinical practice (Škrgat S)
    - TSLP and periostin in biological material of a patient with asthma (Korosec P)
    - Clinical and immunological aspects of bronchial thermoplastic (Marc M)
    - Lung function and cellular and immunological profile of the airways in the top swimmers (Marčun R)

Biologic therapy in asthma and clinical role of biomarkers

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Introduction: Severe difficult-to-control asthma represents a small minority of the whole asthmatic population but this subset of the disease has a major impact on the direct and indirect asthma healthcare costs and the overall burden of asthma. Although most asthmatics can be managed with a combination of anti-inflammatory drugs and bronchodilators, patients who remain symptomatic despite maximum combination treatment represent a complex and heterogeneous group of patients. Our current understanding of the immune pathology of asthma has identified multiple mediators as potential therapeutic targets, and these are currently under development.

Targeting the Th2 pathway

To date, most of monoclonal antibodies have focused on the Th2 asthma phenotype (e.g., interleukin-4, interleukin-13, and interleukin-5), since these proteins are thought to be major drivers of the inflammatory component of asthma. New therapies in the form of humanized antibodies against these Th2 targets have shown encouraging results.

Up until now, the first and as yet only biological agent licensed for the treatment of asthma is omalizumab, specifically for severe allergic asthma. **Omalizumab** is a humanized monoclonal antibody that binds to the Fc of free IgE molecules, reducing free circulating IgE and blocking its binding to the receptors present on mast cells, basophils, and dendritic cells, which prevents inflammatory cells from releasing mediators when in contact with allergens. Omalizumab decreases the density of FcεRI and FcεRII expression on basophils, mast cells, and dendritic cells, and decreases airway inflammation. A reduction in expression of FcεRI on dendritic cells and its binding to IgE may decrease the allergen presentation processIt has a steroid sparing effect. We have had experience in omalizumab treatment of 44 severe asthma patients since 2007 in Slovenia. As in other reports we have demonstrated a reduction in the rate of asthma exacerbation, improvement in asthma control and the quality of life.

Mepolizumab is a humanized monoclonal antibody against IL-5 and selectively and effectively inhibits eosinophilic inflammation in the airways. it is reasonable to consider anti–interleukin-5 therapy for patients with severe asthma who are receiving high doses of systemic glucocorticoids and who continue to have an elevated eosinophil count in sputum or blood regardless of their atopic status. Although persistent blood eosinophilia may be sufficient to identify patients who are likely to have a response to this treatment, whether this biomarker is sufficient or is as effective as airway eosinophilia in monitoring the response to treatment remains to be seen.

Lebrikizumab anti IL-13. Interleukin-13 induces bronchial epithelial cells to secrete periostin, a matricellular protein. It increases the migration and survival of eosinophils and increases the production of mucus by inducing goblet cell hyperplasia. Lebrikizumab is a humanized monoclonal antibody that targets IL -13. Studies of anti IL-13 have shown mixed results. Treatment with lebrikizumab reduced the rate in of asthma exacerbations, which was more pronunced in the periostin high patients than in the periostin low patients. Similar effect was seen in lung function tests, measured through FEV1. But despite these improvements, lebrikizumab treatment did not lead to clinically meaningful placebo corrected improvements in asthma symptoms and quality of life.

Non-Type 2 Biologic approaches

Approximately half of all asthmatic patients do not have evidence of Type 2 inflammation. Type 2 low asthma is currently defined as the apparent absence of type 2 cytokines. This non Th2 group is poorly defined, clinically heterogenous, and without specific biomarkers, making molecular phenotyping and targeted therapy approaches difficult. Some might lack type 2 inflammation because corticosteroids have substantially reduced that pathway. Non type 2 patients generally have adult onset disease, often in association with obesity, postinfectious, neutrophilic and smoking related factors, and are less likely to be atopic/allergic. Among possible targeting options TNF□, anti ILRA brodalumab are under investigations. Some data indicate, that azitromycin could be beneficial in patients with noneosinophilic severe asthma.

The role of biomarkers in asthma phenotyping

Research efforts are now focusing on elucidating the phenotypes Th2- high or Th2-low. There is an increasing need to use biomarkers to indicate the group of patients who will be a responder to a targeted treatment.

Biomarkers

Type 2 molecular phenotypes

Biomarkers are needed to target type 2 therapies to the correct patients. Type 2 biomarkers identified to date include periostin, fraction of exhaled nitric oxide (FeNO), and sputum/blood eosinophils. In a

study of Bobolea and coworkers, periostin levels in sputum were associated with persistent airflow limitation, but were similar in Th2 high and Th2 low patients. On the other hand the study of Jia and coworkers showed that serum periostin was a good predictor of airway inflammation. Mean periostin levels were significaly higher in eosinophil high as compared to eosinophil low subjects. Periostin was also the best predictor of sputum and tissue eosinophilia, showing superiority to blood eosinophils, IgE and Fe NO.

Treatment guided by sputum eosinophils reduces the frequency of asthma exacerbations. Unfortunately, sputum induction and differential sputum cell counts are only feasible in specialised clinics, not always successful and do not give immediate results. Sputum eosinophilia is defined as 3% of eosinophils or more in sputum cell count. A blood eosinophil cut off of > $0.15X10^9$ cells/L was introduced to detect eosinophilic asthma and to predict reduction in asthma exacerbation. According to study results of Westerhof et al, FeNO and blood eosinophils had comparable diagnostic accuracy to detect sputum eosinophilia irrespective of asthma fenotype such as obese and nonobese, atopic and nonatopic, ex smoking and never smoking and severe and mild to moderate asthma patients. In future clinical practice both markers, preferably in combination, may become the preferred method to access eosinophilic airway inflammation and to guide targeted treatment in adult asthma patients with different phenotypes. In the same study, total IgE was less accurate in detecting sputum eosinophilia in atopic and obese patients than in nonatopic and nonobese patients.

Noneosinophil asthma has been defined as asthma with a sputum eosinophil count of less than either 2 or 3%, whilst neutrophilic inflammation has been defined with cut off points varing from 60-76%. Noneosinophilic asthma was in fact the most predominant form of disease in many described asthma cohorts, and neutrophilic asthma constituted around 20%.

Conclusion: A multidisciplinary team is needed to do a good asthma fenotyping and choosing the right biologic therapy for severe asthma patients. Asthma register and asthma network are good tools in this approach and follow up of these patients.

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TSLP and periostin in biological material of patients with asthma

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TSLP (Thymic Stromal LymphoPoietin)

TSLP, which was discovered as a growth factor for lymphocyte progenitors, is now recognized as a protein released primarily from epithelial cells in response to irritating stimuli. It initiates signaling pathways leading to inflammation driven by type 2 helper T (Th2) cells. Zhou et al. (1) have first demonstrated a critical role for TSLP–TSLP receptor interactions in promoting inflammation in animal models of airway hyper responsiveness. Different recent studies confirmed Zhou observations. For example, a recent study using a murine model of HDM-induced allergic inflammation in the lung demonstrated that TSLP blockade ameliorates disease (2). In support of its role in human asthma, gain-of-function polymorphisms in TSLP have been associated with asthma and allergic airway disease in patients. Furthermore, TSLP signaling was shown to promote asthmatic airway remodeling pathways in human lung fibroblasts, and its expression was found to be significantly increased in bronchial biopsy specimens from patients with severe asthma (3).

In 2014 Gauvreau et al. (4) have showed that 5 to 12 weeks of treatment with a humanized monoclonal antibody (AMG 157) against a TSLP, blunted asthma attacks evoked by the inhalation of allergens. In this study, the investigators used the most predictive model for the assessment of drug effects in asthma, allergen bronchoprovocation. Importantly, anti-TSLP antibody blocked both the early and late asthmatic responses. How do we explain that? It is unlikely that TSLP is released directly in response to the actual allergen challenge, and TSLP does not contract airway smooth muscle. Previous trials targeting interleukin-4 or interleukin-13, two downstream cytokines induced by TSLP, have been found to be effective in allergen challenge or treatment trials. Thus, it is likely that the anti-TSLP treatment indirectly inhibited such pathways; this likelihood is supported by the observed reduction in the number of eosinophils in induced sputum and the level of nitric oxide in exhaled air. As the authors point out, it is unclear whether the reduced eosinophil numbers are responsible for the inhibition of the allergen-induced responses or whether such a reduction follows another event explaining the protective effect. These results also indicate that there are two fundamentally different ways to inhibit allergen-induced asthmatic responses. Whereas direct antagonism of mast-cell mediators may block the acute response, long-term inhibition of regulatory networks appears to inhibit allergen responses by reducing the mechanisms that sustain the immunologic and inflammatory processes. These findings raise the question of whether TSLP is a master switch in the signaling between airway epithelium and other inflammatory cascades or whether it is part of a concerted action by several parallel pathways (e.g., those involving interleukin-33, interleukin-25, and interleukin-17).

TSLP also regulates basophil development and peripheral basophilia (5). Critically, TSLP-elicited basophils exhibited distinct phenotypic and functional characteristics from classical IL-3–elicited basophils. Most notably, they lacked the ability to degranulate in response to IgE-mediated FcεRI signaling but were potent producers of IL-4 in response to IL-3, IL-18, or IL-33 stimulation (5). These observations provoke the hypothesis that there TSLP-elicited, IgE-independent basophil responses that might contribute to inflammation in some asthmatic patients. Interestingly prior studies have shown that asthmatic patients exhibit phenotypically distinct basophil populations in the peripheral blood, some of which respond robustly to IgE-mediated activation, whereas others are minimally responsive (6). As such, uncovering the precise roles of IgE-activated versus TSLP-activated basophils might help to clarify the complex inflammatory mechanisms that underlie asthma.

We have recently analyzed serum TSLP concentrations in 41 stable asthmatic patients, 24 COPD (12 stable and 12 during exacerbation) and 14 healthy controls. Asthma patients have significantly higher systemic TSLP concentrations (median 203 pg/ml) comparing to patients with COPD (median 34 pg/ml) and comparing to healthy controls (median 44 pg/ml). There was a trend of higher TSLP concentration in uncontrolled asthma and in smokers with asthma in comparison to controlled asthma, but the differences did not reached statistical significance (Fig 2). The ROC curve analysis between patients with asthma and COPD showed a high AUC of 0.88. In addition there was no difference between stable and exacerbated COPD patients. Our results suggest that TSLP is a systemic asthma biomarker and that might represent an immunological tool in differential diagnosis in obstructive lung disease. Further studies are needed to confirm these interesting results.

Periostin

Microarray studies of gene expression in the airway epithelium of asthmatic patients have shown a greater than four-fold increase in periostin compared with healthy controls making periostin among the most highly expressed genes in asthma (7). Periostin in human bronchial epithelial cells and lung fibroblasts is inducible by IL-4 and IL-13. Periostin, secreted by the airway epithelial cells in response to stimulation by IL-4 and IL-13, has been shown to have downstream effects of mediating collagen synthesis and fibrillogenesis by binding collagen and activating transforming growth factor beta (TGF-β). It was demonstrated that periostin, secreted basally by the airway epithelial cells in response to IL-13, has autocrine effects on epithelial cell function, including activation of TGF-b and upregulation of collagen as well as TGF-b-mediated activation of fibroblasts. Thus, periostin may contribute to the mechanisms of airway remodeling in asthma. Importantly patients with high pretreatment levels of serum periostin had greater improvement in lung function with anti-IL13 treatment than did patients with low periostin (8).

Jia et al. (9) identified serum periostin as a systemic biomarker of airway eosinophilia in severe, uncontrolled asthmatics. No other study confirmed these observations. More recently, a study by Kanemitsu et al. (10) demonstrated that high serum periostin levels (>95 ng/ml) were associated with a decline in FEV1 of at least 30 ml per year in patients receiving inhaled corticosteroids

We have also recently analyzed serum periostin concentrations asthma patients and found an increased periostin in about 30% of controlled asthma patients and in about 15% of uncontrolled asthma patients. Despite the recent evidence supporting a potential role for periostin as a biomarker much work remains to better clarify the potential utility of periostin in both clinical research and clinical practice.

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Clinical and immunological aspects of bronchial thermoplasty

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Introduction

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation in which the two key features are a history of variable respiratory symptoms and evidence of variable expiratory airflow limitation.

Chronic inflammation involving several inflammatory cells and multiple mediators results in characteristic pathophysiological changes of the airways and is strongly associated with airway hyper-responsiveness and asthma symptoms. A**irway hyper-responsiveness** is one of the most recognized pathophysiologic features in asthma. It results due to excessive contraction of hyperplastic and hypertrophic airway smooth muscle, thickening of the airway wall by oedema and structural changes (features of more pronounced angiogenesis and remodelling) and exaggerated constriction due to activation of airway cholinergic nerves. **Remodelling** and chronic inflammation are most probably tightly connected processes, it is presumed that remodelling is a consequence of long term chronic inflammation, but some studies are suggesting the independent role of the remodelling.

The current asthma therapy is mainly targeting different processes in inflammatory cascade (non-specific anti-inflammatory effects of corticosteroids, anti IgE, anti-IL5). Bronchial thermoplasty (BT) is so far the only approved asthma therapy that directly influences remodelling. There are quite convincing reports from randomized studies about the clinical improvement after treatment, but exact mechanisms that are the basis of beneficial outcome in asthma patients are not completely understood. Some animal and human studies clearly showed that BT resulted in structural changes of the airway wall. There are only scarce reports on the effects of BT on immunologic response and a lot still has to be explored.

Inflammation in asthma

The most prominent inflammatory cells in asthmatic airways are activated mast cells, eosinophils and T cells (especially T helper 2 lymphocytes – Th2). **Mast cells** activate bronchoconstriction by releasing potent mediators: histamine, cysteinyl leukotrienes and prostaglandin D2. **Eosinophils** may apart from releasing pro-inflammatory cytokines and chemokines directly damage airway epithelial cells and can further influence airway remodelling by releasing growth factors (TGFβ).

T lymphocytes seem to be the key orchestrating cells in asthma. Activated **Th2** cells stimulate eosinophilic inflammation and IgE production by B lymphocytes by producing cytokines IL4, IL5, IL9 and IL13.

There are many mechanisms that regulate Th2 activation in asthma. Dendritic cells (DC) are elevated in asthma patients and differ in cytokine, prostaglandin (PG) and chemokine synthesis. They stimulate T cells to produce IL4, high amounts of PGE2, which decreases IL12 and increases CCL17, CCL22, all causing the promotion of Th2 cell differentiation and recruitment. Recently thymic stromal lymphopoietin (TSLP) has emerged as a key mediator, which promotes DC-induced Th2 differentiation. On the other hand, the Th2 cytokine IL-4 reduces Fas ligand (FasL), while Th1 cytokines IFNg, TGFβ and IL-2 increase FasL expression. As a result Th2 cells express less FasL and are more resistant to apoptosis than other T cell subtypes. The latest also plays an important role because FasL expressing T cells are pivotal during the resolution of airway inflammation.

Th17 cells also play an influential role in asthma pathogenesis particularly in asthmatics with severe disease who fail to respond to corticosteroid treatment. They primary stimulate the recruitment.of neutrophils and also eosinophils (IL17, IL22, IFNγ). Further they can be also involved in remodelling by stimulating goblet cell hyperplasia, mucin expression, activate and promote expansion of fibroblasts and have direct effect on bronchial smooth muscle cell contractility (Il13). Th17 differentiation is stimulated by IL6, IL 23 and TGFβ.

Apart from inflammatory cells also **structural cells** of the airways release many chemokines and cytokines that are important mediators in asthma inflammation. Airway epithelial cells and smooth muscle cells release multiple cytokines, chemokines and lipid mediators involved in asthma inflammation, symptoms and remodelling.

Remodelling in asthma

Airway remodelling consists of epithelial injury, goblet cell hyperplasia, sub-epithelial layer thickening, hyperplasia and activation of airway smooth muscle and angiogenesis. It is present also in early stages of asthma, so it can develop early in asthma pathogenesis and may play role in disease progression in some asthma patients. Triggers of remodelling are not clear. Previously it was thought

that chronic inflammation was responsible for remodelling but the two processes can occur as two separate aspects of asthma disease. Some of Th and eosinophilic cytokines have potent remodelling properties (TGFβ, IL 5, IL11, IL 17). There are some reports of possible negative effects on airway remodelling by corticosteroids, anti-IgE, anti-IL5, anti-IL13, anti-IL25 and anti-VCAM-1, but according to current knowledge no pharmacologic treatment can efficiently influence this process, the irreversible airway obstruction developed despite regular recommended asthma treatment. The progression of airway remodelling could be a consequence of structural and functional changes in the airways due to abnormal injury and repair of the airway tissue, so strategies for preventing acute exacerbations that can cause these features could be the important issue.
Airway smooth muscle cells (ASM) which are hyperplastic and more activated in asthma airways are not just responsible for excessive bronchoconstriction. They have also a regulatory role. ASM are highly productive cells. Among many other inflammatory and angiogenetic mediators they produce IL2, IL5, IL6, IL8, IL10, VEGF, EGF, IFNγ, angiogenin, βFGF. So, they are capable of stimulating abnormal inflammatory response, angiogenesis and finally influencing remodelling. Targeting ASM cell to reduce its activity may act with double potential. First, it has the potential to diminish airway contraction by reducing numbers of ASM cells. Second, reduced numbers of ASM cells will reduce the secretion of inflammatory and angiogenetic mediators with profound beneficial effects.
Other structural cells that are involved in airway remodelling **are fibroblasts and myo-fibroblasts** by producing connective tissue components that are involved in this process (collagens, proteoglycans).

Bronchial thermoplasty (BT), technique, safety
BT is recommended as a potential non-pharmacologic treatment option for highly-selected adult asthma patients who remain symptomatic despite appropriate use of recommended therapeutic regimens and referral to an asthma speciality centre (GINA and British thoracic guidelines, evidence B).

BT is a treatment that involves 3 separate bronchoscopic procedures performed 3 weeks apart. The basis of BT is application of radiofrequency energy to airways as small as 3 mm, creating heat using a catheter connected to a radiofrequency generator. The expected result of the delivered heat to the airways is a reduction of airway smooth muscular mass, which is believed the basis for symptomatic improvement. BT is currently the only asthma therapy approved by FDA that directly targets airway remodelling.

Safety studies have demonstrated that this is a safe procedure without evidence of scarring or stenosis in the airway after the procedure. Because of the potential peri-and post-operative complications (mild to moderate asthma exacerbation) patients need to be chosen carefully and followed closely afterward. BT is indicated in uncontrolled adult asthma patients despite regular use of high dose inhaled corticosteroids and long acting bronchodilators. Post bronchodilator FEV1 in stable phase should be higher than 60%. The patients shouldn't smoke in a year before the procedure and shouldn't smoke more than 10 pack-years in their life-time.
Contraindications to BT are known intolerances to medication used during bronchoscopy, relevant comorbidities which might increase the risk of peri-interventional complications, pacemaker or defibrillator, acute infection or asthma exacerbation, or need for continuous of more than 8mg metil-prednisolon daily use.

BT - Histologic and immunologic aspects
Preclinical studies have shown that BT results in a **reduction in ASM** as well as airway hyper-responsiveness in an animal model. Further, studies using animal tissues exposed to high temperatures suggest that BT may cause disruption of actin-myosin interaction with an immediate loss of ability of the part of the ASM to generate a mechanical response. The immediate response is followed by induction of cell death over the next 1-24 hours, and a marked long term reduction in ASM mass over the following weeks and months due to increased apoptosis, necrosis and disruption of ASM proliferation and migration. The result is widening of the airways and diminished ability of active constriction. Considering a fact that ASM is a source of many inflammatory mediators a result of BT may also be attenuation of the airway inflammation.
In first human trial that included nine cancer patients with lobectomy of previously treated lobe a 50% reduction in the ASM mass after BT was shown. Apart from the effects on ASM BT was shown to **reduce the amount of vascular smooth muscle mass**.

Published results of the studies observing the inflammatory response following BT are scarce. There is a report of histologic findings in post-BT biopsies of three severe asthma patients. Its results showed a decreased smooth muscle mass after BT, but focusing on submucosal eosinophilic infiltrates the results were inconsistent.
Another published study of 11 BT treated patients with severe asthma showed significant changes in airway inflammation in the first weeks after treatment. They showed a substantial decrease of inflammatory mediators **TGFβ1** and **RANTES/CCL5** in bronchoalveolar lavage (BAL) fluid 3 and 6 weeks post BT in all patients. Further, the cytokine tumor-necrosis-factor-related apoptosis-inducing ligand **(TRAIL**), which induces apoptosis in several cell types, was increased in concentration both 3 and 6 weeks post bronchial thermoplasty.

There are no published studies measuring T cells or other inflammatory cells or cytokine levels after BT. Preliminary results of different T cell phenotypes in BAL of four treated asthma patients at our clinic didn't show any convenient effect of BT on T cell subtypes, activation or differentiation.

BT clinical aspects
The positive clinical effects of BT were confirmed in many studies. As the ASM decreases the expected consequence is diminished airway hyper-responsiveness, which was also shown to happen on animal models. Further, less symptoms and decreased rate of severe exacerbations are expected.

The first prospective study of BT in mild to moderate asthma patients resulted in a significant reduction of symptoms and a significant reduction of the bronchial hyper-responsiveness even 24 months after treatment. The first randomized AIR study of patients with moderate asthma showed less symptoms and less minor asthma exacerbations in the treated group. The results of double blind randomized study AIR2 which included 288 patients clearly showed the clinical benefits of BT with 32% less severe exacerbations, 84% less emergency department visits, 66% less days lost from work, school or activity, 73% less hospitalizations and better quality of life (AQLQ – asthma quality of life questionnaire) in the treated group. The positive effects of BT were clearly shown also in severe asthma patients included in RISA trial. The BT group showed a persistent improvement in symptoms as well as a decrease in use of rescue medication, more patients weaned off their oral steroids during the study.
In the 2 to 5-year follow-up period after BT in patients with mild, moderate or severe refractory asthma there was a clear absence of clinical complications based on acute exacerbation reporting, health care utilization events, and the maintenance of stable lung function (no deterioration of FEV1). There were no observed structural changes in bronchial wall or lung parenchyma. Results support the long-term safety of BT for at least 5 years in patients with severe refractory asthma.

Four patients with uncontrolled asthma who were treated with BT at our clinic in the period from Nov 2013 till March 2014 reported less exacerbations in the following year after the treatment and minor to moderate improvement in symptoms.

Conclusion
Bronchial thermoplasty is an effective treatment for carefully selected uncontrolled asthma patients. The treatment is invasive and needs special equipment and skills, but has significant effect on the structural cells of the airway wall, remodelling, probably also influences inflammatory response, and offers long-term beneficial clinical effects with minor side effects.

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Dihalne poti pri vrhunskih plavalcih / Airways in ellite swimmers

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Vpliv bazenske vode na dihala

S plavanjem začno otroci relativno zgodaj, nekateri že kot dojenčki. Večinoma ga izvajamo v zaprtih vodah, kjer je zaradi zagotavljana mikrobiološke neoporečnosti potrebno kloriranje vode. Namenjeno je uničevanju in preprečevanju razmnoževanja povzročiteljev okužb. Pri kloriranju bazenske vode nastanejo dezinfekcijski produkti. Najpomembnejši so kloramini (npr. trikloramin) in trihalogenmetani(npr. kloroform). Kloramini nastanejo, ko reagira v vodi klor z urinom in znojem. Te spojine povzročajo tipičen bazenski vonj. Povzročajo draženje očesne veznice in konjuktivitis. Trihalogenmetani ali haloformi nastanejo kot stranski produkt kloriranja vode. Najbolj znan predstavnik je kloroform, ki je netopljiv v vodi in prehaja v bazenski zrak. Zato je koncentracija kloroforma v pokritih višja kot v odprtih bazenih. Kloramini in triklorhalogenmetani lahko dražijo dihalne poti in povzročijo vnetno reakcijo. Nekatere študije kažejo na to, da vsakodnevna večurna izpostavljenost bazenu poveča riziko za bronhitis, astmo in alergije, kar lahko ima pomembne implikacije pri plavalcih, predvsem pri mlajših osebah. Po drugi strani so poznane raziskave, ki vzpodbujajo redno telesno aktivnost, vključno s plavanjem, pri bolnikih z astmo. Večina študij je pokazala, da plavanje nima negativnega vpliva na astmo. V nekaterih študijah celo dokazujejo, da je redno plavanje znižalo incidenco astme pri otrocih.

Z naporom sprožena bronhokonstrikcija

Poleg klora in klorovih spojin, lahko bronhokonstrikcijo pri plavanju sproži tudi napor. S telesnim naporom sprožena bronhokonstrikcija je opredeljena kot prehodno, reverzibilno zoženje spodnjih dihalnih poti, ki sledi fizični aktivnosti. Zgodi se v prisotnosti ali odsotnosti klinično prepoznane astme. V tuji literaturi se uporablja izraz exercise-induced bronchoconstriction (EIB). Termin z naporom sprožena astma (exercise induced asthma) se ne uporablja več, saj telesna aktivnost ne »povzroča« astme, ampak sproža bronhokonstrikcijo. Z naporom sprožena bronhokonstrikcija je odraz preodzivnosti dihalnih poti in je pogosto prvi znak astme, pa tudi znak, ki zadnji v vrsti izzveni po poslabšanju astme. Z naporom sprožena bronhokonstrikcija se pojavi pri do 90% bolnikov z astmo in pri 40% tistih, ki imajo alergijski rinitis. Posamezniki s težjim potekom in neurejeno astmo imajo imajo z naporom povzročeno bronhokonstrikcijo pogosteje kot tisti bolniki, kjer je astma urejena ali je potek bolezni lažji. V splošni populaciji je prevalenca z naporom sprožene bronhokonstrikcije 7-20%. Pri športnikih, pri katerih je ta delež višji (okoli 50%) pa je prevalenca odvisna od vrste športa, okoliščin, kjer se šport izvaja in ravni maksimalne obremenitve.

Z naporom sprožena bronhokonstrikcija se pojavi zaradi izgube vode iz dihalnih poti, ki je posledica gretja in vlaženja velikih volumnov zraka v kratkem času. Glavna determinanta za težo odgovora dihalnih poti je vsebnost vode v vdihanem zraku in raven ventilacije med telesnim naporom.

Preden vdihani zrak doseže spodnje dihalne poti se mora v fizioloških pogojih ogreti in navlažiti (37 stopinj celzija in 44 mg H2O/L). Do kakšne mere se bo vdihani zrak ogrel in navlažil je odvisno od temperature in vlažnosti vdihanega zraka ter od minutne ventilacije posameznika.Toplota in vlaga prehajata iz mukoze v vdihani zrak zaradi temperaturnih in tlačnih gradientov. Med tem procesom poteka ohlajanje dihalnih poti. V mirnem dihanju se zrak ogreje in navlaži že v zgornjih dihalnih poteh, torej ko prehaja mimo nosne sluznice. Pri telesnem naporu se minutna ventilacije poveča tudi preko 30 L/min, način dihanja se spremeni iz dihanja preko nosu na dihanje preko odprtih ust. Na ta način pri povečani ventilaciji prehaja v spodnja dihalna pota premalo vlažen in topel zrak, potrebno vlaženje in gretje zraka tako prevzamejo spodnja dihalna pota.

Na epitelij spodnje dihalne poti se prilega tanka plast vode, ki predstavlja takojšnji vir vlaženja vdihanega zraka. Epitelij ima vlogo absorbcije med mirnim dihanjem, med povečanjem ventilacije pa prevzame funkcijo sekretorne površine zato, da nadomesti primanjkljaj v vodni plasti. Osmolarnost vodne plasti je 290 do 320 mOsM, vsebuje natrij, klorid, kalij in kalcijeve ione. Med povečanjem minutne ventilacije preko 40 L/min grozi dehidracija in povečanje osmolarnosti vodne plasti epitelija. Hitro nadomeščanje vode se zgodi s kondenzacijo vode iz izdihanega zraka, ki prihaja iz alveolov in je zato toplejši kot mukoza dihalnih poti. Drugi mehanizem nadomeščanja vode je preko osmotskega gradienta iz bronhialne cirkulacije do površine epitelija dihalne poti z namenom vzpostavljanja normalne osmolarnosti. Kljub tem homeostatskim mehanizmom pa matematični modeli ocenjujejo, da se iz spodnjih dihalnih poti izgubi okoli 40% vode v minuti v temperaturnih pogojih med 22- 26 stopinj celzija, 40% vlažnosti in ventilaciji 60L/min.

Opisana izguba vode na nivoju dihalne poti kot odgovor na povečano ventilacijo je ključni začetni stimulus za nastanek z naporom sprožene bronhokonstrikcije.

Patofiziologija z naporom sprožene bronhokonstrikcije

Pri razlagi mehanizma z naporom sprožene bronhokonstrikcije obstajata tve teoriji: termalna in osmotska teorija.
Termalna teorija temelji na razlagi, da ohlajanje dihalnih poti ob izparevanju vode povzroča vazokonstrikcijo bronhialnega žilja. Pri ponovnem segrevanju pa prihaja do zoženja dihalnih poti zaradi mehaničnih razlogov: ponovna polnitev žilja, povečana prepustnost žilja in edema stene dihalne poti. Teorija torej temelji na vaskularnem dogodku, ki naj ne bi bil vezan na sproščanje mediatorjev ali kontrakcije gladke mišice.
Nasprotno pa osmotska teorija temelji na ideji, da je primarna motnja povečana osmolalnost v tekočinski plasti epitelija, ki pa zajame tudi epitelijske celice in submukozo. Hiperosmolarno okolje aktivira in spodbuja celične mehanizme k sproščanju različnih mediatorjev. Mediatorji vključno z levkotrieni in prostanglandini nato sodelujejo pri vnetju dihalne poti in okvari respiratornega epitelija. Dodatni mediatorji, ki prispevajo k brohokonstrikciji sproženi z naporom izhajajo iz senzornih živčnih končičrv dihalnih poti. Slednje aktivirajo levkotrieni, po aktivaciji sproščajo nevrokinine, ki končno povzročajo bronhokonstrikcijo.
Poškodba dihalne poti predstavlja naslednji mehanizem, ki igra pomembno vlogo pri razvoju z naporom sprožene bronhokonstrijkcije pri vrhunskih atletih. Med intenzivno vadbo, ki se ponavlja in je dolgotrajna postanejo mala dihalna pota tista, ki morajo prevzeti vlogo vlaženja in gretja zraka. Zaradi dehidracijske okvare dihalnega epitelija se vklopijo mehanizmi popravljanja: povečana prepustnost drobnega žilja in eksudacijo plazme. Poleg tega se verjetno spremenijo kontraktilne lastnosti gladke muskulature, ki postane bolj občutljiva na stimuluse zaradi ponavljajočega izpostavljanja produktom plazme. Ta tip okvare lahko pojasni preodzivnost dihalnih poti za metaholin pri atletih, ki trenirajo v hladnem okolju. Bronhialna preodzivnost te vrste lahko izzveni po prenehaju intenzivnih treningov. Pri tem tipu okvare tako verjetno ne prihaja do preoblikovanja dihalnih poti in stanje kot kaže ni predispozicija za nastanek kronične bolezni.

Dihalne poti pri plavalcih
Pri tekmovalnem plavanju imamo dva možna mehanizma, ki lahko povzročata bronhokonstrikcijo, napor in klorove spojine v bazenski vodi in zraku. To področje patogenetsko ni raziskano V literaturi so še vedno nasprotujoči podatki o pomembnosti enega in drugega mehanizma. Naša študija, ki je trenutno v zaključni fazi, želi odgovoriti na vprašanje, kaj se dogaja v pljučih tekmovalnih plavalcev na celičnem in imunolškem nivoju, kakšne so razlike pri plavalcih, ki so izpostavljeni različnim koncentracijam klorovih spojin in različni intenziteti treninga.

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6. **Immunotherapy** (Zidarn) 11:15-12:45
    - Guidelines for immunotherapy with inhaled allergens (Eržen R)
    - Overview of immunotherapy in Slovenia (Košnik M)
    - Compliance with the treatment of patients on immunotherapy (Rezelj M)
    - Immunotherapy and atopic dermatitis, food allergy and oral allergy syndrome (Lalek N)
    - Immunotherapy in the elderly (Kopač P)

Sublingual immunotherapy

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Specific immunotherapy is a treatment method in which an allergen is administered to a patient in order to achieve immune tolerance. It has traditionally been performed by a subcutaneous injections of allergen. In recent years sublingual immunotherapy (SLIT) is developed which is user friendly, carries much lower risk of serious side effects so it could be performed at home.

The first SLIT randomized trial was published in 1986. In 1998 SLIT was firstly accepted as an alternative to SCIT in the WHO position paper.

Immunotherapy is the only treatment that alters the abnormal immune response underlying allergic disease. The precise mechanism of action is still not fully understood. The allergen may be retained within the oral mucosa for several hours after sublingual administration and thus enable local and systemic effects on the immune system. Local mechanismis including enhanced production of IL - 10, TGF - β and activins may play a role in the maintenance of oral tolerance. Within first weeks of SLIT increase of sIgE concetration is observed, followed also with the increase in sIgG4 concentration. The mechanism of succesful immunotherapy is likely to involve induction of IL-10 producing regulatory T lymphocytes and switch from Th2 to Th1 immune response.

Moderate to severe allergic rhinoconjunctivitis with or without asthma is the main indication for SLIT. Patients with asthma as the sole manifestation of respiratory allergy could benefit from SLIT, but more studies are needed. SLIT might have positive effects in selected sensitized patients with atopic dermatitis.

To be eligible for SLIT patient must have a clinical history of the disease, proven IgE sensitization to an allergen either with skin prick tests or with serologic tests, and clear relationship between symptoms and exposure to an allergen to which the patient is sensitized. Relevant allergens are of crucial importance for the efficacy and safety of immunotherapy. Monosensitized patients are ideal candidates for SLIT, but single allergen SLIT may be effective also in polysensitized patient.
Failure of pharmacological treatment is a frequent provoking factor for introduction of SLIT. Candidates for SLIT are also patients experiencing side effects of the pharmacological treatment and those who refuse long term pharmocotherapy or injections. SLIT may also be considered as an initial treatment.

Contraindications for SLIT are medical conditions where SLIT could provoke worsening of the concomitant disease or more frequent and severe side effects are expected. They include severe or poorly controlled asthma and serious cardiovascular diseases, autoimmune disorders, malignant neoplasias and acquired immunodeficiencies. SLIT should be administered with caution to patients receiving beta-blockers or angiotensin-converting enzyme inhibitors. Uncomplicated SLIT is not terminated during pregnancy, but we do not initiate SLIT in a pregnant woman.

In SLIT allergen in the form of tablet or drops is administered sublingually, held under the tongue for 2 minutes and the rest is swallowed. Administration should take place in fasting condition (or food should be avoided at least 5 minutes after the administration of an allergen) and at the same hour every day.
In the case of persistent rhinoconjunctivitis the allergen is applied daily for consecutive 3 years. The build up phase in which the allergen dose is gradually increasing to a maintenance dose is performed under medical supervision and then administration continues once daily and is self-administered by the patient at home. Thera are different schemes for the build up phase (rush, ultra rush...) with no difference in the frequency of side effects between them.
In the case of intermitent rhinoconjunctivitis the treatment is typically initiated 12 to 16 weeks prior to the allergen season and maintained through the end of the pollen season. Immunotherapy is thus performed pre-seasonally and co-seasonally during three consecutive years.

Dose modification is required in the case of persistent troublesome local side effects, antihistamines could also be helpful in that case. Oropharyngeal infection, major dental surgery, acute gastroenteritis, asthma exacerbation, PEF < 80% of personal best value and simultaneous viral vaccination are situations in which administration of allergen should be postponed.

SLIT is self-administered at home, so patients should have written instruction about their action concerning side effects.
Local side effects are very frequent (affecting up to 75% of patients), but usually mild, resolve spontaneously and requires no dosage modification. They include itching, swelling of the lips or mucosa under the tongue. Occasionally tongue edema or oropharyngeal edema occur. Systemic side effects are extremely rare, small number of cases have been reported.

SLIT is terminated after 3 -5 years of administration if the patient is asymptomatic or has mild symptoms for two consecutive years. Poor compliance with the treatment, appearance of any contraindication during treatment, persistent troublesome local side effects or repeated systemic side effects should also result in the termination of SLIT. We terminate SLIT also in the absence of a clinical response to the treatment after 2 years.

Many clinical studies have consistently shown that AIT can achieve substantial clinical results by improving nasal and ocular symptoms and by reducing medication need. AIT also improves quality of life, prevents progression of AR to asthma, and reduces new sensitizations. Clinical efficacy persists after discontinuation of AIT.

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Organisation of immunotherapy in Slovenia

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Introduction: Allergen immunotherapy (IT) is a unique mode of treatment of IgE mediated allergic diseases. It is very efficient in appropriately selected patients, but also time consuming and requires many outpatient visits. Thus proper patient selection and convenient accessibility are prerequisites for successful outcome of IT. An obligatory prerequisite for performing IT is patient's safety. Thus IT should be performed by specially trained medical teams, who knows contraindications and precaution measures for immunotherapy, have ability to monitor patients and manage possible side effect, particularly anaphylactic shock.
The aim of the article is to present the network of IT services for adult patients in the country.
Methods: Members of Slovenian Association of Allergy and Clinical Immunology were sent a questionnaire. They were asked, whether they perform allergy skin prick and epicutaneous tests and IT. In the case of positive answer, they were asked about the number of patients treated, allergens used and the mode of IT (subcutaneous-SLIT or sublingual-SLIT). Where allergists work in a group (like hospitals), they sent cumulated data for the whole group.
Results: 26 answers were received. Detailed data are presented in the table 1. All 26 perform skin prick tests (SPT). Allergens used are Stallergen and HAL. 4 perform epicutaneous tests, using HAL allergens. At two locations epicutaneous tests are performed at the dermatology department.
23 perform IT: 22 with inhalant allergens (10 SCIT, 20 SLIT). Beside pollens and house dust mite, 4 perform also IT with animal allergens and 2 with moulds. Total number of patients treated is as follows: pollen 331 SCIT, 564 SLIT; House dust mite 104 SCIT, 241 SLIT; animal dander and moulds: 11 patients, majority SLIT.
Venom immunotherapy (VIT) is initiated in Golnik. Aproximatelly 150 new adult patients are offered VIT every year. Maintenance VIT for Gorenjska and all patients with complications during VIT is performed in Golnik hospital. Patient from Ljubljana region with uncomplicated maintenance VIT receive VIT in Golnik outpatient department in Ljubljana. In those two locations (Golnik/Ljubljana) 538 patients (307 wasp and 231 bee) are receiving maintenance VIT. Maintenance VIT for uncomplicated patients is organised also in satellite centers: Maribor (77 patients), Topolšica (70 patients), Celje (80 patients), Novo Mesto (64 patients), Izola (10 patients).

Table 1. Locations where allergy diagnsotics and therapy is awailable

Location	**Allergy tests**		**Inhalation allergens IT**		**Venom maintenance IT**
	SPT	**Epicutaneous**	**SCIT**	**SLIT**	
DC Bled	yes	no	no	no	no
Hudoklin (Trebnje)	yes	no	no	yes	no
Izola (Bolnišnica)	yes	no	no	no	yes
Klinika Golnik (lokaciji Golnik in Ljubljana)	yes	yes	yes	yes	yes
Kopriva (Litija)	yes	no	no	yes	no
Koren (Slovenj Gradec)	yes	no	no	yes	no
Kotrle (Koper)	yes	no	no	yes	no
Kramer (Celje)	yes	no	no	yes	no
Letonja (Jesenice)	yes	yes	no	yes	no
Lopert (Murska Sobota)	yes	no	no	yes	no
Maček (Ljubljana)	yes	no	no	yes	no
Mesić (Sežana)	yes	no	yes	no	no
Novo Mesto (Bolnišnica)	yes	no*	yes	yes	yes
Prezelj (Slovenj Gradec)	yes	no	no	no	no
Remeda (Domžale)	yes	yes	yes	yes	no
Ržek (Postojna)	yes	no	no	yes	no
Sežana (Bolnišnica)	yes	no	yes	yes	no
Šadl (Nova Gorica)	yes	no	no	no	no
Šegota (Celje)	yes	no	no	yes	no
Topolšica (Bolnišnica)	yes	no	yes	yes	yes
Triller (Murska Sobota)	yes	yes	yes	yes	no
UKC Ljubljana	yes	no*	yes	no	no
UKC Maribor	yes	no*	yes	yes	yes
Ulčar (Kamnik)	yes	no	no	yes	no
Zalokar (Ljubljana)	yes	no	yes	yes	yes
ZD Celje	yes	no	yes	yes	yes
Sum	**26**	**4 (+3)**	**11**	**20**	**6**

SPT-Skin prick test; IT-Immunotherapy; SCIT-Subcutaneous immunotherapy; SLIT-Sublingual immunotherapy;
*-epicutaneous tests are performed at the dermatology department

COMPLIANCE WITH THE TREATMENT OF PATIENTS ON IMMUNOTHERAPY WITH INHALED ALLERGENS

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Key words: immunotherapy, compliance, adherence, drop out

Background

Immunotherapy (IT) is an effective treatment for respiratory allergy. Inadequate compliance or early termination of treatment results in low or absent clinical effect. IT requires significant time commitment by the patient, who must undergo regular injections for subcutaneous immunotherapy (SCIT) or daily self-administration of the allergen extract for sublingual immunotherapy (SLIT), during 3 years.
According to established definitions, compliance is the extent to which the patient's behavior matches agreed recommendations from the prescriber. (1)
Early termination of treatment with immunotherapy leads to suboptimal and shortened benefits from immunotherapy. The problem of lack of adherence of patients during immunotherapy results in a significant loss of time, effort and money, resulting in a significant burden for patients, as well as society and health care systems. (2,3) The economic consequences are also measured in the failure to achieve the objective of modifying the progression of the disease and the occurrence of asthma (4).

Methods

Our objective was to find out the adherence/percentage of drop out of patients that have received subcutaneous immunotherapy and sublingual immunoterapy at the University Clinic of Respiratory and Allergic Diseases, Golnik, during the years 2008 to 2014. In this study, we only considered the number of dropout patients as an objective measure of noncompliance.

Drop outs

Charts of all the patients that started immunotherapy for inhalatory allergens in the period 2008-2014 were retrospectively evaluated. We defined a drop out as a patient that failed to complete the full 3 years treatment. We performed a telephone survey, where we asked the patients about their reasons for termination of treatment, as well as determining their employment status, level of education, whether they live in urban or rural areas and the distance from their home address to our clinic.

Economic

We calculated the cost for one year of immunotherapy in terms of medication required. For SCIT, we estimated an average of 12 visits per year (as most of our patients receive perennial treatment) where one allergen shot is received per visit. We calculated the number of dropout patients per 6ml of allergen. We also calculated the cost of the visit considering the points we charge the Health Insurance institute of Slovenija which value is eu 74,30 for the visit for aplication of the alergen.
For SLIT we estimated the cost of the allergen required for 12 months for perennial dropouts and 4 months for seasonal allergens. We calculated separately the season and perennial costs and multiplied it by the number of dropouts.

Results

829 patients started with immunotherapy between 2008 and 2014, 529 of which were treated by SLIT and 300 by SCIT. 216 (26%) patients failed to adhere to treatment and where thus classified as dropout patients. We observed a dropout of 15% (49) for patients treated with SCIT, whereas a significantly higher percentage (of about 32%) was observed for those patients treated with SLIT (167).

Patient dropout population: We observed an even distribution in terms of sex of dropout patients, with 77 males (48%) and 83 females (52%). The mean age of dropout patients was 37 years old. The mean distance from their home address to the clinic was 37.16km, and the mean time for which the patients received treatment was 12 months.
47 (28%) of them were treated with perennial and 118 (71%) with seasonal allergens (Table 1).

Table 1. Prescribed immunotherapy in dropout patients

SCIT dropout	**Alergen**	**N (%)**
Seasonal 23 (76%)	Birch	11 (36%)
Periannal 7 (23%)	Birch + grass	2 (6%)
	Grass	10 (33%)
	Mites	7 (23%)
	Total	30 (100%)
SLIT dropout	Allergen	N (%)
Seasonal 95 (70%)	Ambrosia	6 (4%)
	Birch	33 (24%)
	Hazel	1 (0.7%)
	Betulaceae	7 (5%)
	Trees	3 (2%)
	Grass	45 (33%)
Periannal 40 (30%)	Alternaria	3 (2%)
	Mites	36 (26%)
	Cat	1 (0.7%)
	Total	135 (100%)

SLIT compliance: 17 of the 135 dropout patients continued treatment in another clinic (11 patients) or did not begin treatment after receiving the allergen.(6 patients)
Different reasons were claimed by the remaining 119 patients for their premature termination of treatment as shown in table 2.

Table 2. Reasons for dropout

Reasons of dropout	**SLIT (%)**	**SCIT**	**TOTAL**
1. Side effects	**39 (32%)**	3**(10%)**	**42 (28%)**
2. Forgotten prescription/forgot to get the injection	**19 (16%)**	**5(17%)**	**24 (16%)**
3. Time consuming	4 **(3%)**	**4(13%)**	8 **(5%)**
4. Economic reason	1 **(0.8%)**	0	1 **(0.6%)**
5. Lack of supplementary health insurance	0	0	0
6. IT has not been successful	**12 (10%)**	**8(27%)**	**20 (13%)**
7. Unrelated illness prevented me from continuing with therapy	**9 (7.5%)**	1**(3.4%)**	**10 (6%)**
8. I do not trust IT therapy	0	1**(3/4%)**	1 **(0.6%)**
9. Pregnancy	6 **(5%)**	1**(3.4%)**	7 **(4%)**
10. Death	1 **(0.8%)**	0	1 **(0.6%)**
11. I did not know I had to continue	**11 (9%)**	1**(3.4%)**	**12 (8%)**
12. Relocation or studying abroad	5 **(4%)**	3**(10%)**	8 **(5%)**
13. Problems disappeared	**7 (5.8%)**	1**(3.4%)**	8 **(5%)**
14. I opted for alternative therapies	4 **(3%)**	1**(3.4%)**	5 **(3%)**
15. Problems with the doctor	1 **(0.8%)**	0	1 **(0.6%)**
	119 (100%)	**29 (100%)**	**148 (100%)**
continued treatment in another clinic	11	1	12
did not begin treatment after receiving the allergen	6	0	6

The main reason reported by patients was side effects (39 patients), followed by 19 patients forgetting going to the clinic to get the prescription.
The number of reasons that were reported by patients which could be preventable (number 2, 3, 11, and 15) made up a total of 35 cases.

SCIT compliance: From 30 dropout patients, one continued with treatment abroad,
In this case, the main reason for early termination reported was that IT was not successful for 8 patients, followed by 5 patients forgetting to go to the clinic to receive the shot (table 2). A total of 12 patients out of 29 terminated treatment due to reasons that could be preventable (2, 3, 8, 11, 14)

Economic results: The cost of SLIT for year round perennial allergen treatment is 1000 eu per year and 400 eu for seasonal allergens. In SCIT the cost is 190 eu for allergen plus 74.30 eu for visits.
The estimated total cost of early termination is 49300 eu for SLIT (1700 eu for 17 perennial and 47600 for 119 seasonal dropouts) and eu 31366 for SCIT (5510 eu for allergen plus 25856 eu for 348 visits). Therefore, the cost of early termination of IT treatment can be estimated to around 80666 eu.

Discussion
Measuring compliance is difficult, as it can carry many technical problems. Especially for SLIT, where the information we get is given by the patients only. I this study, we only considered the number of dropout patients during immunotherapy as an objective measure of noncompliance.
From published literature, it seems that the dropout rates are not caused directly by the immunotherapy itself, but it is more related to other factors.(5) Research carried out in Austria demonstrated that certain patient characteristics, such as level of education, had a significant effect on the decision of patients to begin immunotherapy treatment (6). Moreover, in Denmark it has been found that patients with the highest levels of education, in particular those with a university degree, were much more likely to seek SIT compared with patients with lower levels of education. Although in Denmark immunotherapy is not free for the patient, the wealth status of patients was not an influential factor in their commitment with SLIT (7).
Other studies identified important influencing adherence, such as the presence of allergic rhinitis in families (as positive for adherence), positive opinions by the patients on the effectiveness of immunotherapy, and little need of taking alternative symptomatic medications (3).
In addition, study conducted in the US has also highlighted that age is also an important factor, as significantly more adherence was observed in elderly patients compared to younger ones. (8) When analyzing doctor's opinions about the reasons for better adherence, the study showed that the most important reason is the patient's perception on clinical efficacy, followed by the possibility of reimbursement of expenses and the absence of side effects. The importance of patient education, regular monitoring and ease of use of medications was also noted (9). Recent studies reported inconvenience as a mayor cause of noncompliance/lack of adherence. Other known causes include cost of the treatment, side- effects, and poor efficacy (10). A recent article suggested that the major factor improving compliance is a secretary who would remind the patients to come for the injection or prescription. (11)
Studies addressing adherence of SIT are lacking in the literature. In real life, economic costs and patient education are key factors that contribute to the adherence of treatment. More efforts in order to educate patients may improve adherence in immunotherapy in the future (12,13,14). The economic burden was exposed by a study conducted in the Netherlands where a very low compliance was found. (persistance of 7% in SLIT and 23% in SCIT). The cumulative total costs of patients who did not complete 3 year of immunotheraphy was estimated at €10.04 million.(15) The amount calculated for SLIT in Slovenia is similar to that in the Netherlands.

Conclusions
The percentage of dropout patients was as expected. In total, the number of preventable dropout cases was of 51, which represents about 32% of the total dropout patients. We observed that for SLIT, the percentage of dropout patients was twice as much as for SCIT. It must be highlighted that the number of side effects observed was high, compared to the ones described in literature. We also observed a higher number of patients whose reason to terminate therapy was that they forgot to attend our clinic for obtaining shots and who did not know they had to come back.
The level of education, their region of residence or distance to the clinic were not a significant factor influencing the dropout. In terms of the type of allergen, most dropouts were seasonal allergens. This could be due to breaks without receiving medication or lack of symptoms between seasons, which could contribute to forgetting to attend the clinic.

We believe implementing measures to identify patients who fail to attend to receive their injections or prescriptions is crucial and necessary. The creation of an easy to use application for clinics where patient data could be stored and would allow warning not only patients, but also medical personnel about when the patient is due to attend the clinic to obtain a new prescription or shot, would be a convenient and cheap solution.

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Immunotherapy, atopic dermatitis, food allergy and oral allergy syndrome

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Nowadays allergen specific immunotherapy (ASIT) is a standard treatment for a group of IgE mediated respiratory allergies and insect venom allergies. It long-term effect has been documented in numerous prospective double blind controlled studies. However, long term effects after the usage of ASIT in treatment of atopic dermatitis (Ad) and food allergy (FA) are not really proven and results from rare studies done in the field bring discouraging results. Regardless of that, The Allergen Immunotherapy Practice Parameter Update in its third edition from 2011 states: "there is also some evidence that patients with AD with aeroallergen sensitivity might benefit from immunotherapy", and Update from 2012 states: "On the basis of several studies of dust mite immunotherapy, the clinician might consider allergen immunotherapy in selected patients with AD with aeroallergen sensitivity" (1, 2).

There aren't many prospective controlled studies on the subject of ASIT and AD. Up till now, there are only about twenty trials describing treatment of ASIT in AD. Most of the studies done before 2012 were uncontrolled, not randomized and were observational in nature.
The last meta-analysis of efficacy of ASIT for AD was performed in 2013. This meta-analysis has some methodology issues and also inconsistency with data of studies analyzed. It considered 8 studies from 1972 to 2012. In its conclusion the authors found moderate-level evidence for the efficacy of ASIT in the treatment of AD. Said in more practical words, you need to treat three patients with ASIT in order to improve one patient with AD (3).
Similarly, a few months later in 2012, Gendelman and Lang issued a systematic review of 7 double-blinded randomized controlled trials using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. 5 of the trials were also included in the meta-analysis mentioned beforehand. They analyzed 5 trials using subcutaneous ASIT, 1 trial using sublingual ASIT and 1 trial using intradermal ASIT. 5 studies used dust mite allergoid, 1 study used grass pollen allergoid and 1 study used mixture of aeroallergen antigens. In all studies ASIT prove to generate overall clinical improvement, but not always statistically significant. Most often it was more effective in patients with moderate to severe AD, except in 1 study where it was effective only in a group children with a mild AD. The studies also showed decrease in classical medication (skin moisturizes, topical glucocorticosteroids or calcineurin inhibitors, systemic antihistamines) use. Adverse effects were common, but were usually mild in nature no life-threatening event was mentioned. The problems of almost all this studies are a low number of patients studied, unusual high efficacy rate of placebo in control groups, and a different scoring system used for determining severity of AD. There was also a high rate of dropouts, which were not included in final analysis. We can imagine, if the treatment showed no effect, the patient lost an interest to participate further and this represent rational bias of the trial, since this patient was not longer included in analysis (neither as a failure of treatment). At the end Gendelman and Lang concluded that there is only "a week recommendation for the use of specific immunotherapy for AD" (4).
The most recent article published in May of 2015 from Poland describing long-term efficacy of ASIT in patients with AD in relation to improvement of quality of life in AD (DLQI - Dermatology Life Quality Index) discloses the persistence of effectiveness of ASIT in long-term aspect but not in statistically significant manner (5).

Explorations of biomarkers in most of the studies using ASIT in AD were consistent with trials done with ASIT in respiratory allergies. Overall there were no significant changes in concentration of total serum IgE and allergen-specific IgE, statistically significant rise in allergen-specific IgG4 was noted, alongside with concentration of IL-10, TGF-β1 and a decrease in concentration of IL-4.

The prevalence of AD in developed countries in children is around 20 % and around 2 % in adults. Around 10 % of adults with FA have concomitant AD. The number is even more staggering in children. Classical FA is usually a result of primary sensitization against stable food allergens, this occurs in gastrointestinal tract. The most common types of FA in older children and adults are the result of cross-reactivity to pollen related allergy and also to animal aeroallergens. This allergens are a part of pan-allergen families and represent quite conserved proteins with similar functions (e.g. defense, structure, storage proteins etc.) amongst different species. Clinically, reaction to food allergen are very fast, usually the symptoms appear within minutes after ingestion and up to two hours. By far the most common reaction represents contact urticaria of the oropharyngeal sites (previously known as oral allergy syndrome - OAS). Symptoms and signs also include skin (generalized urticaria, angioedema,

contact urticaria, AD), gastrointestinal tract (nausea, vomiting, cramps, diarrhea), respiratory tract (rhinitis, angioedema of larynx, bronchospasm) and cardiovascular system (anaphylaxis).

For a couple of years now, we can read articles describing clinical and immunological efficiency of ASIT in treatment of FA. Along with effectiveness, much has been done to increase its safety. New methods of application of food allergen are being developed for treatment of FA, two of most promising are oral immunotherapy (OIT) and already mentioned SLIT. Their safety profile is much greater than that of SCIT (serious systemic side effect, even deaths). In contrast to respiratory and venom allergies, the goal of ASIT in primary FA is usually to achieve a state of unresponsiveness to a certain concentration of specific food allergen. Meaning, we want the patient to tolerate at least a small quantity of critical food allergen without developing systemic allergic reaction (e.g. for peanut the goal is to tolerate approximately 5 g of peanut protein that is equivalent to 16 - 18 peanuts). There are many randomized, prospective and controlled studies consistently describing desensitization effect of ASIT (to egg, milk, peanut...) and reaching the state of unresponsiveness to culprit allergen using DBPCFC four or six weeks after stopping ASIT for most of the participant receiving active treatment in contrast to placebo groups. Only a hand of the researchers preformed a long-term follow-up and their results were discouraging. Firstly, there was a problem with a compliance to treatment (in adult trials most of the participant discontinued treatment after six months or a year). Secondly, there is still a lack of consensus, how long should the patients be treated to achieve a state of long-term tolerance. It is now being more and more recognized, that ability to tolerate food after discontinuation of ASIT can not be maintained. Thirdly, even biomarkers suggest that desensitization effects of ASIT in FA are modest in comparison to ASIT in respiratory and venom allergies, especially using SLIT.
OIT seems to be more successful in that way and there are more methods to enhance its tolerogenic effects. This can be done with processing allergens improving their safety and also efficacy. Instead of using alergoids, a peptide immunotherapy is now being developed. By adding sugar moietes to peptide they can boost function of tolerogenic dendritic cells to induce more Tregs. With new mucosal vaccine will be possible to deliver allergens in nanoparticles or bacterial vectors, which will turn immune system away from Th2 polarization. Toll-like receptor 9 agonists also drive immune response toward Th1. Dietary intervention can also enhance the efficacy of ASIT by using probiotic mixtures, some herbal formulas, nondigestible oligosaccharides or n-3 long chain polyunsaturated fatty acids. Some of the methods are already in clinical use for some years now. UC Golnik uses as adjunct treatment to ASIT to enhance desensitization omalizumab. Fusion proteins DARPins are being developed also for binding free IgE and displacing of IgE from FcεRI to improve the safety of ASIT in similar way as omalizumab (6).

The elimination diet is still recommended when primary FA is diagnosed and culprit allergen is determined. Symptomatic therapy should be performed in accordance to guidelines. When talking about FA as a result of pollen cross-reactivity, the allergic reactions are usually mild, local in nature (e.g. contact urticaria of the oropharyngeal sites). If the symptoms are intrusive we recommend the patients to avoid food accountable in raw form and try to cook it, since most of the cross-reactive allergen are thermo labile. We never suggest avoidance in context of patient sensitization tests alone, avoidance is always advised based on clear clinical picture or provocation tests.
The results of ASIT efficacy in ameliorating mucosal symptoms in aeroallergen cross-reactive allergy are inconsistent. In our experience some patients do benefit from ASIT not only in terms of respiratory symptoms relief, but can also tolerate a few bites of apple, but not whole apple after starting birch-pollen specific immunotherapy (e.g. when talking about contact urticaria of the oropharyngeal sites because of cross-reactivity to Bet v 1 in birch-pollen allergic patients). Because of inconsistent results of numerous studies, for now we can not recommend ASIT for patient who suffer from cross-reactive aeroallergen allergies without respiratory symptoms.

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Immunotherapy for respiratory allergies in the elderly

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Introduction

People of 65 years of or more are fastest growing segment of the population in development countries. It is estimated that in year 2030 20% of world population will be older than 65 years [1] . In Slovenia there is at the moment 17% of population older than 65 years.

Allergic diseases such as allergic rhinitis and asthma have long been consider as diseases of children and young adults, it has also been considered that people outgrow their inhalant allergies. Prevalence of allergic disease is indeed lower in in elderly (5-10%) than in younger population (30%). However, due to this common opinion, different presentations, lower sensitivity of in vivo and in vitro tests are allergic diseases often underdiagnosed in elderly population. Also, when diagnosed are allergic diseases in elderly often undertreated as pharmacotherapy can have troublesome risks, side effects and unwanted interactions with other medication. Immunotherapy for allergy treatment is often dismissed as inappropriate as it is considered not efficient enough or not safe enough in elderly

The aging of immune system – immunosenescence

With age the function of innate and adaptive system decreases. Immunosenescence is constellation of age related changes to the immune system, resulting in greater susceptibility to infection and reduced responses to vaccination [2].

The size of the hematopoietic compartment of bone marrow in elderly decreases and is replaced by fatty adipose tissue. There is decreased thymic and bone marrow output of functional naive T cells immune cells and accumulation of dysfunctional cells. Peripheral B cell numbers do not decline with age, but have dysregulation in function: a lower antibody response and a decreased ability to produce high affinity antibodies, production of low- affinity antibodies instead of high affinity, increased oligoclonal expansion, decline in total serum IgE and reduced MHC II class expression. Also effector cells are affected by ageing: there is reduced degranulation and dysregulation of function in mast cells, reduced degranulation and reduced superoxide production in eosinophil, reduced antigen presentation of T cells, dendritic cells [1])

Clinical effects of this immunological effects are increased susceptibility to infection, malignancy, autoimmune disorder, decreased response to vaccination and impaired wound healing. Efficacy of influenza vaccine in young adults: 70-90%, while in elderly population is 15-53%. There is also rapid decline of antibody responses with a reduction in seroprotective rates between 1 and 5 months after vaccination [3]. Also in vaccination with strong protein antigen such as tetanus there is strong reduction of protective levels to 16-20% 10 years after vaccination in patient elderly than 60 years. (reduction to 97% in young adults) [2]

Allergy diagnosis in elderly

In vivo and in in vitro tests for allergy have lower sensitivity in elderly than in general population. Atopy decreases with aging .The prevalence of atopy in younger adults is estimated on 30%, while in elderly is 8%. Positive skin prick response decreases with age. Possible explanation for “false negative” skin test responses in elderly may be also in aging of the skin and atrophy. There are fewer cell layers, decreased cellularity and collagen in skin. Marked reduction in blood vessel and mast cells offers less potential binding sites for allergen and less histamine to produce wheal and flare [4]

Total serum IgE values decreases with age. Also specific IgE decreases with age in patients with allergic rhinitis, asthma and insect allergy. Interestingly there is no decline in IgE in patients with atopic dermatitis, in patient sensitized to ragweed, and in patient with very high serum IgE [5]. There are also some data that new sensitization to pollen can occur in elderly [6] .

Elderly and allergic rhinitis or allergic asthma:

Prevalence of allergic rhinitis (AR) in is lower in elderly (5.4-10.7%) than in children (40%) or adults (10-30%). There is also difference in culprit allergen in young and older population. Elderly spent more time indoors and indoor allergen (mites, molds, pets, cockroach) might be more important in elderly than in younger population.

However symptoms of allergic rhinitis like nasal obstruction, postnasal drip, cough may be worsened by physiological changes that occur with the age: weakening of septal cartilage, loss of nasal tip support leads to nasal obstruction, decreased mucocilliary clearance – cough, postnasal drip, drying of mucosa. Reduction of blood flow can lead to progressive nasal atrophy and to anthropic rhinitis, rhinitis medicamentosa. Patients over 50 years have higher frequency of isolated ocular symptoms [1,7]

Prevalence of asthma in the elderly is estimated around 6-10%. Asthma in elderly could be underdiagnosed because symptoms such as wheezing, cough, and dyspnea are easily mistaken as an expression of other more common condition such as heart failure, chronic obstructive pulmonary disease, anemia, or gastro-esophageal reflux [1] .

Due to physiological changes pharmacotherapy can have troublesome risks, side effects and unwanted interactions with other medication. With age homeostatic mechanisms reduce, renal function and biotransformation in the liver decrease.
First generation antihistamines should be avoided in elderly, while second generation antihistamines are safe. Antihistamines requiring dose reduction in renal dysfunction are cetirizine, ebastine, fexofenadine, levocetirizine. Antihistamines requiring dose reduction in hepatic dysfunction are cetirizine, ebastine, levocetirizine, loratidine. Topical nasal antihistamines and nasal lavage with isotonic saline are considered safe. Use of topical nasal steroids does not increase risk for osteoporosis or cataracts, but there are reports of increased risks for glaucoma. Topical nasal decongestives are not recommended as they could aggravate nasal dryness, and also have side effects such as confusion, urine retention, glaucoma. All topically used drugs could cause local irritation and drying of the nasal mucosa.
Anileukotriens are not recommended due to decreased clearance. The main limitation of use of inhaled steroids for asthma in elderly is inability of proper use. There are data that inhaled steroids are associated with higher risk of osteoporosis, glaucoma, cataracts. Long acting inhaled beta agonist are considered safe, while short acting beta agonists can cause cardiotoxicity [1]

Immunotherapy in elderly
Regarding the problems with pharmacotherapy of allergic diseases in elderly immunotherapy seems to be an option at least to reduce the use of medication.
The American Academy of Allergy, Asthma & Immunology recommend in the latest guidelines for immunotherapy: »Immunotherapy can be considered in the treatment of patients of all ages, and the risk/benefit assessment must be evaluated in every situation. Some patients might be taking medications that could make treatment of anaphylaxis with epinephrine more difficult, such as b-blockers, or might have significant comorbid medical conditions, such as hypertension, coronary artery disease, cerebrovascular disease, and/or cardiac arrhythmias. Some of these conditions can occur more frequently in older subjects. However, immunotherapy can provide significant benefits in the older adult population and should be considered if the appropriate indications are present and there are no significant comorbid conditions. The patient's age alone should not preclude the consideration of allergen immunotherapy, and clinical benefits have been reported.« [8]
Use of b-adrenergic blocking agents and maybe also ACE inhibitors is a risk factor for more serious and treatment resistant anaphylaxis; however anaphylaxis is extremely rare in immunotherapy with inhalant allergen. Therefore concomitant use of b-blockers and allergen immunotherapy should be carefully considered from an individualized risk/benefit standpoint and incorporate the patient's preferences in the medical decision making process [8].

There are only few studies concerning efficacy of immunotherapy in elderly. Assero assessed on a small group of patients (n:39, median age 59 yeas) the efficacy of subcutaneous immunotherapy with birch or ragweed allergen. The efficacy was compared with a similar group of patient who refused immunotherapy (n:33, median age 59) and with a group of younger patient (n:33, median age 35 years) who also underwent immunotherapy. Medication score was significantly reduced in both active groups, younger and older, compared to non-active group [6] .
Margona et al compared efficacy of sublingual immunotherapy (SLIT) with house dust mite allergen again in two groups of patients: younger (n 29, aged 18-28 years) and older (n:23, aged 55-86 years), compared to similar non-treated groups. After 3 years of SLIT there was significant reduction in symptom and medication score in both active group, but the global symptoms were lower in younger group [9] .
Bozek et al conducted double-blind placebo controlled study in 111 elderly patients, treated with placebo or sublingual house dust mite immunotherapy (Staloral 300). At the end of the 3-years treatment there was significant decrease in symptom score and in the use of medication in the active group [10] .
The main limitation of this studies is low number of patients, and we still do not have enough well-established evidence based answer regarding efficacy of immunotherapy in elderly [11]. However, none of the studies reported any severe side effect during immunotherapy.

Conclusion

Although immunosenescence does occur are allergic diseases present also in elderly, and that is more commonly than is generally thought. Prevalence of atopy declines with age, while the association between age and serum IgE is dependent on the type of atopic disease and of the amount of total IgE [5] . Treatment of allergic disease in elderly is often complicated with comorbidities, physiological changes that occur in age, and possible drug interactions. Non-drug measures such as allergen avoidance are front line of allergy control in this population. Vaccination responses are reduced in elderly, but there are data that immunotherapy is safe and effective also in elderly population. In patients who otherwise have the indication for specific immunotherapy, there is no absolute upper age limit for initiation of immunotherapy [8].

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PREVALENCE OF MRSA IN A TERTIARY CARE, TEACHING HOSPITAL IN A FIVE-YEAR PERIOD

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Background

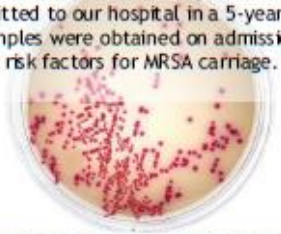
For decades, methicillin-resistant *Staphylococcus aureus* (MRSA) has been a major cause of infection in hospitals and nursing homes. High hand hygiene compliance, screening of admitted patients and a quick and accurate laboratory diagnostic procedure are crucial for prevention and control of MRSA.

The aim of our retrospective analysis was to evaluate the prevalence of MRSA at University Clinic of Respiratory and Allergic Diseases Golnik (UCRAD).

Methods

In the Laboratory for Respiratory Microbiology at UCRAD Golnik we received 28003 screening and clinical samples between January 2009 and December 2013 for detection of MRSA.

Samples were collected from 9771 patients out of 41.267 patients admitted to our hospital in a 5-years period. Screening samples were obtained on admission in all patients with risk factors for MRSA carriage.

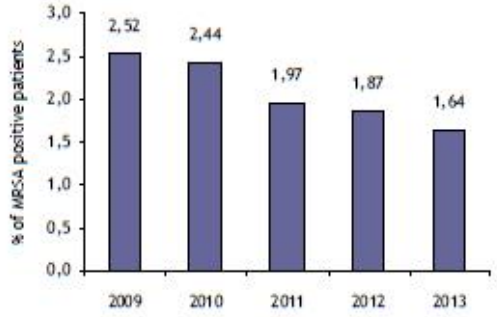


Results

We detected MRSA in 506 (1,8%) samples from 201 (2,1%) patients who were predominantly colonised with MRSA. During the five-year period prevalence of MRSA colonised / infected patients decreased from 2,5% in 2009 to 1,6% in 2013.

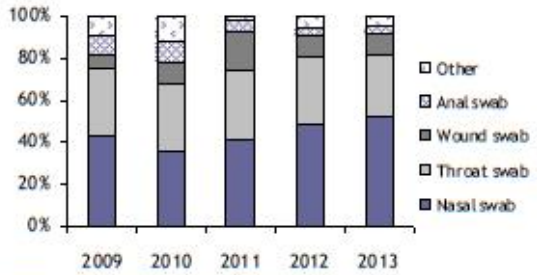
Tabel 1. Prevalence of MRSA at University Clinic Golnik from 2009 to 2013

Year	No. of samples tested for MRSA (n=28003)	No. (%) of MRSA positive samples (n=506)	No. of patients tested for MRSA (n=9771)	No. (%) of MRSA positive patients (n=201)
2009	4777	121 (2,53)	1664	42 (2,52)
2010	5047	102 (2,02)	1761	43 (2,44)
2011	6096	101 (1,66)	2187	43 (1,97)
2012	5711	95 (1,66)	2029	38 (1,87)
2013	6372	87 (1,37)	2130	35 (1,64)



Graph 1. % of MRSA positive patients per year

The majority of positive samples were nasal swabs (44%), followed by throat swabs (32%) and wound swabs (11%).



Graph 2. Distribution of MRSA positive samples

Conclusions

In conclusion, the data show that during the five-year period from 2009 till 2013 the percentage of MRSA colonised / infected patients was low at our clinic. The prevalence was slowly decreasing due to comprehensive strategy to prevent MRSA transmission introduced in our hospital in 2002 and a nationwide programme to prevent and control the spread of MRSA.

Mr. and Mrs. MRSA

klinika GOLNIK

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ANTIMICROBIAL THERAPY OF PNEUMOCOCCAL Community-Acquired Pneumonia

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Introduction

- Community-acquired pneumonia (CAP) is a form of an acute respiratory infection that affects the lungs of the adults either outside the hospital or up to 48 hours after hospitalization and has a high risk of fatal outcome (1, 2).
- Our aim was to evaluate the appropriateness of antimicrobial treatment of CAP, caused by *S.pneumoniae*, at the University Clinic Golnik in 2011 according to the Slovenian guidelines for treating CAP by analysing quality indicators (2).

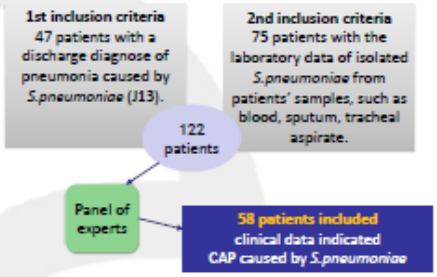
Methods

- A retrospective cohort study was conducted.
- Medical records of patients, who have been hospitalised at the University Clinic Golnik in 2011 due to CAP caused by *S.pneumoniae*, were reviewed.

Quality Indicators:
- the pneumonia severity index (PSI/PORT), oxygen saturation,
- empiric treatment (choice, dose, start and duration),
- blood culture samples, the susceptibility testing (antibiogram),
- the choice of antibiotic, dose and dosing interval after antibiogram.

Outcomes:
- the length of stay, duration of antibiotic treatment and clinical outcome.

Scheme 1: Patient recruitment



Results

Risk factors: 74% of patients older than 65 years; 47% were smokers

Quality indicators:
- PSI/PORT was not documented, oxygen saturation always determined.
- For 76% of patients blood cultures were collected.
- Adequate choice of empiric antibiotic was in 90%.
- Median duration of empiric treatment was 3,5 days.
- Antibiogram was done in 95% of cases.
- 15,5% of antibiotic therapies were changed based on the antibiogram results; only 8,4% represented a step down to the antibiotic with a narrower spectrum of activity.
- Median total time of antibiotic treatment was 12 days.
- Median length of hospital stay was 10,5 days which was in correlation with age of patients (0,561; p<0,001).

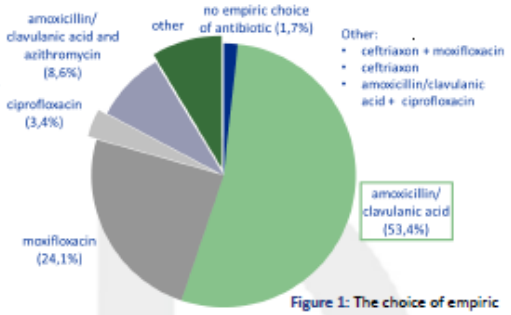


Figure 1: The choice of empiric antibiotic

Clinical outcome: 67% of patients were cured, 24% had pneumonia recurrence, 9% died.

Conclusions

- Measured quality indicators showed fairly good compliance (above 75%) with the guidelines.
- The practice of rare changing of empiric treatment to pathogen specific needs to be changed in order to prevent or reduce occurrence of bacterial resistance.

Literature: 1.World Health Organization. *Pneumonia.* http://www.who.int/mediacentre/factsheets/ (accessed on 1.9.2012)
2. Lejko-Zupanc T., Strle F., Vodopivec-Jamšek V., Žvelc-Kalan G., Šorli J., Sučon M. Priporočila za obravnavo zunajbolnišnične pljučnice odraslih (pneumonija in aspiracijski sindrom). 2010). *Zdrav Vestn.* 2010; 79: 265-284.

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Comparison of two methods for DNA extraction from sputum samples in COPD patients

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Background

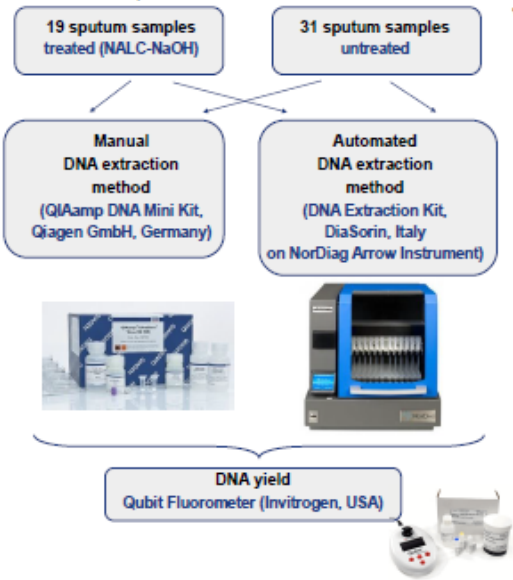
- Acute exacerbations of chronic obstructive pulmonary disease (AE COPD) are in up to 80% of cases caused by microbial pathogens, mainly by *Haemophilus influenzae, Streptococcus pneumoniae* and *Pseudomonas aeruginosa*.
- Molecular techniques hold the potential to improve the speed and sensitivity of laboratory diagnostic of respiratory infections.
- Initial and very crucial step of molecular diagnostic is DNA extraction.
- Currently there is only very limited knowledge on the best method for DNA extraction from sputum samples.

Objectives

- This study is a part of the European JRP HLT08 INFECT-MET.
- The aim was to evaluate the DNA yield of two different extraction methods, manual and automated, in treated and untreated sputum samples from COPD patients.

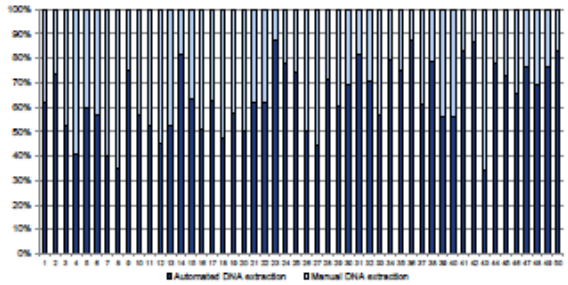
Study design

- 50 good-quality sputum samples (46 well-defined COPD patients admitted to University Clinic of Respiratory and Allergic Diseases Golnik between March 2014 and October 2014)

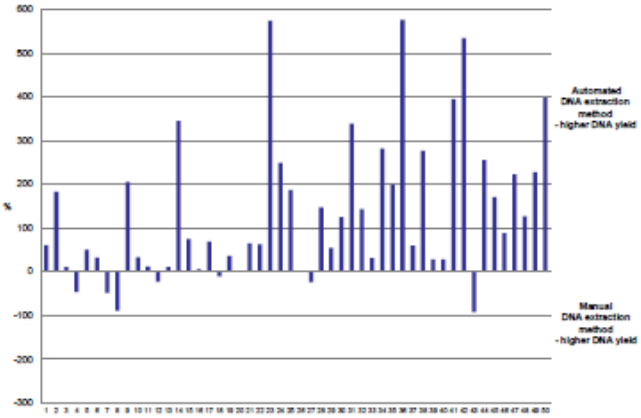


Results

- Out of 50 sputum samples 43 (86%) had higher DNA concetration with automated extraction method.



Graph 1. Proportion of DNA concentrations in automated and manual DNA extraction method in 50 sputum samples



Graph 2. Difference of DNA yield (%) in automated and manual DNA extraction method in 50 sputum samples

- Among 31 untreated sputum samples automated method had higher DNA yield in 25 samples by 142,0% and lower in 6 by 51,5%.
- In 19 NALC-NaOH treated sputum samples automated extraction method had higher DNA yield in 18 samples by 190,3% and lower in only 1 sample by 23,5%.

Conclusions

Automated extraction method:

- more efficient in extracting DNA from sputum samples,
- much easier to perform,
- less time consuming,
- less prone to contamination.

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EMRP
European Metrology Research Programme
A Programme of EURAMET
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GROWTH OF *MYCOBACTERIUM AVIUM* IN VARIOUS CULTURE MEDIA

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Background

Bacteria *Mycobacterium avium* (MA) belongs to the genus *Mycobacterium* whose most famous representative is *Mycobacterium tuberculosis* (MT). MA is with 155 other mycobacteria species a part of the so-called nontuberculous mycobacteria (NTM), which are ubiquitous bacteria in the nature like water, soil, plants and house dust. The aim of our study is to analyse laboratory diagnostics of *Mycobacterium avium* in Laboratory for Mycobacteria Golnik in the period 2013-2014.

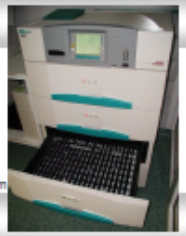

Figure 1. BACTEC MGIT 960 Mycobacterial Detection System

Methods

Primary non-sterile samples were decontaminated with Nalc-NaOH method and inoculated on three media: liquid MGIT tube and two solid Loewenstein-Jensen (LJ) and Stonebrink (ST) media. MGIT tubes were incubated in BACTEC MGIT 960 (BACTEC). LJ and ST were incubated in thermostats on 37°C and ones per week manually checked for growth. Bacteria from positive cultures were dyed by auramine and Ziehl-Neelson method. MA was identified by molecular test GenoType Mycobacterium CM (Hain, Nehren, Germany).

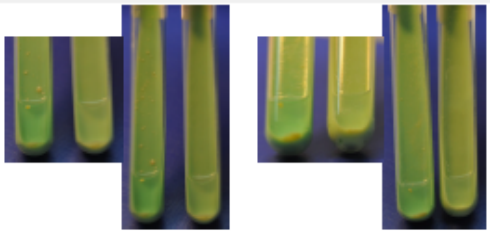

Figure 2. Growth of *M. avium* on solid media LJ and ST.

Table 1. Isolation of *Mycobacterium tuberculosis* (MT) and nontuberculous mycobacteria (NTM) from 16,674 clinical specimens in the period 1.1.2013- 31.12.2014.

Results

Culture medium	CULTURE RESULTS (n=94)		
	No.of POZ (%)	No.of NEG (%)	No. of contaminated (%)
MGIT	89 (94,7%)	5 (5.3)	0 (0)
LJ	42 (44,7 %)	22 (23.4)	30 (31.9)
ST	41 (43,6%)	24 (25.5)	29 (31.9)

Table 2. Growth of *Mycobacterium avium* from 94 clinical samples on 3 different media: MGIT, LJ and ST.

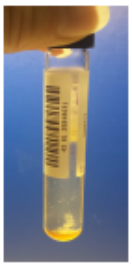

Figure 3. Growth of *M. avium* in liquid medium MGIT.

Conclusions

MA is still relatively rarely isolated from human samples in our country. Liquid MGIT medium is much better for isolation of MA as solid media LJ and ST. Reasons for this are at least three: (i) liquid media are the most optimal for growth of mycobacteria; (ii) MGIT media can be incubated in BACTEC machine, where are ideal conditions for growing and checking for positive cultures is ones per hour (oxygen consumption); (iii) reading of positive cultures on solid media is difficult because the morphology of MA colonies are not very typical and may be overlooked.

Liquid media, especially automated systems can greatly facilitate and improve the isolation of MA from clinical samples.

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Reduction of blood basophil numbers and high affinity IgE receptor expression during anaphylaxis

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Introduction

Anaphylaxis is a severe, systemic allergic reaction that may lead to death, and involves the activation of mast cells and/or basophils through an IgE and its high-affinity IgE receptor (FcεRI). To further investigate the role of basophils in anaphylaxis, blood basophil numbers, activation and FcεRI expression, were examined and followed-up in patients with acute allergic reaction.

Materials and Methods

Blood basophil numbers, CD63 activation, serum tryptase and other blood cells were measured at the time of presentation to the emergency department in 29 patients with acute allergic reaction (blood FcεRI gene expression was analyzed in 14 patients) and then 7 days and 1 month after the anaphylactic episode. The allergic reaction was triggered by insect stings in 27 patients, drug in 1 patient and was idiopathic in 1 patient. We also included 134 *Hymenoptera* allergic (37 also for FcεRI expression analysis) and 10 healthy control subjects. Samples from this group were obtained at least 2 months after the last sting reaction and /or before starting venom immunotherapy.

Results

A marked decrease in basophil numbers and FcεRI expression was observed in patients with acute allergic reaction. In two thirds also a relevant increase in serum tryptase was observed. The recovery of basophil numbers and FcεRI expression became partly evident after 7 days and completely recovered after one month. No significant changes were observed for other blood cells. The ROC area to distinguish between patients with acute allergic reaction and the controls was the highest for FcεRI expression (0.98), followed by the basophil level (0.92) and tryptase measurement (0.87).

Table 1. Demographic and clinical data of subjects with acute allergic reaction.

	subjects with acute allergic reaction n=29
Male/Female	17/12
Age (years), median (IQR)	51 (21)
Culprit	
Wasp	11
Honey bee	6
European Hornet	6
Unknown *Hymenoptera*	4
Iv analgesic	1
Unknown	1
Mueller grade, 1, 2, 3, 4	2, 5, 9, 13
Emergency field treatment, Epi, aH1, ST	10, 27, 27
Time from onset of reaction to blood drew (h), median (IQR)	1.5 (1.5)
Previous anaphylaxis, n (%)	8 (28)

Epi = epinephrine, aH1 = clemastine, ST = methylprednisolone

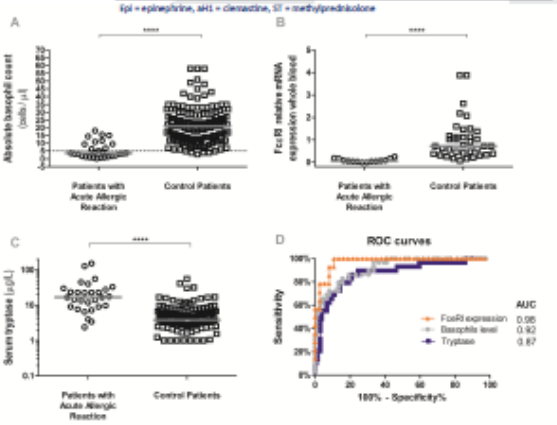

Figure 2. (A) Basophil absolute blood cell count, (B) whole blood FcεRI gene expression and (C) serum tryptase in patients with acute allergic reaction and in control patients and (D) ROC curve analysis. Horizontal line represents median value. **** $P < 0.0001$.

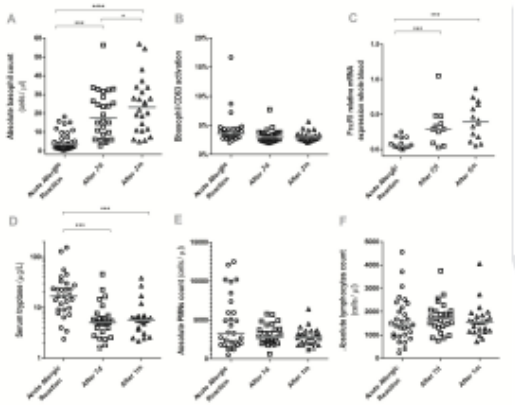

Figure 1. (A) Basophil absolute blood cell count, (B) CD63 activation, (C) whole blood FcεRI gene expression, (D) serum tryptase, (E) PMNs and (F) lymphocytes absolute blood cell count in patients with acute allergic reaction and then after 7 days, and 1 month after the episode. Horizontal line represents median value. * $P < 0.05$; *** $P < 0.001$; **** $P < 0.0001$.

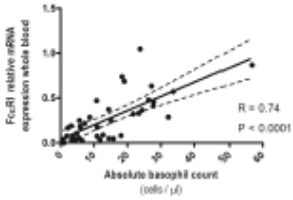

Figure 3. Correlation between basophil absolute blood cell count and whole blood FcεRI gene expression in patients with acute allergic reaction.

Conclusions

We showed that during acute allergic reaction the majority of circulating basophils are removed from the bloodstream. Those marked cellular and relating whole blood FcεRI expression changes could also be a novel biomarker for supporting the clinical diagnosis of anaphylaxis.
All authors declare that there is no conflict of interest.

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Increased basophil allergen sensitivity is associated with adverse systemic reactions during the build-up phase of honeybee venom immunotherapy

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University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia

Introduction

Adverse systemic reactions (SRs) are more common in honeybee venom immunotherapy (VIT) than in wasp VIT. Factors that might be associated with SRs during the honeybee VIT are poorly understood.

Materials and Methods

We included 93 patients that underwent ultra-rush honeybee VIT. The adverse SRs and their severity was compared to various immunological (sIgE, tIgE, basophil CD63 response, baseline tryptase, and skin tests), patient-specific (age, sex, cardiovascular conditions and medications, and other allergic diseases), and sting–specific factors (anaphylaxis severity, time interval to onset of symptoms, and absence of cutaneous symptoms).

Fig.1 Factors correlating with the SRs during VIT

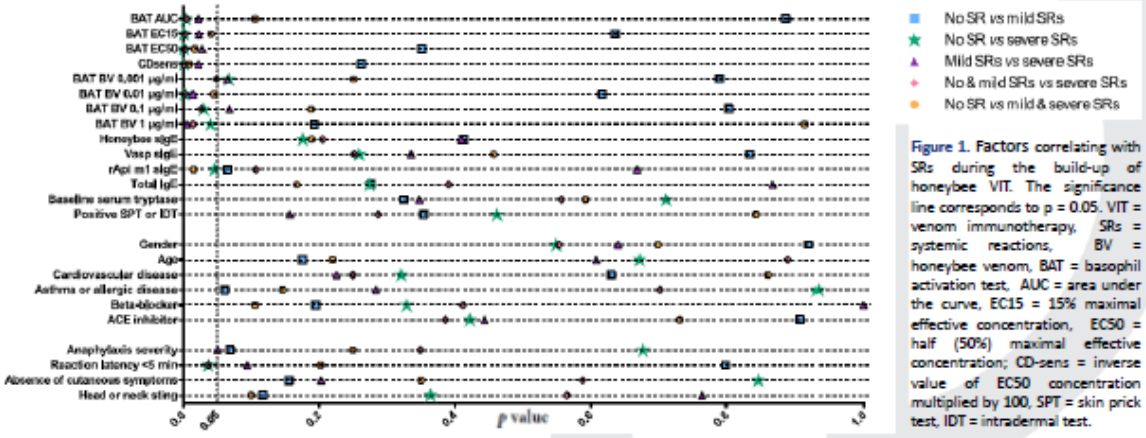

Figure 1. Factors correlating with SRs during the build-up of honeybee VIT. The significance line corresponds to p = 0.05. VIT = venom immunotherapy, SRs = systemic reactions, BV = honeybee venom, BAT = basophil activation test, AUC = area under the curve, EC15 = 15% maximal effective concentration, EC50 = half (50%) maximal effective concentration; CD-sens = inverse value of EC50 concentration multiplied by 100, SPT = skin prick test, IDT = intradermal test.

Table 1. Multivariable Firth's biased reduced logistic regression of risk factors for severe SRs during the build-up phase of honeybee venom immunotherapy.

	log OR (95% CI)	OR* (95% CI)	*p* value
BAT AUC	4.37 (0.33 - 13.22)	79.31 (1.4 - 553682.39)	0.03
Honeybee sIgE	-0.09 (-0.58 - 0.02)	0.91 (0.56 - 1.02)	0.15
Vasp sIgE	0.05 (-0.11 - 0.28)	1.05 (0.89 - 1.32)	0.21
rApi m1 sIgE	0.13 (-0.14 - 1.03)	1.14 (0.87 - 2.81)	0.39
Total IgE	0 (-0.01 - 0.01)	1 (0.99 - 1.01)	0.85
Baseline serum tryptase	0 (-0.22 - 0.06)	1 (0.8 - 1.06)	0.95
Positive SPT or IDT	-1.15 (-4.13 - 1.9)	0.32 (0.02 - 6.66)	0.43
Gender	0.65 (-1.2 - 2.55)	1.92 (0.3 - 12.85)	0.46
Age	-0.04 (-0.12 - 0.03)	0.96 (0.89 - 1.03)	0.26
Cardiovascular disease	1.57 (-0.56 - 3.86)	4.82 (0.57 - 47.67)	0.14
Asthma or allergic disease	0.38 (-4.69 - 4.29)	1.46 (0.01 - 73)	0.83
Beta-blocker	0.07 (-5.74 - 4.42)	1.08 (0 - 82.75)	0.97
ACE inhibitor	-0.09 (-2.7 - 2.6)	0.91 (0.07 - 13.48)	0.94
Anaphylaxis severity	0.39 (-1.18 - 2.09)	1.48 (0.31 - 8.08)	0.61
Reaction latency <5 min	1.03 (-0.6 - 3.34)	2.8 (0.55 - 28.24)	0.22
Absence of cutaneous symptoms	0.35 (-1.84 - 2.79)	1.42 (0.16 - 16.23)	0.75
Head or neck sting	0.94 (-0.71 - 3.67)	2.55 (0.49 - 39.26)	0.27
(Constant)	-3.18 (-8.64 - 1.45)	0.04 (0 - 4.25)	0.18

*corresponds to a one-unit increase

BAT = basophil activation test, AUC = area under the curve, IDT = intradermal test, SPT = skin prick test, OR = odds ratio

Results

Twenty-three patients (24.7%) experienced mild SRs and 13 patients (14%) severe SRs. In five patients with severe SRs the build-up was stopped. High basophil allergen sensitivity, evaluated as dose-response curve metrics of EC15, EC50, CD-sens, AUC, or the response to submaximal 0.01 µg/ml of venom concentration, was the most significant risk factor and only independent predictor of severe SRs and/or build-up stop. Time interval of less than 5 minutes after sting to onset of symptoms and lower specific IgEs to rApi m 1 were also associated with severe SRs. There was no difference in other immunological, patient-specific or sting–specific factors, including the baseline trypates. None of the studied factors was associated with mild SRs.

Conclusions

High basophil allergen CD63 sensitivity phenotype was a major indicator of severe adverse SRs during the build-up phase of honeybee VIT. Possibly role was also showed for short latency to filed sting reaction and low sIgE to rApi m1. Before honeybee VIT, measurement of basophil allergen sensitivity should be used to identify patients with a high risk for severe side effects.

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Občutljivost bazofilcev za alergen *in-vitro* kot napovedni dejavnik za težo sistemske reakcije ob ponovnem piku kožekrilca

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Uvod

Pik kožekrilca pri preobčutljivih osebah lahko povzroči nastanek od blagih do težkih sistemskih alergijskih reakcij (SR). Senzibilizacijo za strup kožekrilca največkrat dokazujemo s kožnimi vbodnimi testi (KVT) in določitvijo koncentracije specifičnih protiteles IgE (sIgE). Glavne celice, ki sodelujejo pri nastanku preobčutljivostne reakcije po piku kožekrilca, so bazofilni granulociti. V diagnostične namene tako lahko uporabimo test določevanja njihove aktivacije.

Namen

Želeli smo ugotoviti, ali z imunološkimi testi lahko ločimo med bolniki, ki so nagnjeni k blagim in tistimi, ki so nagnjeni k težkim sistemskim reakcijam po piku kožekrilca.

Metode

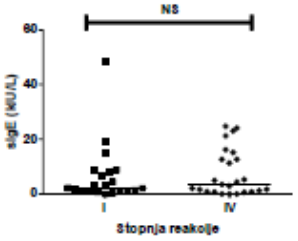
Preiskovance smo glede na stopnjo prebolele reakcije razdelili v dve skupini: osebe z reakcijo I. in osebe z reakcijo IV. stopnje po Muellerjevi lestvici. Med skupinama smo primerjali koncentracijo sIgE, rezultate KVT in občutljivost ter reaktivnost bazofilcev po spodbujanju z alergenom *in-vitro* (basophil activation test - BAT). Reaktivnost in občutljivost bazofilcev smo določili s stopnjo izražanja CD63 pri maksimalni in submaksimalni koncentraciji strupa z uporabo pretočne citometrije.

Rezultati

V raziskavo smo vključili 61 bolnikov: 24 s SR I. in 37 s SR IV. stopnje. Med skupinama ni bilo statistično pomembnih razlik v starosti (p=0.22), spolu (p=0.43) in koncentraciji sIgE (p=0.63).

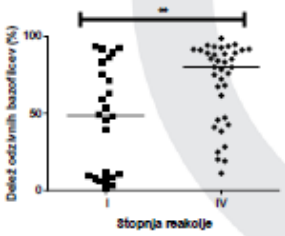
Osebe s SR IV. stopnje so imele statistično pomembno pogosteje pozitivne **kožne vbodne teste** (p <0.05), večjo **reaktivnost** (mediana vrednost 80.1% proti 48.7%; p <0.01) in **občutljivost** bazofilcev (mediana vrednost 49.5% proti 6.9%; p <0.01) kot osebe s SR I. stopnje.

Slika 1: *Koncentracija specifičnih protiteles IgE pri skupini s sistemsko reakcijo I. stopnje in skupini s sistemsko reakcijo IV. stopnje.*



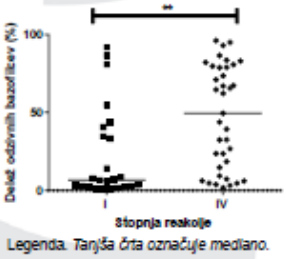
Legenda. *Tanjša črta označuje mediano. NS- razlika med skupinama ni statistično pomembna; sIgE – specifična protitelesa IgE.*

Slika 2: *Reaktivnost bazofilcev. Delež odzivnih bazofilcev pri maksimalni koncentraciji strupa 1 µg/ml pri skupini s sistemsko reakcijo I. stopnje in skupini s sistemsko reakcijo IV. stopnje.*



Legenda. *Tanjša črta označuje mediano.*
***p <0.01*

Slika 3: *Občutljivost bazofilcev. Delež odzivnih bazofilcev pri submaksimalni koncentraciji strupa 0,1 µg/ml pri skupini s sistemsko reakcijo I. stopnje in skupini s sistemsko reakcijo IV. stopnje.*



Legenda. *Tanjša črta označuje mediano.*
***p <0.01*

Zaključki

- Koncentracija sIgE se med osebami z lažjo in težjo reakcijo po piku kožekrilca ne razlikuje.
- Osebe, ki po piku kožekrilca doživijo SR težje stopnje, imajo pogosteje pozitiven KVT.
- Osebe, nagnjene k težkim SR po piku kožekrilca, imajo večjo specifično občutljivost in reaktivnost bazofilcev.

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Ali se da predvideti, kateri bolniki bodo imeli zaplete med imunoterapijo s strupom čebele

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Izhodišče

Bolnike, ki so utrpeli težjo preobčutljivostno reakcijo po piku čebele ali ose, zdravimo s specifično imunoterapijo (SIT). Med SIT lahko pride do alergijske reakcije. Te so pogostejše pri SIT s strupom čebele.

Namen

Želeli smo preveriti, ali imajo parametri, ki vplivajo na težo preobčutljivostne reakcije po piku čebele, napovedno vrednost tudi za pojav stranskih učinkov med SIT s strupom čebele.

Metode

V prospektivno kohortno raziskavo smo vključil 93 za strup čebele alergičnih bolnikov, ki smo jih zdravili s SIT. Najprej smo analizirali težo preobčutljivostne reakcije glede na demografske (starost, spol), imunološke (specifični IgE (sIgE) proti strupu čebele, celotni IgE (cIgE), sIgE proti pelodu oljne repice (OSR), sIgE proti rekombinatnemu alergenu fosfolipazi A2 (rApi m 1), koncentracija serumske triptaze) in klinične parametre (pozitivni kožni vbodni testi, pik na glavo/vrat, časovni interval manj kot 5 minut od pika do pojava simptomov, odsotnost kožnih simptomov in znakov, pridružene srčno-žilne bolezni, astma ali alergijski rinitis, zdravljenje z zaviralci adrenergičnih receptorjev beta in z zaviralci angiotenzin pretvarjajočega encima (ACE)). Nato smo analizirali vpliv istih parametrov in teže preobčutljivostne reakcije po piku čebele na pojav stranskih učinkov SIT.

Rezultati

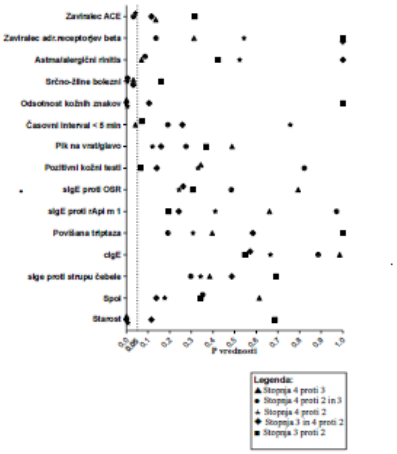
Dejavniki tveganja za nastanek težje preobčutljivostne reakcije po piku čebele so bili: višja starost, časovni interval manj kot 5 minut od pika do pojava simptomov, odsotnost kožnih znakov in simptomov, srčno-žilne bolezni, zdravljenje z zaviralci ACE. 35 bolnikov je imelo zaplete med SIT s strupom čebele. Samo nižje vrednosti sIgE proti rApi m 1 so napovedovale pojav stranskih učinkov.

Tabela 1. Osnovne značilnosti bolnikov, vključenih v raziskavo.

	n	%
Število bolnikov	93	
Povprečna starost (razpon let)	47,6 (18-78)	
Moški/ženske	65/28	
Stopnja preobčutljivostne reakcije po Müller-ju		
4	34	36,6
3	44	47,3
2	15	16,1
Lokacija pika[1]		
Glava/vrat	44	46,3
Dlan	14	15,4
Roka	16	17,6
Noga	9	10
Stopalo	6	6,6
Trup	2	2,2
Časovni interval		
<1	4	4,3
1-5	43	46,7
6-15	34	37
16-30	10	10,8
31-60	1	1,1
>60	1	1,1
Pridružene bolezni		
Srčno-žilne bolezni	29	31,2
Astma/alergični rinitis	10	10,7
Redna terapija		
Zaviralci adrenergičnih receptorjev beta	4	4,3
Zaviralci ACE	14	15,1
Pozitivni kožni vbodni testi[2]	51	58,6
Pozitivni sIgE proti strupu čebele[3]	88	100
Pozitivni sIge proti rApi m 1[4]	63	70,7
Pozitivni sIgE proti OSR[5]	25	28,4
Povišana koncentracija serumske triptaze[6]	5	5,7

[1]Pri dveh bolnikih ni bilo podatka o lokaciji pika

Graf 1. Demografski, imunološki in klinični parametri, analizirani glede na težo preobčutljivostne reakcije po piku čebele. Za vsak posamezen parameter in možno primerjavo med stopnjami preobčutljivostne reakcije so prikazane njihove P vrednosti. Za statistično analizo smo uporabili nepami t-test, Mann-Whitney-ev test ali Fisher's exact test. Prekinjena črta označuje statistično pomembno mejo (P = 0,05)



Graf 2. Demografski, imunološki in klinični parametri, analizirani glede na pojav stranskih učinkov zdravljenja s SIT s strupom čebele. Za vsak posamezen parameter so prikazane njihove P vrednosti. Za statistično analizo smo uporabili nepami t-test, Mann-Whitney-ev test ali Fisher's exact test. Prekinjena črta označuje statistično pomembno mejo (P = 0,05).

The placement of novel in-vitro diagnostic tests in Hymenoptera sting allergy diagnosis

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Introduction

A lack of practical parameters for how to use SSMA (species-specific-major-allergen)-antibodies and BAT in routine clinical practice, led us to construct a study to evaluate different ways to incorporate those tests to practice

Materials and Methods

177 patients appointed to our university clinic for Hymenoptera sting allergy diagnosis, in the 4 months period, were included to the study. For each, a detailed sting history and 3 pairs of laboratory tests (sIgE, SSMA-antibodies and BAT) were performed. Different in-vitro diagnostic procedures were constructed, evaluated and compared between each other by means of over and under diagnosis.

Results

The procedures were validated on 142 patients with unequivocal culprit history. The procedures that depended on simple cut-offs of single diagnostic tests (sIgE-only, SSMA-only, BAT-only procedure) either over (up to 40%) or under-diagnosed (up to 17%) a significant number of patients (Figure 1). The stepwise diagnostic procedures (Figure 2) that relied on single positivity of at least one test pair result, markedly decreased the number of over-diagnosed patients (10%), but the number of under-diagnosed was still high (9.2%). For that reason an algorithm based diagnostic procedure (Figure 3), which relied on multiplication of ratios of SSMA-antibody and BAT test pair results was constructed. With it, the number of over-diagnosed patients remained at the low level of stepwise diagnostic procedures (12%), whilst the number of under-diagnosed (3.5%) ones was the lowest of all the tested procedures.

Figure 2. (left): Flowchart with stepwise 1 diagnostic procedure, showing step 1, 2,3 and 4; * u.d – under diagnosed; ** w+b wasp and bee sting allergic patient;***m-missdiagnosed; ****o.d.-over diagnosed

Figure 3. (bottom): Histogram of algorithm values (BAT and SSMA-antibodies) on a whole sample(n=142; upper diagram) and on a sample of sIgE+/+ patients (n=61; lower diagram). Wasp (W) allergic patients are colored blue, bee (B) allergic patients are red and bee and wasp (W+B) allergic patients are green. Almost all color mixing and double positive patients are clustered around zero

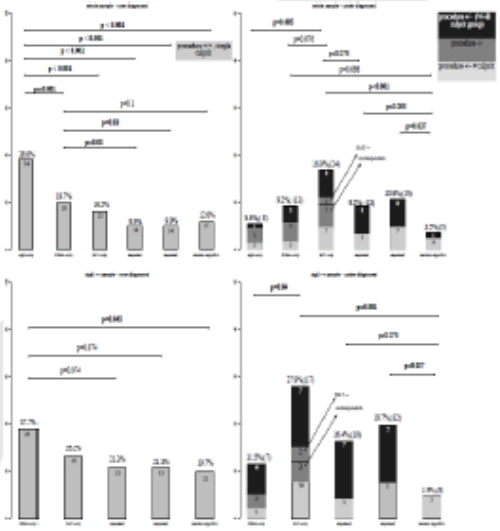
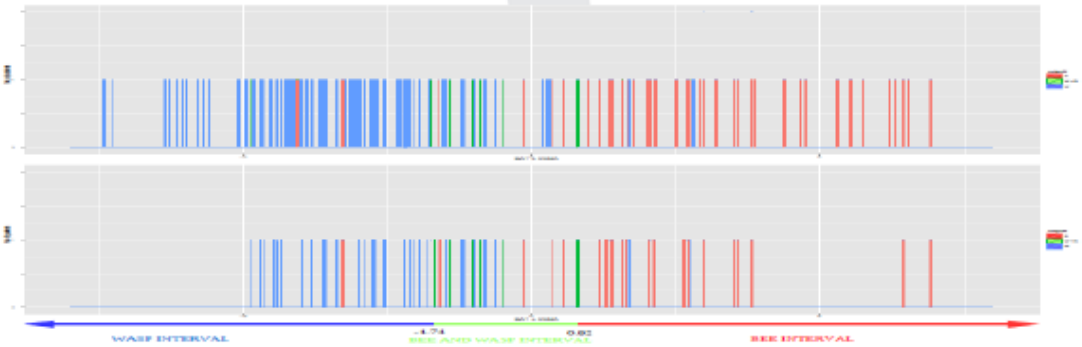


Figure 1. Number (proportion) of over/under-diagnosed patients with each of the diagnostic procedures on a whole and on a sIgE +/+ sample (in the underdiagnosed sample exact cause for under-diagnosis is indicated)



Conclusions

Incorporation of SSMA-antibodies and the BAT in the form of the stepwise or the algorithm based diagnostic procedures significantly enhances accuracy in diagnosing Hymenoptera-sting allergy.

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Clinical and immunological differences between HDM sensitized versus allergic patients

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BACKGROUND

Sensitization to house dust mite does not always correlate with clinical allergy. Whether the presence of allergen-specific IgE transforms into clinical allergy depends on a complex interplay of multiple factors, including a family history of atopy, the levels of total serum IgE (tIgE), sIgE or IgG, epitope-specificity of IgE and their degree of polyclonality, unidentified serum factors, the balance of T regulatory cells and Th1/Th2 cells, the polymorphisms of the high affinity receptor for IgE (FcεRI) and other factors regulating the activation of FcεRI-bearing cells

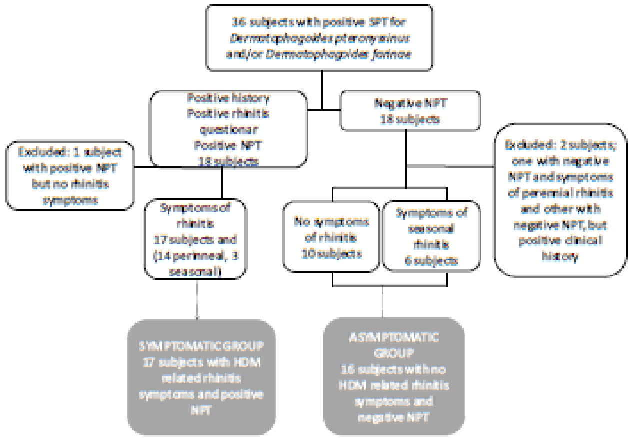
OBJECTIVES

With this study we evaluated clinical and immunological differences between patients with confirmed allergic airway disease and subjects with clinically irrelevant IgE sensitization to house dust mite.

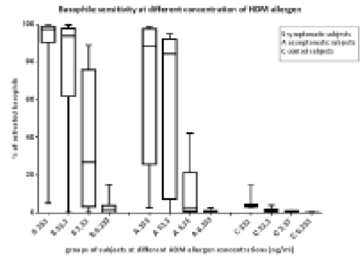
MATERIALS & METHODS

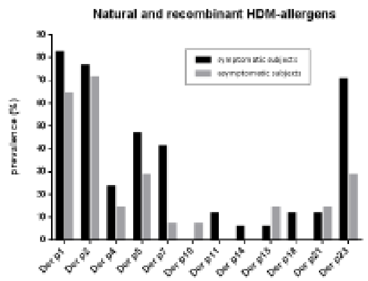
36 subjects with positive skin prick test for *Dermatophagoides pteronyssinus* and/or *Dermatopagides farinae* were included into the study and divided in symptomatic and asymptomatic group on the basis of clinical history and nasal provocation test with four log concentration of house dust mite-allergen. In both groups the following immunological parameters were evaluated: CD 63 basophile response to *in vitro* stimulation using four log concentration of *D. pteronyssinus*-allergen extract, serum specific IgE to *D. pteronyssinus*, specific IgE to natural and recombinant house dust mite-allergens, total IgE and specific IgG to *D. pteronyssinus*. 13 control subjects with negative skin prick for *D. pteronyssinus* and *D. farinae* and negative house dust mite nasal provocation test were also included.

RESULTS



	Symptomatic subjects (n=17)	Asymptomatic subjects (n=16)	Control subjects (n=10)
Age (years)	27 (18-54)	27 (19-51)	26 (24-56)
Sex (male/female)	2/10	8/9	2/8
SPT D. ptec (mm)	4.5 (0-9)	4.5 (0-12)	0
and/or far. (mm)	5 (0-10)	4 (0-8)	0
NPT (pos./neg.)	17/0	0/16	0/10
History of allergic rhinitis (perin./seas.)	14/3	0/6	0/0
sIgE to D. pter. (kU/mL)	12.4 (0-100)	2.34 (0-41.7)	0 (0-1.46)
tIgE (kU/mL)	77.2 (17-1361)	127 (15.7-443)	40.40 (6.88-154)
sIgE to D. pter. /tIgE	0.1460 (0-0.476)	0.0302 (0-0.209)	0 (0-0.00948)
sIgG to D.pter. (mgA/L)	15.8 (4.22-30.0)	12.4 (4.09-64.3)	11.4 (5.07-21.5)





CONCLUSIONS

In our study we found no significant differences among symptomatic and asymptomatic group for: SPT, serum levels of sIgE, tIgE, IgG.

The difference in basophile sensitivity to *D. pteronyssinus*-allergen extract and the difference in prevalence of specific IgE to rDer p7 and rDer p23 house dust mite-allergens proved useful for distinguishing clinical phenotype of allergic sensitization.

REFERENCES

References:
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Napovedna vrednost specifičnih Ige proti rekombinantnim alergenom pršice za ločevanje simptomatske in asimptomatske senzibilizacije

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IZHODIŠČE

Alergeni kožojede pršice so najpogostejši razlog za razvoj celoletnega alergijskega rinitisa in alergijske astme. Znanih je vsaj 23 naravnih in rekombinantnih alergenov pršice.

NAMEN

Zanimalo nas je, ali lahko na podlagi senzibilizacije z določenimi alergeni pršice ločimo klinično pomembno obliko alergijske bolezni zaradi pršice od asimptomatske senzibilizacije.

METODE

Vključili smo osebe s pozitivnim kožnim vbodnim testom (KVT) z alergenom pršice *Dermatophagoides pteronyssinus* in/ali *Dermatophagoides farinae*. Osebe smo razdelili v skupino z alergijsko boleznijo zaradi alergena pršice (AB) in asimptomatsko, z alergenom pršice senzibilizirano skupino (AS) na podlagi vprašalnika o simptomih alergijske bolezni, vprašalnika o kvaliteti življenja in nosnega provokacijskega testa z *D. pteronyssinus*. Pri obeh skupinah smo primerjali koncentracijo specifičnih protiteles IgE (sIgE) in IgG4 (sIgG4) proti *D. pteronyssinus*, celokupnih protiteles IgE (cIgE) ter sIgE proti naravnim in rekombinantnim komponentam alergena pršice.
Vključili smo tudi 9 kontrol z negativnim KVT in negativnim nosnim provokacijskim testom z alergenom *D. pteronyssinus*.

REZULTATI

17 oseb je imelo alergijsko bolezen (AB), 16 oseb je imelo senzibilizacijo brez simptomov alergijske bolezni (AS). sIgE proti rekombinantni komponenti rDer p7 so bila prisotna pri 7/17 AB in pri 1/16 AS (P = 0,0454) in proti rDer p23 pri 12/17 AB in 4/16 AS (P = 0,0192). AS in AB so bili senzibilizirani z nDer p1, rDer p2 and rDer p5, vendar statistično pomembne razlike med skupinama nismo dokazali. sIgE proti ostalim rekombinantnim komponentam alergena pršice rDer p10, rDer p21, rDer p4, rDer p11, rDer p14, rDer p15 in rDer p18 so bila redko prisotna. Statistično pomembne razlike med skupinama nismo dokazali pri koncentraciji sIgE in sIgG za *D. pteronyssinus* ter v razmerju sIgE/cIgE.

Graf: Pogostost sIgE proti posameznim naravnim in rekombinantnim alergenom pršice pri simptomatskih in asimptomatskih osebah s pozitivnim kožnim testom z alergenom pršice

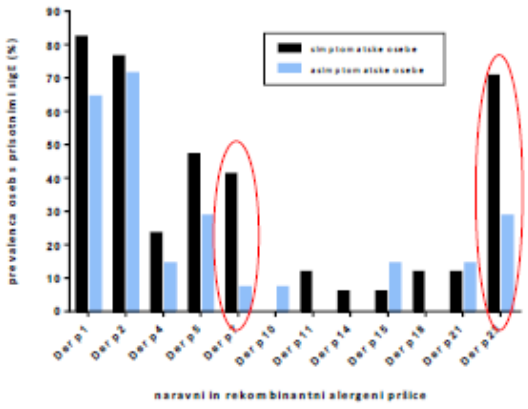

Tabela: Demografski podatki in imunološke značilnosti Preiskovancev.
*P-vrednost predstavlja razliko med AB in AS.

	AB	AS	Kontrole	*P-vrednost
Število	17	16	9	
Starost (leta)	27 (18-54)	27 (19-51)	26 (24-56)	
Spol (moški/ženske)	2/10	8/9	2/8	
Premer urtike pri kožnem testu s pršico D.pter. (mm)	4.5 (0-9)	4.5 (0-12)	0	0.8064
Premer urtike pri kožnem testu s pršico D.far. (mm)	5 (0-10)	4 (0-8)	0	0.4228
NO (ppb)	35 (17-99)	26 (16-80)	12 (9-30)	0.2735
sIgE za D. pter. (kU/L)	12.4 (0-100)	2.34 (0-41.7)	0	0.0867
tIgE (kU/L)	77.2 (17-1361)	127 (15.7-443)	40.40 (6.88-154)	0.7448
sIgG za D.pter. (mgA/L)	15.8 (4.22-30.0)	12.4 (4.09-64.3)	11.4 (5.07-21.5)	0.4950

ZAKLJUČKI

Prisotnost sIgE proti komponentama alergena pršice rDer p7 in rDer p23 se je izkazala kot dobro diagnostično orodje za določanje kliničnega fenotipa alergijske bolezni zaradi pršice.

Vrednost testa aktivacije bazofilcev za ločevanje simptomatske in asimptomatske senzibilizacije

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Izhodišče

Senzibilizacija z alergenom pršice se ne odraža vedno s simptomi alergijske bolezni.

Namen

Želeli smo oceniti klinične in imunološke razlike med bolniki z alergijsko boleznijo (AB) in asimptomatskimi senzibiliziranimi (AS) osebami z alergenom pršice.

Metode

Vključili smo osebe s pozitivnim kožnim vbodnim testom (KVT) s pršico.
Glede na klinično sliko, vprašalnik o simptomih rinokonjunktivitisa, vprašalnik o kvaliteti življenja pri bolnikih z rinitisom, ter glede na rezultate nosnega provokacijskega testa s pršico smo jih razdelili na bolnike z alergijsko boleznijo in asimptomatske senzibilizirane.
V obeh skupinah smo merili CD 63 odziv bazofilcev na spodbujanje *in vitro* z *D. pteronyssinus*, specifična protitelesa IgE (sIgE) in IgG (sIgG) v serumu za *D. pteronyssinus*, celokupna protitelesa IgE (cIgE) ter koncentracijo dušikovega oksida (NO) v izdihanem zraku.
V kontrolno skupino smo vključili 9 oseb z negativnimi KVT in negativnim nosnim provokacijskim testom s pršico.

Rezultati

17 oseb je imelo alergijsko bolezen (AB), 16 oseb je imelo senzibilizacijo brez simptomov alergijske bolezni (AS).
Občutljivost bazofilcev AB (mediana vrednost CD sens = 18,75) je bila statistično pomembno višja v primerjavi z AS (mediana vrednost CD sens = 2,91; P = 0.0285). Med skupinama ni bilo statistično pomembne razlike v velikosti urtike pri kožnem vbodnem testu za alergen *D. pteronyssinus* in *D. farinae*, v koncentraciji sIgE in sIgG za alergen *D. pteronyssinus*, v razmerju sIgE/cIgE ter v koncentraciji NO v izdihanem zraku (tabela 1).

Slika 1. Odziv bazofilcev na spodbujanje z različnimi koncetracijami alergena pršice. Odziv pri koncentraciji 3,33 ng/ml odraža občutljivost bazofilcev, ker je ta koncentracija na strmem delu krivulje odmerek-odziv.

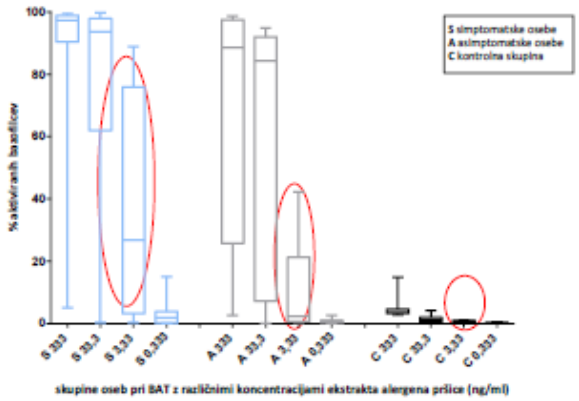

Tabela 1. Demografski podatki in imunološke značilnost. Podatki so prikazani z mediano in razponom.
*P-vrednost predstavlja razliko med AB in AS.

	AB	AS	Kontrole	*P-vrednost
Število	17	16	9	
Starost (leta)	27 (18-54)	27 (19-51)	26 (24-56)	
Spol (moški/ženske)	2/10	8/9	2/8	
Premer urtike pri kožnem testu s pršico D.prer. (mm)	4.5 (0-9)	4.5 (0-12)	0	0.8064
Premer urtike pri kožnem testu s pršico D.far. (mm)	5 (0-10)	4 (0-8)	0	0.4228
NO (ppb)	35 (17-99)	26 (16-80)	12 (9-30)	0.2735
sIgE za *D. prer.* (kU/L)	12.4 (0-100)	2.34 (0-41.7)	0	0.0867
tIgE (kU/L)	77.2 (17-1361)	127 (15.7-443)	40.40 (6.88-154)	0.7448
sIgG za D.pter. (mgA/L)	15.8 (4.22-30.0)	12.4 (4.09-64.3)	11.4 (5.07-21.5)	0.4950

Zaključki

- Bolniki z alergijo za pršico imajo značilno bolj občutljive bazofilce za ta alergen od oseb, ki imajo asimptomatsko senzibilizacijo.
- Merjenje občutljivosti bazofilcev za alergen pršice je dobro diagnostično orodje za razlikovanje med simptomatskimi bolniki z alergijskim rinitisom in osebami s klinično nepomembno senzibilizacijo z alergenom pršice.

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Immunological changes precedes clinical effects of omalizumab in venom immunotherapy

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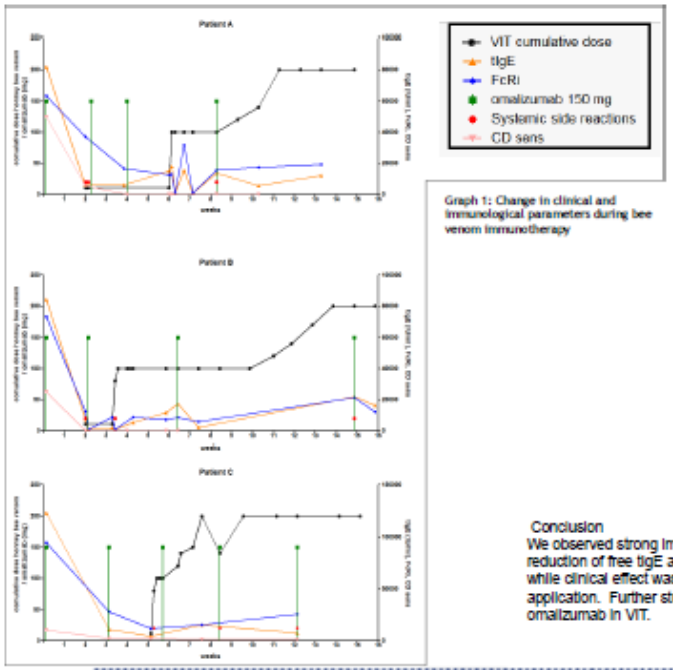
Background
Systemic side reactions (SSR) represents important problem in hymenoptera venom immunotherapy (VIT). High sensitivity of basophils predicts SSR in VIT. Pretreatment with omalizumab can reduce SSR during initiation phase of VIT. Omalizumab inhibit basophil and mast cell activation by allergens and basophil allergen threshold sensitivity (evaluated by CD-sens). It causes rapid reduction of total IgE levels (tIgE) and of the FCERI expression on basophils.

Method
We report on 3 cases of bee-venom allergic patients, where rush bee venom immunotherapy (HAL, Netherlands) initiation was unsuccessful several times due to severe SSR grade 2-4 (evaluated according to Cox et al) at cumulative dose of median of 10 ug of venom. Patients characteristics are summarized in table 1. Patients were than pre-treated with omalizumab 150 mg 2 weeks before rush VIT was initiated, than every 4 weeks. Basophil activation tests with serial bee venom concentration from 0,00001 µg /ml to 1 µg/ml was made and number of total IgE and FCeRI receptors on basophils were measured before each application of omalizumab. CD-sens was calculated as inverted value for the allergen concentration giving a 50% of maximum activation.

Patient	A	B	C
Age	56	56	39
Sex	M	F	M
Comorbidities	no	COPD	no
Basal triptase (ug/L)	7,13	7,8	12,3
Specific IgE to honeybee venom (kIU/L)	3,36	5,65	7.82
Total IgE (IU/ml)	15,8	82	321
Muller grade reaction at field bee sting	IV	IV	IV
Diagnostic BAT (%) 1/0.1/0.01 µg/mL honeybee venom	76/90/72	74/71/55	74/80/38
CD sens honeybee venom	50000,0	25000,0	10020

Table 1. Patients characteristics

Results
All patients had highly sensitive basophils with high CD-sens values (15000-55000). After 1st application of omalizumab we observed marked and statistically significant decrease in CD-sens (to 0.1 -20% of initial value) and also significant decline in free tIgE (to the 7-9% of initial value) while FCeRI density on basophils decreased to 16- 58% of initial value (Table 2). Interestingly rush-VIT was again unsuccessful in patient A and B due to severe grade 2 SSR at cumulative dose of 11.1 mcg. In patient C we waited with VIT until 2nd application. After 2nd application of omalizumab we did not observe further significant decline in Cd-sens, free tIgE or FcRI . VIT was successfully initiated with minor grade 1 SSR 2 weeks after 2nd application of omalizumab in all three patients. In several weeks cumulative dose of 200 ug was achieved, all immunological parameters stayed stable at low levels. Change in in clinical and immunological parameters during bee venom immunotherapy are summarized in Graph 1.



Graph 1: Change in clinical and immunological parameters during bee venom immunotherapy

	Application of omalizumab	Total IgE (IU/ml)	FcRI	CD sens
Patient A	before	81947	63434	50000
	1	5842	37082	5555,6
	2	6232	16870	99,8
	3	15043	12853	4,2
Patient B	before	84439	73251	25000
	1	7733	12428	9,4
	2	1654	8832	5,3
	3	2204	5916	3
Patient C	before	123014	94190	10020
	1	10815	27931	2428
	2	4362	11624	1722
	3	7371	15184	1218

Table 2: Decrease of tIgE, FcRI and CD sens after each application of omalizumab 150 mg

Conclusion
We observed strong immediate immunological changes on basophils, significant reduction of free tIgE and FCeRI already 2 weeks after first application of omalizumab, while clinical effect was observed only after another application and 3-6 weeks after 1st application. Further studies are needed, probably on mast cells, to evaluate effects of omalizumab in VIT.

bolnišnica GOLNIK

Izoliran angioedem po ACE inhibitorjih

Študentki: Eva Cafuta Maček, Cita Zupanc, Medicinska fakulteta, Univerza v Ljubljani
Mentor: prof.dr. Mitja Košnik, Univerzitetna klinika za pljučne bolezni in alergijo, Golnik

IZHODIŠČE

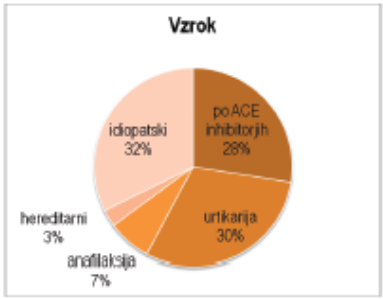
Angioedem je lokalizirano otekanje podkožja in submukoze. Nastane zaradi degranulacije mastocitov ali povečane koncentracije bradikinina. Najpogosteje otečejo jezik, ustnice, obraz in žrelo. Otekanje grla je lahko življenjsko ogrožujoče.

NAMEN

Namen naše raziskave je bil ugotoviti delež z ACE zaviralci povzročenega angioedema.

METODE

Naredili smo retrospektivno presečno analizo bolnikov, ki jim je bila postavljena diagnoza angioedem v Univerzitetni kliniki Golnik med leti 2000 in 2014. Podatke smo pridobili iz podatkovne zbirke Birpis. Nato smo poklicali bolnike in dopolnili anamnezo.



Grafikon 1: Vzrok AE v Sloveniji (skupno število bolnikov: 538)

Grafikon 2: Najpogostejša lokacija AE. Drugi simptomi in znaki: izpuščaj - 22 (14,9%), abdominalne bolečine - 6 (4,1%), dušenje - 45 (30,4%), bolečina - 8 (5,4%), rdečica - 9 (6,1%), srbenje - 18 (12,2%).

Angioedem po ACE inhibitorjih:

Št. epizod	do 2; 52 (38,5%) 3 do 10; 48 (32,4%) več kot 10; 48 (32,4%) ni podatka; 6 (4,1%)
Teža epizode	blaga - 35 (23,6%) zmerna - 57 (38,5%) močna - 45 (30,4%) ni podatka - 11 (7,5%)
Zdravljenje najhujše epizode	niso iskali zdravniške pomoči - 34 (23%) osebni zdravnik oz. urgenca - 67 (45,3%) hospitalizacija - 33 (22,3%) ni podatka - 14 (9,4%)

ZAKLJUČEK

Prejemanje zaviralcev ACE je najpogostejši razlog za pojav izoliranega angioedema.

KLINIČNA UPORABNOST

Prvi ukrep pri bolniku z angioedemom je vprašanje, ali bolnik prejema ACE inhibitor. Če ga prejema, zdravilo zamenjamo. S tem rešimo tretjino problemov. Le, če se angioedemi nadaljujejo, je potrebna nadaljnja diagnostika.

DIAGNOSTIC CHALLENGES IN PATIENTS WITH PERENNIAL RHINITIS

Mark Kačar, Mira Šilar, Renato Eržen, Klemen Jenko, Tanja Soklič, Izidor Kern, Peter Korošec, Mihaela Zidarn

BACKGROUND & AIM

Perennial allergic rhinitis is a common chronic illness affecting the quality of life of millions of patients. Making the proper diagnosis is made harder by the multitude of similar illnesses of different etiologies, as well as the shortcomings of the diagnostic methods used.

The aim of our study was to ascertain the accuracy and usefulness of a wide array of procedures used to diagnose perennial allergic rhinitis. Our prediction was that advanced (and ultimately more expensive) methods would reveal allergy in seemingly »idiopathic« cases where skin prick testing proved inconclusive.

The use of questionnaires also provided us with insight into the most common and disruptive aspects of the illness.

Perennial AR differential diagnosis:

- ·smokers' rhinitis
- ·infectious rhinitis
- ·occupational rhinitis
- ·rhinitis medicamentosa
- ·rhinitis due to chemical or physical irritants
- ·non-allergic rhinitis with eosinophilia syndrome (NARES)
- ·hormonal rhinitis (changes in estrogen/thyroxin/GH levels)

INCLUSION CRITERIA

- Age 18-40yrs
- Perennial allergic rhinitis symptoms using ARIA questionnaire

EXCLUSION CRITERIA

- Sensitization to pet allergens (cat, dog)
- Seasonal allergic rhinitis
- Confirmed nonallergic causes of rhinitis
- Pregnancy

METHODS

- ENT examination to exclude nonallergic causes of rhinitis

- Quantification of serum sIgE to *Dermatophagoides pteronyssinus*, *D. farinae* and mould mix

- In vitro basophil activation test with *D. pteronyssinus*

- Skin prick test with GALEN standard European allergen series

- Cytology of nasal lavage to diagnose patients with NARES

- Quantification of sIgE to *D. pteronyssinus* in nasal lavage supernatant to diagnose local allergic rhinitis

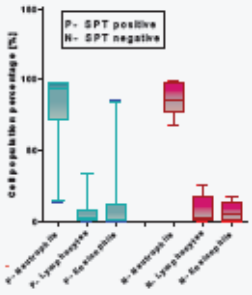
RESULTS

Out of 76 referrals:

- 21 patients exceded the cut-off age,
- 17 had symptoms of seasonal AR ,
- 3 showed symptoms not matching allergic rhinits and
- 15 refused further diagnostic procedures.
- 1 patient was excluded on the basis of her ENT examination.

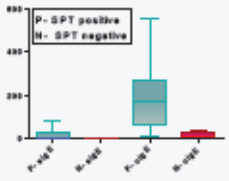
Skin prick tests were positive for *D. pteronyssinus* and/or *farinae* in **7 cases**, **3 other patients** had positive SPTs to perennial allergens; *Alternaria*, *Aspergillus*, *Dijelaj* and *Pulularia*. **9 patients** that were included in the study had all negative SPT's.

No new cases of local allergic rhinitis were proven as nasal provocation testing with *D. pteronyssinus* along with quantification of nasal sIgE for *D. pteronyssinus* were negative in all patients with negative skin prick tests.



Nasal eosinophilia (>3%) was proven in 2 patients with positive SPTs whilst a tentative diagnosis of NARES can be given to 4 other patients (SPT-negative with nasal eosinophilia)

CONCLUSIONS



SERUM TOTAL AND *D. PTERONYSSINUS*-SPECIFIC IgE LEVELS

Patients with no sensitization had significantly lower total IgE levels (mean of 16.59, range 8.78-37.40) than patients with positive SPTs (mean of 1824, range 7.08-557.0)

In vitro serum sIgE quantification confirmed no additional sensitizations among SPT-negative patients.

In vitro basophil activation testing confirmed hypersensitivity in all patients with proven SPTs. **1 IU/ml** gave a sensitivity of **100%** (95% CI between 59.04 and 100%) and a specificity of **90.91%** (95% CI between 58.72 and 99.77%). One patient with negative skin prick tests was found to have a positive BAT to *D. pteronyssinus* at a concentration of 1 IU/ml.

1 IU/ml gave a sensitivity of **85.71%** (95% CI between 42.13% and 99.64%) and a specificity of **100%** (95% CI between 71.51% and 100%)

The prevalence of non-allergic rhinitis was found to be approximately 53%. The entity known as local allergic rhinitis, alleged to be the cause of up to half the cases of non-allergic rhinitis, was not confirmed - either by nasal provocation testing with *D. pteronyssinus* extract or by quantification of sIgE for *D. pteronyssinus* in nasal lavage supernatant.

Quantification of total serum IgE has a high negative predictive value, potentially allowing physicians to exclude allergies from differential diagnoses.

Validation of BAT testing with a wide spectrum of house dust mite recombinant allergens

Mira SILAR[1], Yvonne RESCH[2], Mihaela ZIDARN[1], Susanne VRTALA[2], Peter KOPAC[1], Mitja KOSNIK[1], Rudolf VALENTA[2], and Peter KOROSEC[2]
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2. Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna,

Insert your Logos

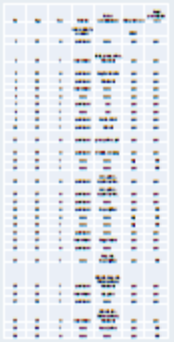
BACKGROUND

- There is a lack of studies regarding the validation of recombinant allergens in BAT testing
- The aim of this study was to establish the optimal dose-response curves for several potent house dust mite (HDM) allergens: Der p 1, Der p 2, Der p 5, Der p 7, Der p 10, Der p 21 and Der p 23

Criteria for validation:
Ideally consider before validation
Commonly defined between or after work done

MATERIALS & METHODS

30 clinically well-characterized subjects



Age: 17-53
Males: 14
Females: 16
Healthy controls: 3
SPT: 27 pos + 3 neg

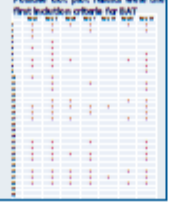
Laboratory testing:

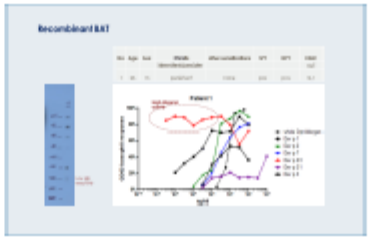
- sIgE for HDM, Total IgE (ImmunoCAP)
- Dot plots
- Basophil activation test (BAT)

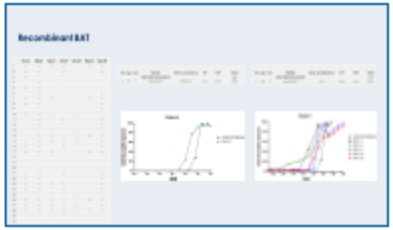
RESULTS

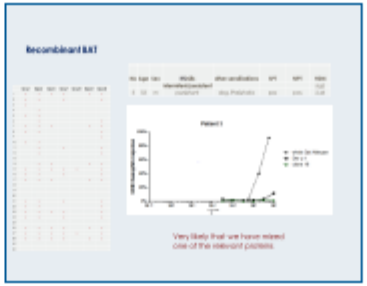
sIgE for HDM, Total IgE (ImmunoCAP)

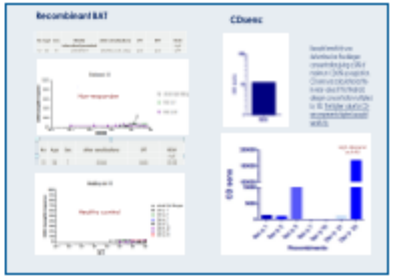
Dot plots
Positive dot plot results were the first indication criteria for BAT



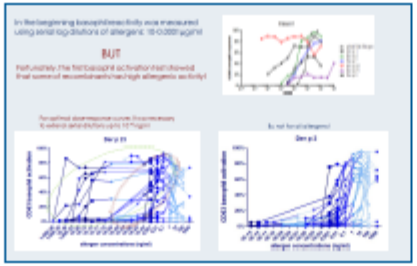








SUMMARY



CONCLUSIONS

- A wide range of recombinant allergen concentrations is necessary to reach the whole dose response curve (Der p 23 and also Der p 5 sensitizations resulted in very high allergenic activity).
- BAT recombinant testing should be performed in two steps: first IgE measurements and second BAT stimulation, because of limited resources of recombinant allergens, patient's blood, laboratory hans-on time and finally, also money.

E – KRONIČNA URTIKARIJA

Julij Šelb dr.med [1], prof. dr. Mitja Košnik dr.med [1]
[1]University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

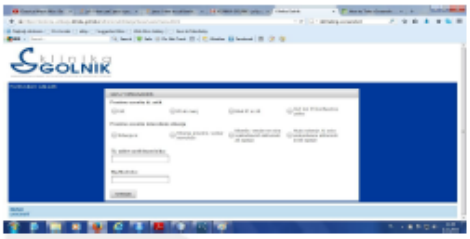
Ozadje

Na Kliniki Golnik za spremljanje bolnikov s težjo obliko kronične urtikarije, ki se zdravijo z omalizumabom, uporabljamo dva vprašalnika : urticaria activity score 7 (UAS 7) vprašalnik ter vprašalnik o kakovosti življenja. Prvi mesec po uvedbi zdravljenja, bolniki na UAS 7 vprašalnik odgovarjajo vsak dan, kasneje pa 7 zaporednih dni v mesecu. Na vprašalnik o kakovosti življenja bolniki odgovarjajo 1 krat na mesec. Do pred 15.9.2014 so bolniki v obliki Excell – ovih tabel pošiljali rezultate vprašalnikov lečečim zdravnikom, ki so nato na podlagi rezultatov prilagajali zdravljenje. Celoten proces je bil manj praktičen in zamuden, predvsem pa zdravnik ni imel ažurnih podatkov o aktivnosti bolezni, od česar je odvisna odločitev o aplikaciji zdravila.

Metode

Razvili smo spletno aplikacijo, ki omogoča bolnikom izpolnjevanje UAS 7 vprašalnika in vprašalnika o kakovosti življenja. Aplikacija je sestavljena je iz dveh delov - dela za bolnike in dela za zdravnike, do katerih se dostopa preko ločenih spletnih naslovov. Oba naslova gostujeta na strežniku klinike Golnik.
Bolnikom uporabniške račune ustvarjajo zdravniki, ki so uporabniki aplikacije. Ob generiranju uporabniškega računa bolnik na e-poštni naslov prejme obvestilo prijavi v spletno aplikacijo z uporabniškim imenom in geslom, ki sestoji iz 8. simbolov.
Ob primernih datumih (prvi mesec po vpisu vsak dan, kasneje, ko se lečeči zdravnik odloči da bo spremenil interval, pa 7 zaporednih dni v mesecu), bolnik dobiva e-poštna sporočila z obvestilom o potrebi po izpolnjevanju vprašalnikov ter povezavo za dostop do spletnega naslova aplikacije. Odgovori na rešene vprašalnike, se shranjujejo v bazo podatkov na strežniku klinike Golnik. Rezultate lahko pregleduje bolnikov lečeči zdravnik preko prijave v predel aplikacije, ki je namenjen zdravnikom.

Na potrebo po pregledu rezultatov zdravnika ob primernih datumih opomni e-poštno sporočilo, ki ga aplikacija pošlje na zdravnikov e-poštni naslov.
Podatki se preko telekomunikacijskega omrežja med strežnikom in uporabnikom prenašajo kriptirani z visokostopenjskim kriptiranjem (TLS, 128 bitni ključ). Za prenos veljajo načela t.i. močne enkripcije, zaradi česar je aplikacija v skladu z 2.odstavkom 14. člena zakona o varovanju osebnih podatkov . (slika – predel za bolnike)



Rezultati

V 38 dneh delovanja aplikacije smo v sistem vpisali 5 bolnikov, ki so 64 – krat (od pričakovanih 77 – krat) izpolnili vprašalnik UAS7 (83% odzivnost) in 6 - krat (od pričakovanih 9 – krat) rešili vprašalnik o kakovosti življenja (67% odzivnost).
V zadnjih 11 dneh od dneva obdelave podatkov (23.10) je bila odzivnost za reševanje vprašalnika UAS7 večino dni 100%.
Sistem je deloval brez napak, ena bolnica je imela težave s prijavljanjem v sistem, ki so bile posledice menjave gesla in so izginile, ko smo ji ponastavili geslo.

Zaključki

Odzivnost bolnikov je bila dobra. Odzivnost se je v zadnjem obdobju, najverjetneje ker so se bolniki na aplikacijo navadili, še povečala. Pritožb uporabnikov ni bilo. Zato bomo z nudenjem storitve nadaljevali.

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Comparison of diagnostic sensitivity of basophil activation test (BAT) and specific IgE in patients with confirmed immediate amoxicilline hypersensitivity

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University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

BACKGROUND

Because of low sensitivity and specificity of in-vitro tests for penicillin, allergy skin testing (ST) and drug provocation tests (DPT) are the mainstays of the diagnostics of hypersensitivity reactions to those antibiotics.

OBJECTIVES

We wanted to analyze:

- if sensitivity of BAT is better than that of sIgE against amoxicillin / penicillin.
- Where BAT fits into diagnostic algoritm

MATERIALS & METHODS

Design: open, retrospective study
Patients: presumably immediate penicillin/amoxicillin hypersensitivity (immediate reaction or delayed urticaria) in majority up to a year after episode. Patients had positive either ST or DPT (few exceptions). Control patients (majority of them) had positive late ST, or negative DPT. In-vitro tests were performed after in-vivo tests.
BAT: Allergens prepared by Buhlmann as well as commercially available drugs.
BAT was considered positive when stimulation index was >2 and at least 5% of basophils were activated by allergen.
BAT was considered true positive in patients with immediate ST or DPT reaction. In patients with delayed ST or DPT reaction a negative BAT was considered true negative.

REFERENCES

ENDA (European Network for Drug Allergy). Diagnosis of immediate-type beta-lactam allergy in vitro by flow-cytometric basophil activation test and sulfidoleukotriene production: a multicenter study. J Investig Allergol Clin Immunol 2009;19:91-109.

RESULTS

Table 1.- Amoxicillin

Patient	BAT Stimulation Amoxi SI	BAT Id Amoxi SI	BAT PENG SI	BAT PENV SI	sIgE penV	CAP penG	CAP amox	Culprit	Reaction	Beginning	Skin tests	DPT	
1	1,68	6,66	ND	ND	<	<	<	amoxicilin	anaphylaxis	immediately	amoxicilin+clav id positive		True positive
2	3,88	ND	20,66	20,66	<	<	3,88	amoxicilin	anaphylaxis	immediately	amoxicilin+clav id positive		True positive
3	2,15	3,66	1,62	1,62	<	<	<	amoxicilin	anaphylaxis	20 minut	amoxicilin+clav prick positive		True positive
4	2,15	3,07	ND	ND	<	ND	<	amoxicilin	anaphylaxis	30 minutes	amoxicilin+clav prick positive		True positive
5	3,91	ND	ND	ND	ND	ND	ND	amoxicilin	anaphylaxis	20 minutes	amoxicilin+clav prick positive		True positive
6	3,46	ND	ND	ND	ND	ND	<	amoxicilin	urticaria	20 minut	amoxicilin+clav id positive		True positive
7	4,91	ND	ND	ND	ND	ND	<	amoxicilin	urticaria	7 days	amoxicilin+clav negative	amoxicillin positive (immediate)	True positive
8	ND	2,52	ND	ND	ND	ND	<	amoxicilin	urticaria	30 minutes	amoxicilin+clav prick positive		True positive
9	3,77	3,66	ND	ND	<	ND	1,51	amoxicilin	urticaria	30 minutes	amoxicilin+clav prick positive		True positive
10	5,06	ND	ND	ND	ND	<	7,08	amoxicilin	urticaria	30 days	amoxicilin+clav negative	amoxicillin, 14 days, negative	False positive
11	1,15	ND	ND	ND	<	<	<	amoxicilin	anaphylaxis	immediately	amoxicilin, prick positive		False negative
12	1,15	1,23	ND	ND	<	<	<	amoxicilin	anaphylaxis	1 hour	amoxicilin+clav id positive		False negative
13	1,14	0,41	ND	ND	ND	ND	ND	amoxicilin	urticaria	5 days	amoxicilin, prick positive		False negative
14	1,41	ND	ND	ND	0,82	1,41	1,05	amoxicilin	urticaria	2 hours	amoxicilin+clav prick positive		False negative
15	1,05	ND	ND	ND	<	<	ND	amoxicilin	urticaria	6 days	amoxicilin+clav neg	amoxicilin+clav positive (immediate)	False negative
16	1,05	0,82	0,50	0,50	ND	ND	ND	amoxicilin	urticaria	20 minutes	amoxicilin, prick positive		False negative
17	0,39	ND	ND	ND	ND	ND	ND	penicillin	? (childhood)	??	amoxicilin, id positive		False negative
18	0,65	ND	ND	ND	ND	ND	ND	amoxicilin	urticaria	5 days	amoxicilin+clav neg	amoxicilin+clav positive (immediate)	N/A
20	0,31	ND	1,58	1,58	<	<	<	amoxicilin	anaphylaxis	20 minutes	amoxicilin+clav negative	ND	True negative
19	ND	1,59	ND	ND	ND	ND	ND	amoxicilin	urticaria	6 days	amoxicilin+clav late id positive	ND	True negative
21	1,05	1,04	ND	ND	ND	ND	ND	amoxicilin	urticaria	2 hours	amoxicilin+clav late id positive	ND	True negative
HC A	0,05	1,09	ND	ND	ND	ND	ND	No	No		No		Healthy controls
HC B	0,07	0,83	ND	ND	ND	ND	ND	No	No		No		Healthy controls
HC C	0,46	0,69	ND	ND	ND	ND	ND	No	No		No		Healthy controls

Amoxicillin		
%	BAT	No
42,86	True positive	9
14,29	False positive	1
36,84	False negative	7
4,76	True negative	1
Healthy controls	True negative	3

5 anaphylaxis, 3 immediate urticaria, 1 delayed urticaria, 6 positive ST+D prick, 2 id; 1 negative ST (positive DPT)
1 delayed urticaria — positive ST and DPT
2 anaphylaxis*, 5 delayed reactions — 6 positive ST+D prick, 2 id; 2 negative ST (positive DPT) *anaphylaxis: 2 positive DT
2 delayed reactions, 1 anaphylaxis — 2 positive late id ST, 1 negative ST

	BAT	sIgE
Prevalence	0,63	0,60
Sensitivity	0,56	0,22
Specificity	0,75	1,00
False negative rate	0,47	0,78
False positive rate	0,25	0,00
Predictive value of a positive test	0,82	1,00
Predictive value of a negative test	0,57	0,46
Reliability	0,67	0,53

Table 2.- Penicillin V

Patient	BAT PENG SI	BAT PENV SI	sIgE penV	CAP penG	CAP amox	Culprit	Reaction	Beginning	Skin tests Pen G	DPT	
1	1,67	2,33	<	ND	ND	Pen V	urticaria	30 minutes	prick positive		True positive
2	2,65	4,02	<	<	ND	Pen V	urticaria	20 minutes	id positive		True positive
3	0,32	0,26	22,40	<	ND	Pen V	anaphylaxis	2 hours	prick positive		False negative
4	<	0,62	<	<	ND	Pen V	urticaria	1 day	negative	positive	False negative
5	0,76	1,19	<	<	ND	Pen V	urticaria	2 hours	ND	positive	False negative
6	<	0,81	ND	ND	ND	Pen V	urticaria	?	negative	positive	False negative
7	0,94	0,94	<	ND	ND	Pen V	?	?	negative	positive	False negative
8	1,00	0,56	7,42	ND	1,26	Pen V	rush	?	neg	positive	False negative
9	0,67	0,28	<	<	<	Pen V	palmar pruritus	1 hour	id positive		False negative
10	0,28	0,28	<	<	<	Pen V	palmar pruritus	1 hour	id positive		False negative
11	0,49	1,35	<	<	ND	Pen V	anaphylaxis	5 days	late positive		True negative
12	<	0,47	<	<	ND	Pen V	urticaria	1 day	negative	negative	True negative
13	ND	0,82	<	<	<	Pen V	angioedema	5 days	negative	ND	True negative
14	0,74	1,08	<	<	<	Pen V	angioedema	?	negative	negative	True negative
15	ND	0,74	<	<	ND	Pen V	rush	5 days	late positive		True negative
16	ND	1,58	<		ND	Pen V	? (childhood)	?	negative	ND	True negative

Penicillin V		
%	BAT	No
12,5	True positive	2
0	False positive	0
50	False negative	8
37,5	True negative	6

BAT	sIgE	
0,63	0,60	Prevalence
0,20	0,22	Sensitivity
1,00	1,00	Specificity
0,80	0,78	False negative rate
0,00	0,00	False positive rate
1,00	1,00	Predictive value of a positive test
0,43	0,46	Predictive value of a negative test
0,50	0,53	Reliability

BAT was positive at the highest concentration only (amoxiciline 0,833 mg/ml; penicilin V 1,33 mg/ml):

Amoxiciline (table 1):
9 true positive BAT. In only 2 patients we found positive sIgE.
6 false negative BAT. 1 skin test positive patients was also sIgE positive.
1 false positive BAT. ST positive, sIgE positive, DPT negative.
4/18 pts had a history of delayed urticaria but positive immediate tests.

Penicilin V (table 2):
2 true positive BAT. Both sIgE negative.
7 false negative BAT. In 2 patients we found positive sIgE. 1 of those was ST negative.

CONCLUSIONS

- BAT has much higher diagnostic sensitivity in patients with immediate hypersensitivity to amoxicillin compared to ImmunoCAP sIgE.
- BAT was only positive in the highest concentration.
- Most of BAT or sIgE positive patients were ST positive.
- Not all patients with positive IgE tests reacted in DPT
- Many delayed urticaria seems IgE mediated
- Further analyses are necessary to identify groups of patients who might benefit from BAT. We hypothesize, that BAT might be used to confirm diagnosis in skin test negative patients **with a history of severe immediate reaction** to amoxicillin / penicillin V thus avoiding DPT

Disclosures

In relation to this presentation, I declare that there are no conflicts of interest.

Immunological changes precedes clinical effects of omalizumab in venom immunotherapy

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Background

Systemic side reactions (SSR) represents an important problem in *Hymenoptera* venom immunotherapy (VIT). High sensitivity of basophils predicts SSR in VIT. Pretreatment with omalizumab can reduce SSR during the initiation phase of VIT. Omalizumab inhibits basophil and mast cell activation by allergens and basophil allergen threshold sensitivity (evaluated by CD-sens). It causes rapid reduction of total IgE levels (tIgE) and of the FcεRI expression on basophils.

Methods

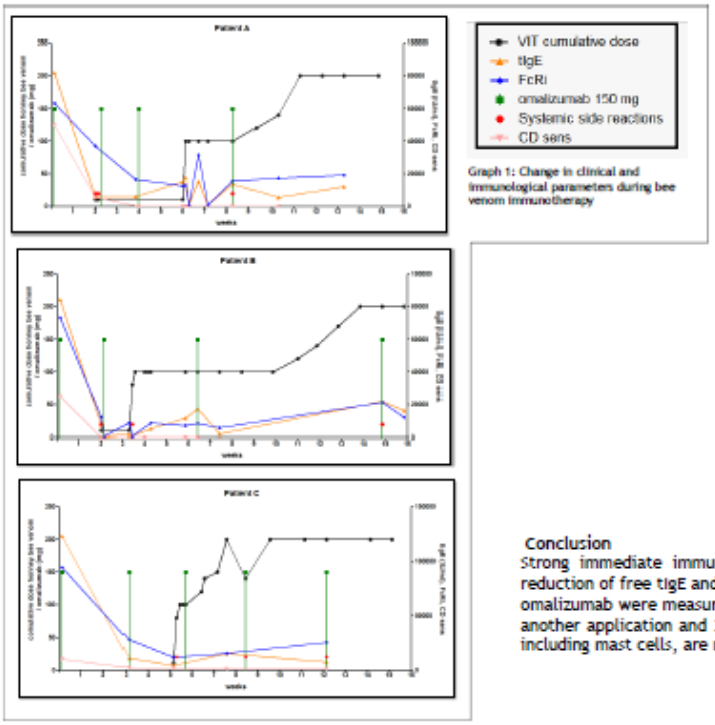
We report on 3 cases of bee-venom allergic patients, where rush bee venom immunotherapy (HAL, Netherlands) initiation was unsuccessful several times due to severe SSR grade 2-4 (evaluated according to Cox et al) at cumulative dose of median of 10 ug of venom. Patients were than pre-treated with omalizumab 150 mg 2 weeks before rush VIT was initiated, than every 4 weeks. Patients characteristics are summarized in Table 1. Basophil activation tests with serial bee venom concentration from 0.,00001 µg /ml to 1 µg/ml was made and numbers of total IgE and FcεRI receptors on basophils were measured before each application of omalizumab. CD-sens was calculated as inverted value for the allergen concentrations giving a 50% of maximum activation.

Patient	A	B	C
Age	56	56	39
Sex	M	F	M
Comorbidities	no	COPD	no
Basal triptase (ug/L)	7,13	7,8	12,3
Specific IgE to honeybee venom (kIU/L)	3,36	5,65	7.82
Total IgE (IU/ml)	15,8	82	321
Muller grade reaction at field bee sting	IV	IV	IV
Diagnostic BAT (%) 1/0.1/0.01 µg/mL honeybee venom	76 / 90/ 72	74/ 71 /55	74/ 80/ 38
CD sens honeybee venom	50000	25000	10020

Table 1: Patients characteristics

Results

All patients had highly sensitive basophils with high CD-sens values (15000-55000). After 1st application of omalizumab we observed marked and statistically significant decrease in CD-sens (to 0.1 -20% of initial value) and also significant decline in free tIgE (to the 7-9% of initial value) while FcεRI density on basophils decreased to 16- 58% of initial value (Table 2). Interestingly rush-VIT was again unsuccessful in patient A and B due to severe grade 2 SSR at cumulative dose of 11.1 mcg. In patient C we waited with VIT until 2nd application. After the 2nd application of omalizumab we did not observe further significant decline in CD-sens, free tIgE or FcεRI . VIT was successfully initiated with minor grade 1 SSR 2 weeks after the 2nd application of omalizumab in all three patients. In several weeks cumulative dose of 200 ug was achieved. All immunological parameters stayed stable at low levels. Changes in in clinical and immunological parameters during bee venom immunotherapy are summarized in Graph 1.



Graph 1: Change in clinical and immunological parameters during bee venom immunotherapy

	Application of omalizumab	Total IgE (IU/ml)	FcRI	CD sens
Patient A	before	81947	63434	50000
	1	5842	37082	5555,6
	2	6232	16670	99,8
	3	15043	12653	4,2
Patient B	before	84439	73251	25000
	1	7733	12428	9,4
	2	1854	8832	5,3
	3	2204	5916	3
Patient C	before	123014	94190	10020
	1	10815	27931	2428
	2	4362	11624	1722
	3	7371	15184	1218

Table 2: Decrease of tIgE, FcRI and CD sens after each application of omalizumab 150 mg

Conclusion

Strong immediate immunological changes on basophils and significant reduction of free tIgE and FcεRI already 2 weeks after first application of omalizumab were measured, while clinical effect was observed first after another application and 3-6 weeks after 1st application. Further studies, including mast cells, are needed to evaluate effects of omalizumab in VIT.

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Association between 17q12-17q21.1 polymorphisms, haplotypes and adult asthma

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Background

One of the major asthma susceptibility locus **17q12-17q21.1** harbours several single nucleotide polymorphisms (SNPs) with significant asthma association in diverse ethnic groups. However, data on **adult asthma** association are still conflicting. Locus 17q12-17q21.1 harbours genes which were shown to be involved in inflammation through induction of the pro-inflammatory cytokines (*CSF3;* colony stimulating factor 3) or triggering the unfolded protein response (*ORMDL3;* ORM1-like 3 (*S. cerevisiae*)). For others, such as *MED24* (mediator complex subunit 24) and *GSDMA* (gasdermin A) high expression was reported in lungs. However, for some, such as *PSMD3* (proteasome non-ATPase regulatory subunit 3), *ZBPB2* (zona pellucida binding protein 2) and *GSDMB* (gasdermin B), no functions in asthma were yet proposed. The aim of the current study was to explore the association of **13 tag SNPs in 17q12-17q21.1 region and its haplotypes with asthma risk and different asthma phenotypes in Slovenian adults.**

Methods

We conducted a genetic association study comprising **418 adult patients with asthma** (Table 1) and **288 controls**. Association analysis for 13 tag SNPs and haplotypes from 17q12-17q21.1 locus (Figure 1) for asthma risk was performed. Furthermore, several asthma phenotypes (lung functions, differential blood counts, atopy, smoking and asthma onset) were included in single SNP analysis.

Table 1. Clinical characteristics of asthma patients.

Characteristic	Asthma (total enrolled = 418)
Male, n (%)	160 (38.3)
Age, median (IQR)	45.0 (24.7)
Atopy, n (%)	239 (59.2)
VC%, median (IQR)	100 (20)
FEV1%, median (IQR)	86 (20)
Childhood asthma, n (%)	66 (17.0)
Smoking, n (%)	113 (30.2)
Eosinophil %, median (IQR)	3.0 (3.8)
Neutrophil %, median (IQR)	60.9 (12.8)
Lymphocyte %, median (IQR)	26.6 (11.9)
Monocyte %, median (IQR)	8.1 (3.1)
Basophil %, median (IQR)	0.4 (0.3)

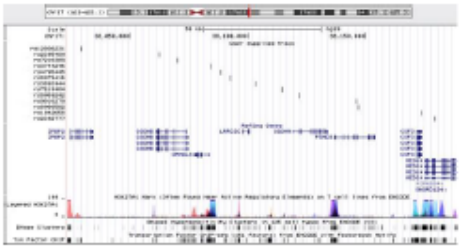

Figure 1. Schematic presentation of analysed SNPs in 17q12-21.1 locus. below (UCSC Genome browser, GRCh37/hg19).

Results

From 13 SNPs in 17q12-17q21.1 locus analysed, 5 were suggestively associated with adult asthma in Slovenian patients (Table 2). The most associated was rs7219080 located in *GSDMA*. Others associated with adult asthma were rs2305480 and rs7216389 in *GSDMB*, rs12936231 in *ZPBP2* and rs4795405 located near *ORMDL3*. Several SNPs were associated with eosinophil blood counts (Table 2).

Asthma phenotypes and 17q12-17q21.1 associations are shown in Table 3. No association was found with lung function or atopy.

Table 3. SNPs associated with asthma phenotypes.

dbSNP	Gene	Allele 1/2	Childhood asthma onset n (%) 1/1	1/2	2/2	Adult asthma onset n (%) 1/1	1/2	2/2	Genotype risk *P* value, OR
rs2305480	*GSDMA*	A/G	8 (12)	28 (42)	30 (45)	59 (18)	161 (50)	101 (32)	0.065[D] 1.80
rs8066582	*PSMD3*	C/T	20 (30)	27 (41)	19 (29)	101 (34)	168 (52)	53 (17)	0.004[R] 2.05
			Ever-smokers n (%)			Non-smokers n (%)			
rs9916279	*PSMD3*	C/T	6 (5)	38 (34)	68 (61)	6 (2)	58 (22)	198 (76)	0.006[D] 2.05

D – dominant genetic model, R – recessive genetic model

Table 4. Asthma associated haplotypes.

Haplotype*	Asthma n (%)	Control n (%)
1: TCCG	167 (40)	79 (28)
2: TTTA	141 (34)	65 (23)
3: CCCA	66 (16)	38 (13)
4: TTCA	33 (8)	12 (4)
5: TTCG	2 (1)	35 (12)
6: TCCA	1 (0)	27 (10)
7: TCTA	3 (1)	20 (7)
8: TTTG	4 (1)	8 (3)

Haplotype vs. others	*P* value	OR (95% CI)
1	0.0007	1.76 (1.27-2.44)
1+2	< 0.0001	2.80 (2.04-3.85)
1+3+6+4	< 0.0001	17.93 (9.38-34.26)
5	< 0.0001	28.77 (6.86-120.70)

Table 2. 17q12-17q21.1 SNPs associated with adult asthma and blood eosinophil %.

dbSNP	Gene	Allele 1/2	Asthma n (%) 1/1	1/2	2/2	Controls n (%) 1/1	1/2	2/2	Genotype risk Adjusted *P* value, OR (95% CI)	Eosinophil %, median (IQR) 1/1	1/2	2/2	*P* value
rs2305480	*GSDMA*	A/G	72 (17)	205 (49)	141 (34)	65 (23)	141 (49)	82 (28)	0.036[D] 1.31 (1.06-1.22)	1.7 (5.5)	3.7 (3.4)	2.3 (2.7)	0.043
rs8093044	*Intergenic*	C/T	131 (31)	206 (49)	81 (19)	78 (27)	156 (54)	59 (18)	NS	2.2 (2.8)	3.7 (3.8)	1.3 (3.1)	0.003
rs4795405	*LOC283*	C/T	144 (34)	204 (49)	70 (17)	86 (30)	137 (48)	65 (23)	0.018[D] 1.54 (1.05-2.26)	2.5 (3.6)	3.6 (3.6)	1.70 (3.5)	NS
rs7216389	*GSDMB*	C/T	90 (22)	206 (49)	122 (29)	80 (28)	137 (48)	71 (25)	0.024[D] 1.32 (1.01-1.21)	1.8 (5.1)	3.6 (3.7)	2.3 (2.8)	NS
rs7219080	*GSDMA*	A/C	57 (14)	181 (43)	180 (43)	42 (15)	151 (52)	95 (33)	0.004[R] 1.60 (1.17-2.21)	0.9 (2.8)	3.7 (3.4)	2.6 (2.5)	0.003
rs8069202	*GSDMA*	A/G	89 (21)	209 (50)	120 (29)	52 (18)	14 (50)	92 (32)	NS	2.1 (2.8)	3.6 (3.8)	2.8 (4.9)	0.009
rs12936231	*ZPBP2*	C/G	118 (28)	212 (51)	88 (21)	69 (24)	140 (49)	79 (27)	0.019[D] 1.54 (1.07-2.19)	2.3 (2.8)	3.6 (3.7)	2.1 (5.2)	NS
rs8079416	*ORMDL3*	C/T	81 (19)	216 (52)	121 (29)	51 (18)	143 (50)	96 (33)	NS	2.1 (3.0)	3.3 (3.7)	2.9 (4.9)	0.047

D – dominant genetic model, R – recessive genetic model

The most significant result of our study is an association of haplotypes consisting of rs9916279, rs8066582, rs1042658 and rs2302777 with asthma risk. These polymorphisms are located in a region harbouring ***PSMD3, CSF3 and MED24* genes** (Table 4).

*Haplotype: rs9916279, rs8066582, rs1042658, rs2302777

Conclusions

We report the importance of analysing **haplotypes in addition to single SNPs** in asthma risk association studies. While only suggestive associations were found for single SNPs and adult asthma risk, association with haplotypes was highly significant; supporting the hypothesis that **17q12-17q21.1 locus harbours an important genetic determinant for asthma risk**. SNPs that comprise haplotypes and SNPs in LD ($r^2 > 0.8$) with them are binding sites for GATA-1, GATA-2 and STAT3 proteins and they cause change in GATA motifs. GATA-1 and GATA-2 were shown to bind and inhibit STAT3, which is required for asthma airway inflammation, eosinophilia and Th2 cells lung recruitment. This data could suggest that the 17q12-17q21.1 polymorphisms do not necessarily affect only the genes located relatively close, such as *ORMDL3*. However, further functional studies are needed. Two of analysed SNPs were associated with childhood asthma onset and one with asthma in smokers, which suggests previously known – **different genetic backgrounds for different asthma phenotypes** or not yet uniformely determined different asthma endotypes.

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Karakteristike bolnikov, ki so bili hospitalizirani zaradi poslabšanja astme

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Namen

Naš namen je bil preučiti značilnosti bolnikov z astmo, ki so zaradi poslabšanja potrebovali hospitalizacijo in ugotoviti dejavnike, ki so morda vplivali na slabo urejenost astme.

Metode

V retrospektivno raziskavo smo vključili 352 bolnikov, ki so bili hospitalizirani v Kliniki Golnik v obdobju štirih let (2009-2012). Na podlagi podatkov, pridobljenih iz informacijskega sistema, smo bolnike razdelili v štiri fenotipske skupine: atopijska astma s pojavom v otroštvu ali odrasli dobi ter neatopijska astma s pojavom v otroštvu ali odrasli dobi. Natančno smo preverjali, kako je bila astma urejena v obdobju zadnjega leta pred hospitalizacijo. Podatki so prikazani kot povprečje s standardno napako.

Rezultati

Pri 77 (21.9%) bolnikov smo zaznali slabo urejenost astme s pogostimi poslabšanji v zadnjem letu pred hospitalizacijo. Med vzroki za slabo urejenost smo ugotavljali statistično pomembno pogosteje zabeleženo slabše sodelovanje bolnikov v primerjavi s skupino z dobro urejeno astmo. Ostali dejavniki tveganja (kajenje, komorbidnost, izpostavljenost alergenom ali dražljivcem) so bili pri bolnikih z neurejeno astmo prisotni, vendar ne signifikantno drugačni med skupinama.

Tabela 1. Značilnosti bolnikov vključenih v raziskavo

Karakteristike bolnikov	Vsi pacienti	Atopijska astma s pojavom v otroštvu	Atopijska astma s pojavom v odrasli dobi	Neatopijska astma s pojavom v otroštvu	Neatopijska astma s pojavom v odrasli dobi
Starost	61 (0,9 %)	40,6 (2,9 %)	59,8 (1,6 %)	46,2 (4,6 %)	67,3 (1,0 %)
Ženske	199	21	62	7	109
Moški	153	13	42	6	92
VCmax(%)	92,4 % (1,0)	98,0 % (2,8)	91,8 % (1,6)	97,2 % (5,9)	91,4 % (1,4)
FEV1max(%)	78,6 % (3,2)	77,7 % (3,7)	73,8 % (1,9)	80,75 % (7,4)	81,1 % (6,4)
BMI(kg/m2)-Mean(SEM)	28,8 (0,3)	26,12 (0,77)	28,31 (0,60)	26,81 (2.03)	29,62 (0,42)

Diagram 1. Delež izbranih fenotipov med astmatiki (n=352)

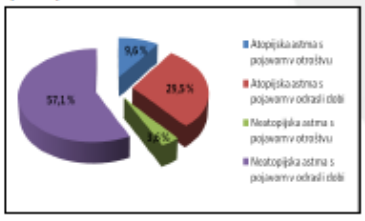


Diagram 2. Pogostost pridruženih bolezni pri vključenih bolnikih (n=352)

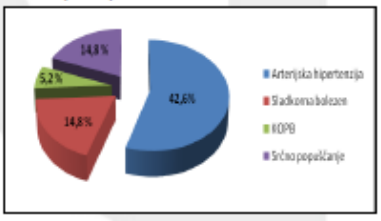
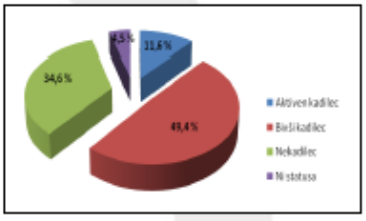


Diagram 3. Kadilski status pri vključenih bolnikih (n=352)



Zaključki

Pri večini hospitaliziranih astmatikov smo ugotovili astmo s pojavom v odrasli dobi, prekomerno telesno težo in vsaj eno od pridruženih kroničnih bolezni. Slabo urejenost astme pred hospitalizacijo smo zaznali pri približno petini bolnikov, pri katerih je od dejavnikov tveganja pomembno izstopalo slabo sodelovanje.

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Reduced expression of let-7a in bronchial biopsies of severe asthmatics

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Introduction

Asthma is a chronic inflammatory airway disease, characterized by airway hiperreactivity, airway obstruction, mucus hypersecretion, and different rates of remodelling. It is one of the most common chronic diseases, affecting more than 300 million people worldwide. A majority of patients achieve good symptom control and minimal exacerbation using regular controller therapy; however, up to 10% of patients classified as severe asthmatics can-not be adequately controlled despite the use of all currently available therapeutic approaches. Previous studies have revealed the potential important role of miRNAs in the regulation of variety of inflammatory processes, including asthma.

Materials and Methods

Twenty-four patients treated at the University Clinic for respiratory and allergic diseases Golnik from 2010 to 2012 with diagnosis of asthma according to The Global Initiative of Asthma (GINA) guidelines, were included. Twelve patients were classified as mild and 12 patients as severe asthmatics. As controls 10 patients were used with no known chronic disease, in six of them bronchoscopy was indicated because of prolonged cough that was finally attributed as a consequence of gastro-esophageal reflux disease (GERD) and four of them had haemoptysis with normal radiologic, endoscopic and lung function findings.

Bronchial biopsies were taken during diagnostic procedures with flexible bronchoscope and were immediately formalin fixed and then paraffin embedded using standard procedures.

Total RNA was extracted from FFPE tissue sections. Quantitative PCR was used to analyse the expression of selected miRNAs, specifically let-7a, miR-21 and miR-223, that were shown to have important roles in asthma pathogenesis, either directly or indirectly repressing the translation of crucial factors such as STAT3, IL-6, IL-1β, IL-13, IFN-γ, TGF-β receptor, TLR4, and VEGF in bronchial biopsies.

Results

We found significantly reduced expression of let-7a in bronchial biopsies from patients with severe asthma in comparison to patients with mild asthma as well as to the non-asthmatic controls. On the other hand, no significant differences in miR-21 and mir-223 expression were found between different groups analysed.

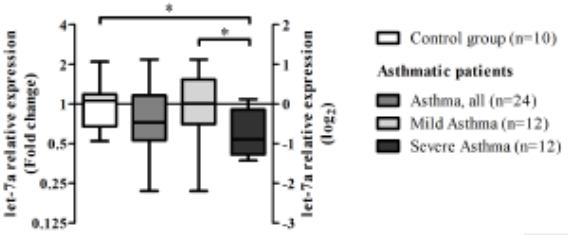

Figure 1. Analysis of let-7a expression in bronchial biopsies from control individuals and patients with different asthma severity. Data are presented as median with range and interquartile range. * $P < 0.05$

Table 1. Characteristics of the study groups.

Study group	Control group n=10	Mild asthma n=12	Severe asthma n=12
Male/Female	4/6	5/7	6/6
Age (years), median (IQR)	53.5 (29.5)	44 (24)	54.5 (17.8)
BMI (kg/m^2), median (IQR)	26 (6.5)	28 (8.6)	30 (6.2)
Vital capacity (%),median (IQR)	104 (6.2)	106 (31.8)	86 (27.8)[a*]
FEV_1 % predicted, median (IQR)	104 (23)	95 (27.6)	67 (24)[b,**]
TI (%),median (IQR)	80 (11.5)	73 (5.5)	52 (18.5)[b,***]
TLCO (%), median (IQR)	88 (23)	91 (22.5)	78 (37)
Hystology of eosinophil bronchitis	0	4	4
Atopy	3	4	6
Smoking status; never, current, ex	4, 4, 2	10, 2, 0	5, 0, 7
No. of M-SAE/year, median (IQR)	/	0 (0)	1 (2.5)[b,**]
No. of MAE/year, median (IQR)	/	1 (0.8)	3 (3.5)[b,**]
Asthma therapy			
LABA/ICS, ICS alone, ALT	/	9, 3, 3	10, 2, 6
OCS continuously, ≥3×, 1–2× per year	/	0, 0, 1	2, 4, 3[a,**]

[a] Statistically different between Severe and Mild asthmatics.
[b] Statistically different between Severe asthmatics and both Mild asthmatics and Controls.
BMI = Body mass index; TI = Tiffeneau index; TLCO = Transfer factor of the lung for carbon monoxide; M-SAE = Moderate-severe asthma exacerbations; MAE = Mild asthma exacerbations; LABA = Long acting beta agonist; ICS = Inhaled corticosteroid; ALT = Antileukotriene; OCS = Oral corticosteroid.
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

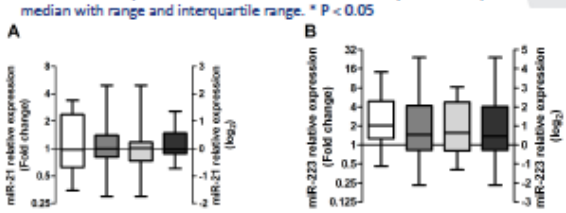

Figure 2. Analysis of (A) miR-21 and (B) miR-223 expressions in bronchial biopsies from control individuals and patients with different asthma severity. Data are presented as median with range and interquartile range.

Conclusions

Reduced let-7a levels in bronchial biopsies of patients with severe, therapy resistant asthma, could not only be used as a potential biomarker to discriminate between different asthma phenotypes, but also might be a target for modulation of treatment at the inflammatory site for a group of patients that are most affected and still lack the efficient treatment.

All authors declare that there is no conflict of interest.

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Immunocytochemistry evaluation of FKBP51 in induced sputum cells as a biomarker of glucocorticoid therapy in asthma

Mihaela Zidarn[1], Susan Wilson[2], Peter Howarth[2]

[1]University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia
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Background

Glucocorticosteroid therapy is a cornerstone of asthma therapy. However, not all patients with asthma improve with such therapy, even at high doses. There is no biological markers in such patients that can determine whether their inadequate response is due to poor compliance or steroid unresponsive disease. We have thus investigated whether the immunohistochemical staining for FK506 binding protein 51 (*FKBP51*) in induced sputum cytospin samples could be used. FKBP51 is a co-chaperone of GR, upregulated by corticosteroids and has been implicated in modulating steroid receptor function.

Methods

Immunostaining for FKBP51 protein expressionn was evaluated in induced sputum cell cytospins from healthy controls and asthmatics (mild and severe). The presence of staining in each entire slide was evaluated by light microscopy.

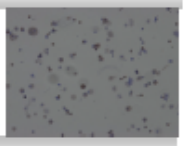

Figure 1:
Example of stained slide

Results

FKBP51 staining was present in macrophages and neutrophils. Other cell types rarely stained. Most neutrophils were stained with the same pattern. Staining was most intense at the border of the nucleus.

Figure 2:
Positive staining for FKBP51 at the border of nucleus was present in 35 of 94 severe asthma patients and in one of 15 mild asthma patients. None of 7 control subjects had a similar staining pattern.

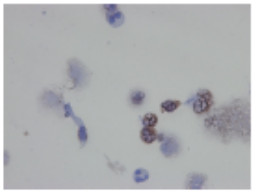

Figure 3:
Staining in macrophages was present in healthy and asthma subjects in similar proportions

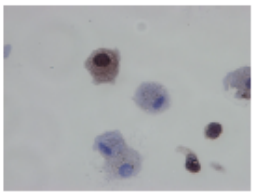

Figure 4:
Staining of eosinophil nucleus was present in one subject with asthma

Figure 5:
In one sample of healthy individual intense staining of the whole nucleus of the neutrophils was present.

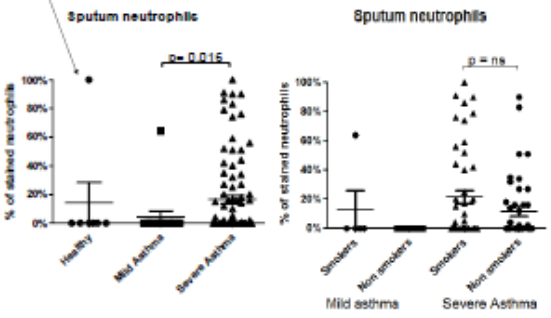

Figure 6:
Staining of sputum neutrophils was significantly more prevalent in patients with severe asthma. The difference between current and ex-smokers and life time non smokers was not statistically significant.

Conclusions

FKPB51 staining pattern in neutrophils from induced sputum of severe asthma patients differs from mild asthma and healthy controls. The accumulation of FKBP51 in these cells may contribute to their steroid resistant disease.

Acknowledgment: The authors would like to thank Clair Barber, Helen Rigden and Jon Ward for contribution.

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Glucocorticoid-induced osteoporosis and adrenal insufficiency in 37 patients with interstitial pulmonary diseases

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[1]University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia

Aim

Osteoporosis is a common complication of glucocorticoid therapy. Awareness has grown in recent years, yet it remains under-diagnosed and under-treated. Our aim was to assess everyday practice in management of glucocorticoid-induced bone disease and possible adrenal insufficiency in patients, treated with methylprednisolone.

Methods

We retrospectively examined documentation of 37 patients treated for interstitial pulmonary diseases at University Clinic of Respiratory and Allergic Diaseases Golnik, Slovenia from November 2013 onwards.

Results

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Nearly all patients 97% (n=37/38) underwent a **dual-energy X-ray absorptiometry (DXA) at the beginning of treatment with systemic glucocorticoids**, but in 21,6% (8/37) of patients the read-out was inaccurate and underrestimated the possibility of fracture.

65% (24/37) of **patients were treated with active form of vitamin D and supplemental calcium. 19% were prescribed bisphosphonates** and another 22% (8/36) should have been treated, but were not due to underrestimation of risk for glucocorticoid-induced bone fracture or due to oversight. Only **32%** (9/28) of patients were **re-evaluated with DXA 6-12 months after** therapy with glucocorticoids was started. Nine patients were lost to follow-up or data was missing.

Bone mineral density was significantly reduced at control in 22% (2/9) of reevaluated patients, yet none of them were treated for osteoporosis. For 2 patients data is missing. In **2 patients** (2/33) there is **evidence of osteoporotic fractures**, yet in 94% (31/33) of patients this crucial data is missing.

Indications for bone-protective therapy in postmenopausal women and men ≥50 years on glucocorticoid therapy:

- Age ≥70 years
- Previous fragility fracture or incident fragility fracture during glucocorticoid therapy
- High doses of glucocorticoids, depending on daily dose and presence or absence of other clinical risk factors
- BMD T-score ≤ −1.5

Recommendations for monitoring bone health during glucocorticoid therapy:

- Assessment of adherence to therapy, including calcium and vitamin D, at each visit
- Measurement of BMD at appropriate intervals
- Annual height measurement
- Vertebral fracture assessment by X-ray or DXA if fracture is suspected

ADRENAL INSUFFICIENCY FOLLOWING GLUCOCORTICOID TREATMENT

48% (n=14/29) of patients stopped treatment with glucocorticoids in the observed period of time, but only 3 (**21%**) **had Synacthen test performed to assess for adrenal insufficiency** (for 6 patients data is missing). In 2/3 the test was either inaccurately performed or the result was not interpreted properly.

Conclusions

While awareness of glucocorticoid-induced osteoporosis is high, identification and treatment of patients at risk and follow-up of these patients can still be improved. Assessment of adrenal insufficiency at termination of glucocorticoid treatment is rarely performed.

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Recovery of invariant NKT cell deficiency and increase of SLAM-SAP signalling factors mRNA expression characterizes sarcoidosis remission: a 4-year longitudinal study

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University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia

Introduction

Invariant Natural killer T Vα24-Jα18-Vβ11 (iNKT) cells play critical role in controlling the strength and character of immune responses and have shown to be important in disorders with increased Th1 responses, such as sarcoidosis. Their exact role as well as factors involved in regulating the development and recruitment of iNKT cells is still to be determined. In our study we followed up iNKT cells and mRNA expression of SLAM-SAP signalling factors, which are important for iNKT development, together with detailed clinical data in newly diagnosed sarcoidosis patients over 4 years.

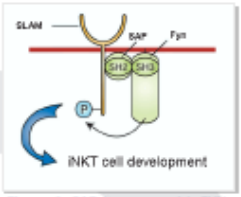

Figure 1. SAP interacts with FYN, facilitating tyrosine phosphorylation of the cytoplasmic domain of a ligand-activated SLAM family member by FYN. Signal transduction pathways downstream of SLAM phosphorylation lead to iNKT cell

Materials and Methods

Detailed clinical, functional, and radiographic evaluation and determination of iNKT peripheral blood cell counts and expression of SLAM-SAP signalling factors, specifically *SLAMF1*, *SLAMF6*, *FYN*, and *SAP*, was carried out at presentation and after 3 months, 1 year, and 4 years of disease follow-up in 29 patients with pulmonary sarcoidosis. We also included 28 healthy control subjects. We used multi-parameter flow cytometry, with antibodies to CD3, Vβ11 and 6B11 in combination with beads, to examine the absolute counts of iNKT cells. Total RNA was extracted from peripheral blood, it was reverse transcribed to cDNA and real-time PCR for the mRNA of interest, was performed.

Results

We demonstrated a marked deficiency of blood and lung iNKT cells and decreased expression of SLAM-SAP signalling factors in patients with newly diagnosed sarcoidosis. During 4 years of disease follow-up, there was a significant increase in blood iNKT cell numbers and in expression of SLAM-SAP signalling factors, mainly *SLAMF1*, *SLAMF6*, and *FYN*. This increase clearly correlated with improvement in patients' clinical symptoms. At the 4-year endpoint, the disease had gone into remission in the great majority of patients and thus also iNKT cell deficiency.

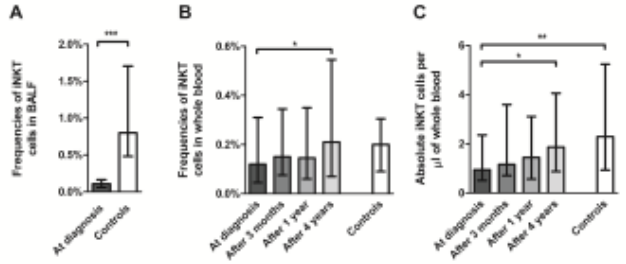

Figure 3. (A) Frequencies of BALF iNKT (CD3⁺ Vα24-Jα18-Vβ11) cells in newly diagnosed sarcoidosis patients and in comparison to BALF of the control subjects; Frequencies (B) and absolute counts of iNKT cells in whole blood (C) of the same patients over 4 years of disease follow-up and in comparison to the healthy control subjects. Data are presented with the median and interquartile range. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

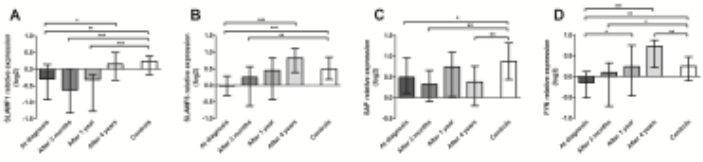

Figure 4. Relative mRNA expression levels of (A) *SLAMF1*, (B) *SLAMF6*, (C) *FYN*, and (D) *SAP* in whole blood of 29 patients with sarcoidosis over 4 years of disease follow-up and in comparison to 28 control subjects. Data are presented with the median and interquartile range.
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

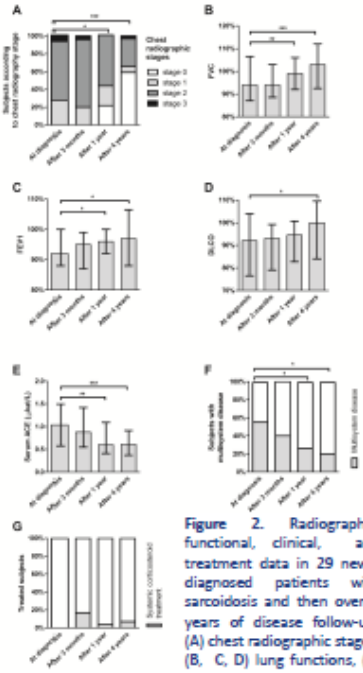

Figure 2. Radiographic, functional, clinical, and treatment data in 29 newly diagnosed patients with sarcoidosis and then over 4 years of disease follow-up: (A) chest radiographic stages, (B, C, D) lung functions, (E) serum ACE levels, (F) manifestations of granuloma in organs other than the lungs, and (G) systemic corticosteroid treatment. Measured data are presented with the median and interquartile range.
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Conclusions

Our longitudinal study showed that recovery of iNKT deficiency in parallel with an increase in expression of SLAM-SAP signalling factors characterizes the clinical remission of sarcoidosis.

All authors declare that there is no conflict of interest.

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CLINICAL PRACTICE OF NON-INVASIVE VENTILATION USE IN ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH RESPIRATORY ACIDOSIS

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[1] Medical Faculty Ljubljana, [2] University Clinic of Pulmonary and Allergic Diseases Golnik

BACKGROUND

- An exacerbation of chronic obstructive pulmonary disease (AECOPD) is one of the commonest causes of emergency admission to hospital[1]. Most AECOPD can be managed in an out-patient department but most severe patients will require hospital admision[2]. An AECOPD requiring hospitalization has a poor prognosis with an in-patient mortality of 7.7%[3] and a median survival of 3.6 years from the first admission[4].
- Overoxygenation is a very important cause of acidosis and hypercapnia. Approximately 20% of patients with an AECOPD are acidotic on arrival in the emergency department and 20% of these patients correct their pH with optimal medical therapy alone[5]. Patients who are acidotic on arrival should be given oxygen to targeting oxygen saturation of 88-92%[6].
- If after 1 hour patient remains hypercapnic and with pH<7.35 non-invasive ventilation (NIV) should be started[7].
- NIV has changed the prognosis of patients with COPD suffering from hypercapnic exacerbations. Acute NIV is now considered the standard of care in the management of acute hypercapnic respiratory failure secondary to COPD[7].
- NIV is ventilation without an invasive artificial airway and results in unloading of respiratory muscles, increase in alveolar ventilation, improvement of dyspnea, reduction of respiratory rate and improvement of arterial oxygenation, hypercapnia and related respiratory acidosis (RA)[8]. It reduces the demand for invasive mechanical ventilation, decreases in-hospital mortality and shortens hospitalization time[7]. NIV may avoid most of the complications related to invasive ventilation and at the same time has a similar degree of efficacy.
- NIV can be administered in intensive care unit (ICU) and also on general wards, emergency departments or NIV wards[9]. If NIV is administered on the ward, it is important to identify risk factors for NIV failure. However, on general wards NIV can be initiated at an earlier stage which reduces hospital mortality and is more cost effective[10].
- Despite clear evidence that NIV is more effective than standard therapy and can be provided at lower cost, the technique has been underutilized[11].

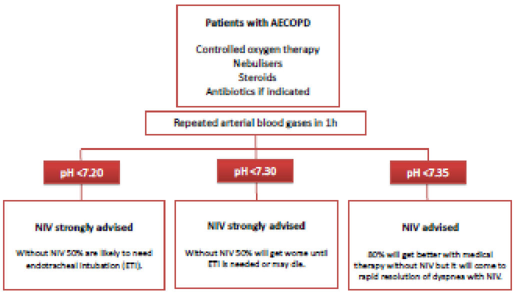

Figure 1: Algorithm to guide the clinical decision on NIV[8].

AIMS

- To evaluate clinical practice of NIV use in AECOPD patients with respiratory acidosis at the University Clinic of Pulmonary and Allergic Diseases Golnik.

METHODS

- A two year retrospective analysis of medical charts of all consecutive AECOPD patients treated in the tertiary respiratory centre in 2013 and 2014 was performed. Patients with the discharge diagnosis of AECOPD were included.
- Patients' age, length of hospitalization, body mass index, comorbid diseases, place of treatment (ICU, normal ward), way of treatment (use of mechanical ventilation), arterial blood gases on admission and discharge, some laboratory tests, pulmonary function tests, chronic NIV use and long term oxygen therapy (LTOT) were checked.
- Statistical analysis was made with SPSS programme.

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RESULTS

- **Final sample included 434 acute exacerbations in 335 patients.** Mean age of the patients was 71±10 years. 64% were men and 36% were women. In 380 cases (87.5%) patients had at least one other disease besides COPD.
- **FEV1:** In 10 (2.3%) cases patient's FEV1 was >80%, in 72 (16.6%) FEV1 was 50-80%, in 214 (49.3%) FEV1 was 30-50% and in 138 (31.8%) cases FEV1 was <30%. All together in 81.1% of cases FEV1 was below 50% which is in 74% of patients.

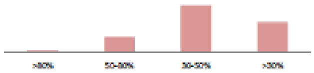


Figure 2: FEV1 in our patients

OVEROXYGENATION, ACIDOSIS and HYPERCAPNIA ON ADMISSION:

- 82 (18.9%) patients were overoxygenated (oxygen saturation >95%) at the time of arrival to the emergency unit.
- In 221 cases (50.9%) of AECOPD patients were hypercapnic with pCO_2>6kPa and in 131 cases (30.2%) pCO_2 was more than 7 kPa.
- On admission 74 patients (17.1%) were acidotic. (pH<7.35).

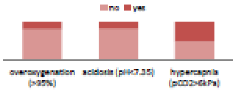


Figure 3: Overoxygenation, acidosis and hypercapnia on admission in our patients

- **After initial treatment** additional 25/360 (6.9%) patients became acidotic and 25/74 (33.8%) acidotic patients improved with pH raising above 7.35 of which 10 (40%) improved mainly due to decreased oxygen flow.

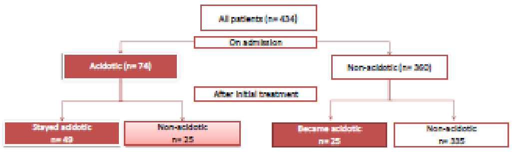


Figure 4: Changes in pH from admission to post-initial treatment time

- **NIV USE:** NIV was used in 38 cases (8.8%). Overall intubation rate was 1.8% (8 cases). 5 patients (1.2%) needed NIV as well as intubation and mechanical ventilation.
- **PLACE OF NIV ADMINISTRATION:** In 58% (22 cases) acute NIV was administered on a NIV unit only, in 8% (3 cases) on NIV ward and also in ICU, in 34% (13 cases) NIV was introduced in ICU only.

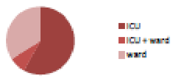


Figure 5: Place of NIV administration

- **USE OF NIV IN RESPIRATORY ACIDOSIS PATIENTS:** In non-intubated acidotic patients NIV was used in 23/86 cases (26.7%). NIV was received by 67% (4/6) patients with pH<7.2, 40% (8/20) with 7.2<pH<7.3 and 18% (11/60) with 7.3<pH<7.35 ($p<0.001$).

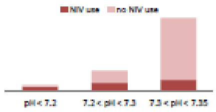


Figure 6: NIV use in respiratory acidosis patients

- **LTOT and chronic NIV:** In 119 (27.4%) cases patients were using LTOT before admission and new LTOT was introduced in 34 (7.8%) cases. Chronic NIV was used by 12 (2.8%) of AECOPD cases before admission and chronic NIV was newly introduced in 9 (2.1%) patients.
- **ICU:** All together 13 patients (3.0%) were admitted to ICU. The ICU mortality was 53.8% (7/13).
- **In-hospital mortality:** Overall in-hospital mortality was 5.3% (23 patients).

CONCLUSIONS

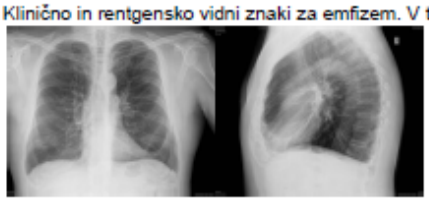
Use of NIV as AECOPD with respiratory acidosis treatment was lower than expected according to guideline recommendations.
Emergency oxygen treatment was inappropriate in some patients and contributed to respiratory acidosis.
The intubation and in-hospital mortality were among the lowest reported in the literature.

Farmakološko in nefarmakološko zdravljenje bolnika z napredovalim emfizemom – klinični primer

Katja Adamič, Aleš Rozman, Tjaša Šubic, Mateja Marc Malovrh
Univerzitetna klinika za pljučne bolezni in alergije Golnik

Leto 2008

57-letni moški s kronično obstruktivno pljučno boleznijo (KOPB), bivši kadilec, brez pridruženih bolezni, je bil prvič v ambulantno obravnavan leta 2008.
Klinično in rentgensko vidni znaki za emfizem. V testih pljučne funkcije ireverzibilna obstrukcija z znižano difuzijsko kapaciteto.



Spirometrija

		Ref	Pre	Pre % Ref	CI	Post	Post % Ref	CI	Post % Chg
VC	Liters	4.23	4.27	101	0.05			0.05	
FVC	Liters	4.23	4.27	101	0.05	4.47	105	0.05	5
FEV1	Liters	3.18	1.65	34	0.72	2.39	40	0.72	18
MEAN	Liters	4.02	2.78	69	0.83	2.88	72	0.83	9
FEV1/SVC %			39						
FEV1/FVC %		79	39		10	29		10	
FEV1/FEV6%		79	40		9	45		9	
IVC	Liters		2.95						
PEF	Liters	8.47	3.32	39	2.12	3.61	43	2.12	8
FEV1/FVC		0.80	0.32	63	0.08	0.39	77	0.80	22

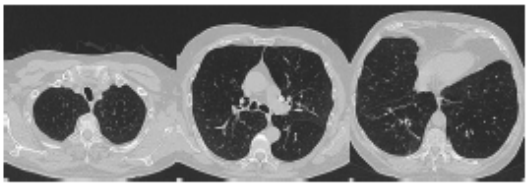
Difuzijska kapaciteta

		Ref	Pre Liters	Pre % Ref
DLCO	ml/mM/Pa min	30.0	3.4	38
DL Adj	ml/mM/Pa min	30.0	3.4	38
DLCO/VA	DLCO/L	1.230	0.82	61
CLIVA	ADJ DLCO/L	1.230	0.81	60
VA	Liters	6.860	4.17	64

Postavili smo mu diagnozo KOPB stopnje 3 po GOLD-u in po smernicah* predpisali inhalatorno terapijo: BUDESONID+FORMOTEROL, TIOTROPIUM, FENOTEROL+IPRATROPIUM.
Svetovana mu je bila rehabilitacija za pljučne bolnike.

Leto 2012

Leta 2012 je bil petkrat hospitaliziran zaradi poslabšanja KOPB ob virusnih in bakterijskih okužbah spodnjih dihal.
Na HRCT viden napredovali obojestranski emfizem z zadebeljenimi bronhi.



Diagnozi:

HUDA KOPB STOPNJE D S PREVLADOVANJEM EMFIZEMA
in
POMANJKANJE ALFA-1 ANTITRIPSINA

Ugotavljali smo pridruženo pomanjkanje alfa-1 antitripsina (heterozigot MZ*).
UZ srca je pokazal ohranjeno sistolno funkcijo levega ventrikla, brez pomembne pljučne hipertenzije.
Perfuzijska scintigrafija pljuč je pokazala neenakomerno perfuzijo pljuč, še posebno v spodnjih tretjinah.
V stabilni fazi KOPB je bil udeležen programa rehabilitacije pljučnih bolnikov. Med fizično aktivnostjo je prišlo do poslabšanja KOPB zaradi povečanega ujetja zraka ob fizičnem naporu.
Na cikloergometriji je zmogel 24% predvidene maksimalne obremenitve, VO_{2MAX} 6.9ml/kg/min.

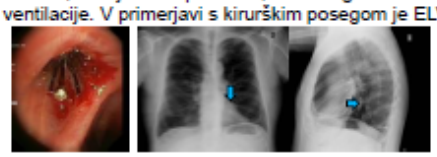
Leto 2013

MOŽNOSTI NEFARMAKOLOŠKEGA ZDRAVLJENJA EMFIZEMA POLEG REHABILITACIJE:

- V stabilni fazi bolezni ni bil v respiracijski insuficienci, trajno zdravljenje s kisikom na domu ali neinvazivna mehanična ventilacija nista bili indicirani.
- Predstavljen je bil kirurgom za možnost kirurškega zmanjševanja volumna, ki ni bila možna zaradi difuznega emfizema.
- Konzilij za transplantacijo pljuč ga je zavrnil zaradi starosti (63let) in relativno stabilne KOPB.
- Odločili smo se za zdravljenje z endoskopskim zmanjševanjem volumna - ELVR.

Leto 2014

ELVR je novejša metoda za zdravljenje bolnikov z napredovalim emfizemom pljuč. Dobre rezultate dosežemo v primeru pravilne izbire bolnika, ki naj ima napredoval, nehomogen emfizem, kompletne fisure med režnji, ki jih nameravamo zdraviti ter odsotnostjo kolateralne ventilacije. V primerjavi s kirurškim posegom je ELVR manj invazivna in reverzibilna metoda.



	pred ELVR	1 mesec po ELVR	4 mesece po ELVR	razlika
VC	3140 ml (76%)	3930 ml (95%)	4100 ml (99%)	+ 960 ml
FEV 1	720 ml (23%)	1020 ml (33%)	1040 ml (34%)	+ 320 ml
TI	23%	26%	25%	+ 2%
TLco	27%	29%	32%	+ 5%
TLC	7300 ml (113%)	7170 ml (110%)	7970 ml (123%)	+ 670 ml
RV	4160 ml (173%)	3240 ml (135%)	3870 ml (161%)	- 290 ml (920 ml)
RV / TLC	57%	45%	49%	- 8% (12%)

PLJUČNA FUNKCIJA IN 6 MINUTNI TEST HOJE (MTH) 1. IN 4. MESECU PO POSEGU

	pred ELVR	1 mesec po ELVR	4 mesece po ELVR	razlika
6 MTH	165m	385m	385m	+130m

Že prvi mesec po posegu je bolnik navajal izboljšanje fizične aktivnosti, po fizičnih naporih mu zadihanost hitreje mine.
Okužbe spodnjih dihal ni imel.

Zaključek

Pri bolnikih z napredovalim emfizemom poleg farmakološkega zdravljenja pomislimo na rehabilitacijo, trajno zdravljenje s kisikom na domu (TZKD), neinvazivno mehanično ventilacijo (NIMV), kirurško zmanjševanje volumna (LVRS), endoskopsko zmanjševanje volumna (ELVR) in transplantacijo pljuč.

HRCT: High-resolution computed tomography; LVRS: Lung volume reduction surgery; ELVR: Endoscopic lung volume reduction

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Predictors of variable functional response to short-term high-intensity exercise training in men with advanced COPD

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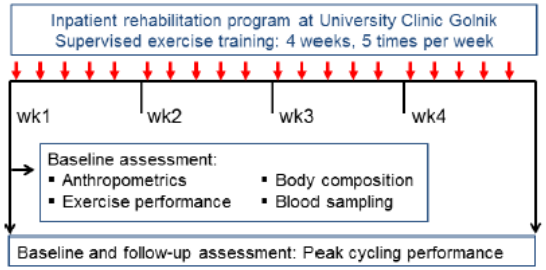
Background

- Impaired exercise capacity in COPD patients → worse clinical outcomes and decreased quality of life
- Exercise training can improve impaired exercise capacity
- Response to standardized training varies

Aim

To characterise metabolic traits among patients with different degrees of response to a short-term high-intensity exercise training.

Methods



Response = change in peak cycling performance[1]:

- no response (<0 W)
- intermediate response (0-10 W)
- response > MCID (> 10 W).

Results

Male patients (N=61, 66±8 years, 85% GOLD III/IV) stratified by exercise responsiveness.

Groups did not differ in age, respiratory function or prevalence of comorbidities.

	A: No response (N=11)	B: Intermediate response (N=25)	C: Response (N=25)	p< 0.05
6-minute walk test (m)	273±82	331±93	370±112	AC
Incremental shuttle walk test (m)	198±70	234±98	300±130	AC
Peak cycling workload (W)	59±27	64±22	64±25	none

Table 1. Baseline exercise performance per group. ANOVA with Bonferroni post-hoc analysis.

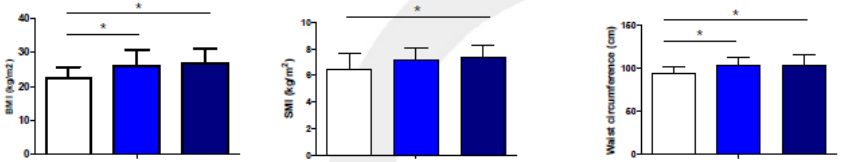


Figure 1. Baseline body composition parameters. * p< 0.05, ANOVA test. Legend: BMI - body mass index. SMI - skeletal mass index.

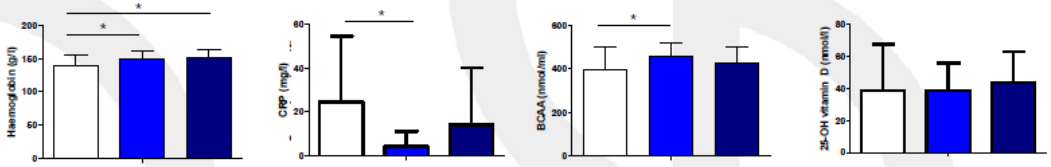


Figure 2. Baseline inflammatory and metabolic biomarkers. . * p< 0.05, ANOVA test. Legend: BCAA - branched chain amino acids.

Conclusion

Low body mass, low muscle mass and markers of inflammation coincide with lack of training response in advanced COPD patients. These patients also show a trend towards depletion of branched-chain amino acids and 25-OH vitamin D in the blood.

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Reference: 1. Cazzola *et al*, ERJ 2008

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EFFICACY OF PEMETREXED - PLATINUM IN THE TREATMENT OF ADVANCED NSCLC: HOSPITAL REGISTRY DATA

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Background

Patients (pts) with advanced non-squamous NSCLC benefit substantially from pemetrexed containing platinum-based chemotherapy (pem/platinum CT). Pem maintenance (mtnc) approach further improves survival in pts with clinical benefit (CB) to induction CT to around 13 months (mo). The aim of our study was to evaluate efficacy of first line pem/platinum in advanced non-squamous NSCLC treated in a routine clinical practice.

Methods

114 pts consecutive treated with first-line pem/platinum CT for advanced non-squamous NSCLC (not EGFR positive) between January 2010 and December 2013 were included. Data were prospectively collected from University Hospital Golnik Lung Cancer Registry (UCG LCR). Until the beginning of 2012 the availability of pem was limited due to reimbursement policy and mtnc pem was not yet available. For survival analysis pts were divided into 2 groups: before and after pem mtnc availability (before pem mtnc and after pem mtnc).

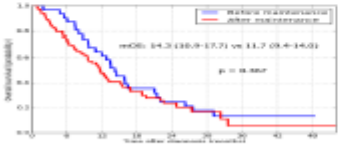
	Before pem mtnc	After pem mtnc
Number of pts	31	83
Gender (%male)	45.2	55.4
Median age (years)	61.3	62.8
Smoker or ex smoker (%)	74.2	91.6
PS WHO: 0-1 2	100% 	88% 12%

Table 1: Pts characteristics

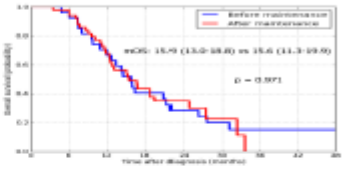
Results

Median OS (mOS) in the whole group (n=114) was 12.5mo (95%CI: 10.7-14.2), with 14.3mo (n=31) and 11.7mo (n=83) for those treated before or after pem mtnc (*Graph 1*). Mean number of pem/platinum CT cycles received was 5 (1-6) in before pem mtnc group and 4 (1-6) in after pem mtnc group. Pts in after pem mtnc group additionally received mean 6 (1-22) mtnc cycles. In selected group of pts with good PS and who received at least 4 induction platinum doublet CT cycles survival in both groups is practically the same despite mtnc approach used in the second group (*Graph 2*).

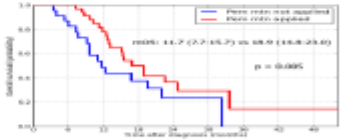
Pts with CB on induction pem/platinum CT who were applied mtnc pem approach had significantly longer mOS compared to those not applied mtnc (*Graph 3*).



Graph 1: *mOS in pts treated with 1st line pem/platinum doublet before vs. after mtnc availability*



Graph 2: mOS in selected pts with PS up to 1 and at leats 4 cycles of platinum doublet CT (n=77), before (n=27) or after (n=50) pem mtnc availability



Graph 3: *mOS in pts with CB (n=58/83) after induction pem/platinum doublet who were (n=35) vs. were not (n=23) applied mtnc pem*

Conclussions

According to UCG LCR data survival of advanced non-squamous NSCLC routinely treated with first-line pem/platinum CT s highly comparable to the results obtained in randomized clinical trials. In our collective of pts, more than 4 cycles of pem/platinum CT led to comparable survival rates to mtnc approach . In adition, if using mtnc approach, it should be implemented in the largest possible number of eligible patients.

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SURVIVAL IN ADVANCED LUNG CANCER PATIENTS PROPOSED TO RECEIVE CHEMOTHERAPY ACCORDING TO DELIVERY: A STUDY BASED ON HOSPITAL REGISTRY DATA

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BACKGROUND

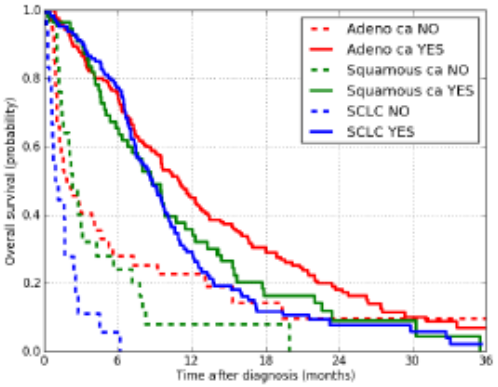
- The benefits of chemotherapy in advanced lung cancer are well known. However, not all patients proposed by a multidisciplinary tumor board (MTB) actually receive it.
- The aim of the study was to evaluate the overall survival (OS) of advanced lung cancer patients according to delivery of initial chemotherapy.

METHODS

- **PATIENT SELECTION:** all advanced lung cancer patients (adenocarcinoma, squamous cell carcinoma, SCLC) proposed for initial Cht by a MTB between Jan 2010 and Dec 2013 were included (n=483); patients who refused Cht (n=11) or failed to come to first appointment (n=27) were excluded, resulting in a final 445 patients included.
- **EVALUATION OF ELIGIBILITY FOR Cht IN ROUTINE CLINICAL PRACTICE:** all patients referred for Cht by the MTB were assess for Cht eligibility by their designated oncologist
- **DATA COLLECTION:** All data were retrieved from our hospital lung cancer registry

RESULTS

Figure 1: OVERALL SURVIVAL OF PATIENTS TREATED OR NOT TREATED WITH Cht



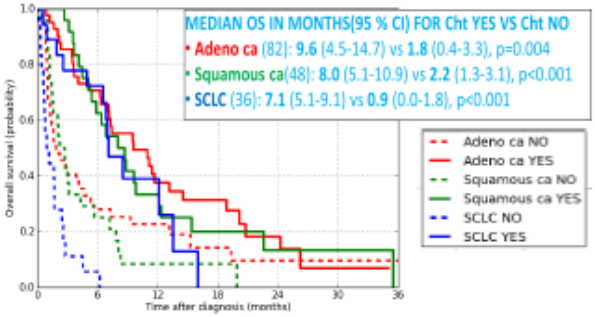
MEDIAN OS IN MONTHS(95 % CI) FOR Cht YES VS Cht NO
- Adeno ca: 11.0 (9.3-12.6) vs 1.8 (0.4-3.3), p<0.001
- Squamous ca: 8.8 (6.8-10.8) vs 2.3 (1.2-3.4), p<0.001
- SCLC: 8.9 (7.6-10.2) vs 0.9 (0.0-1.8), p<0.001

MULTIVARIATE ANALYSIS (COX-REGRESSION) FOR OS:
- Cht YES/NO (p<0.001), histology (p=0.001), PS (p=0.002)
- p>0.05 for gender, age, Charleson comorbidiy score

Table 1: PATIENT & TUMOR CHARACTERISTRICS ASSOCIATED WITH THE DECISION ON Cht TREATMENT

Characteristic	Cht YES (n=361)	Cht NO (n=84)	P-value UV	P-value MV
Gender			**0.010**	0.161
• male	• 226 (63%)	• 65 (77%)		
Age: median (IQR)	• 63.5 (58-71)	• 67 (60-74)	**0.008**	0.071
Performance status			**<0.001**	**<0.001**
• ≤1	• 301 (83%)	• 49 (58%)		
Comorbidity (CCI)			**0.006**	**0.014**
• 0	• 199 (55%)	• 38 (45%)		
Histology			**0.003**	**<0.001**
• Adeno ca (220)	• 179 (50%)	• 41 (49%)		
• Squamous ca (80)	• 55 (15%)	• 25 (30%)		
• SCLC (145)	• 127 (35%)	• 18 (21%)		

Figure 2: OVERALL SURVIVAL OF PATIENTS TREATED OR NOT TREATED WITH Cht FOR MATCHED GROUPS ACCORDING TO PTS in Cht NO GROUP



CONCLUSIONS

- The observed OS rates in patients treated with Cht are in line with data from clinical trials.
- The value of patient and tumor features (CCI, histology) that impact the decision on Cht treatment but not OS should be reconsidered in light of the extremly poor prognosis of advanced lung cancer patients not receiving Cht.
- The survival benefit of Cht remains significant also when patients receiving Cht were matched to the poorer group of patients not receiving Cht. Of note, a steeper decline in OS in the first months of Cht treatment may be seen in the poorer matched group patients as compared to the overall group of patients treated with Cht .

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COMPARISON OF SURVIVAL OF ADVANCED KRAS MUTATED AND KRAS WILD TYPE NON-SQUAMOUS NSCLC– OBSERVATIONAL STUDY BASED ON REGISTRY DATA

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Background

It has been postulated for over 20 years that KRAS mutated (KRASmut) NSCLC, despite being the most common, may be associated with poor outcome. However, multiple studies have shown conflicting results due to heterogenity among the studies. A meta-analysis of 28 studies published in 2005 demonstrated that KRAS mutations were significant prognostic marker in NSCLC of any stage and on the contrary, LACE-Bio pooled retrospective analysis published in 2013 failed to show any prognostic value in 1500 resected KRASmut NSCLC patients(pts).
The aim of our observational study was to evaluate the prognostic value of KRAS mutations in a routine clinical practice and to evaluate the difference in clinical characteristics between long and short term survivals among pts with KRASmut NSCLC.

Methods

Pts with advanced non-squamous NSCLC with known KRAS mutation status who were consecutive treated with first-line ChT between January 2010 and December 2013 and followed at a single institution were included in the analysis. Pts with EGFR positive disease or ALK translocations were not included. All data were collected and obtained from University Hospital Golnik cancer registry database.

Results

68/182 (37.3%) pts with advanced non-squamous NSCLC were tested for KRAS mutation status and 30/68 (33.3%) were KRASmut (all were CODON 12 or 13 mutations).

Figure 1 shows **no significant difference in median overal survival (mOS) between KRASmut and KRAS wild type (KRASwt) pts.**
There was no difference between the groups regarding clinical characteristics (age, sex, smoking status, WHO performance status, Charleson comorbidity index (CCI)) or number of chemotherapy (ChT) lines received.

When among KRASmut pts separate analysis was performed for the groups of **long term** survivals (18 pts, mOS≥ 1year) and **short term** survivals (12 pts, mOS≤1year), no difference regarding clinical characteristics was found (*Table 1*), but as expected long term survivals received 2nd line ChT more often (p=0.006).

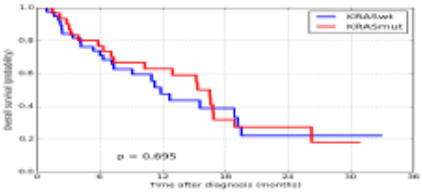

Figure 1: Survival of KRASmut vs. KRASwt NSCLC pts: mOS 15.3mo (95%CI:11.8-15.3) vs.11.8mo (95%CI:10.8-18.9) respectively, p=0.695.

	SHORT TERM SURVIVALS (≤ 12 MONTHS) N=12	LONG TERM SURVIVALS (≥12MONTHS) N=18	P value
MEAN AGE (years)	66.7 (42.5-73.8)	63.5 (42.5-73.8)	0.632
SEX: M W	4 (33.3%) 8 (66.7%)	9 (50%) 9 (50%)	0.301
SMOKING STATUS: Non smoker Smoker/ex smoker	0 (0%) 12 (100%)	1 (5.6%) 17 (94.4%)	0.708
WHO PS: 0-1 2-3	10 (83.3%) 2 (16.7%)	17 (94.4%) 1 (5.6%)	0.347
CCI SCORE: 0 ≥1	5 (41.7%) 7 (58.3%)	8 (44.4%) 10 (55.6%)	0.590
2nd LINE CHT RECEIVED YES NO	3 (25%) 9 (75%)	14 (77.8%) 4 (22.2%)	**0.006**

Table 1: Clinical characteristics and administration of 2nd line ChT in short and long term survivals among KRASmut NSCLC pts.

Conclusions

According to our observations, survival of routinely treated advanced KRASmut non-squamous NSCLC is not different from KRASwt pts. On the basis of commonly used cinical characteristics long or short term survivals in the group of KRASmut pts cannot be identified. Further studies are waranted to discover other markers that probably prognosticate the group of KRASmut advanced NSCLC.

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PD-L1 expression in NSCLC: Expression in tumor cells and tumor infiltrating lymphocytes according to histology

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Background

Recent trials have shown remarkable benefit of PD-1 / PD-L1 immune-checkpoint inhibitors in non-small cell lung cancer (NSCLC). The predictive value and proper methodology of PD-L1 determination remains unclear and the data of PD-L1 positivity according to histology are scarce and contradictory. The association between PD-L1 expression in tumor cells (TCs) and tumor infiltrating lymphocytes (TILs) is yet to be validated. We examined the PD-L1 expression in TCs and TILs separately and put them into perspective according to tumor histology.

Methods

A total of 54 tumor resection specimens of NSCLC patients who underwent surgery at our institution from year 2006 to 2013 were analyzed. 29 patients had adenocarcinoma and 25 patients were diagnosed with squamous cell carcinoma. PD-L1 expression in TCs and TILs was assessed by immunohistochemistry using rabbit monoclonal antibody SP142 (Ventana, USA). The cutoff value was set at H score 25. Baseline characteristics such as age, sex and smoking status are presented in Table 1.

Results

Figure 1. Pattern of PD-L1 expression in NSCLC samples. Positive membraneous reaction in TCs of squamous cell carcinoma (A) and TCs of adenocarcinoma (B); cytoplasmic staining in PD-L1 positive TILs (C)

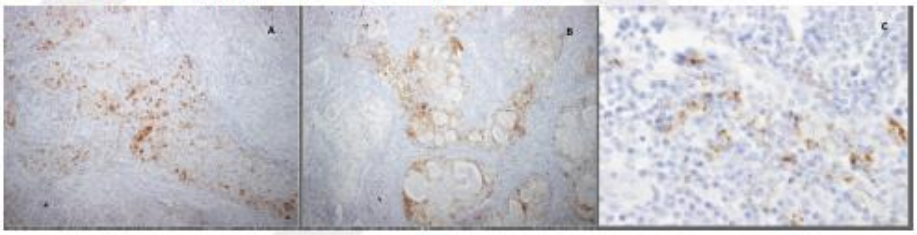

Table 1. Baseline patients characteristics (n=54)

Age (years)	
Median	64
Range	48 - 81
Sex – no. (%)	
Male	34 (63)
Female	20 (37)
Smoking status – no. (%)	
Non-smoker	1 (2)
Former smoker (>1 yr)	21 (39)
Current smoker	25 (46)
Unknown	7 (13)

Table 2. Expression of PD-L1 on TCs and TILs according to tumor histology.

	n tumor specimens	PD-L1 positivity in TCs	n tumor specimens infiltrated by lymphocytes	PD-L1 positivity in TILs
Total	54	19 (35%)	47/54 (87%)	42 (77%)
Adenocarcinoma	29	6 (21%)	26/29 (90%)	22 (76%)
Squamous cell carcinoma	25	13 (52%)	21/25 (84%)	20 (80%)
p value		0,016		0,240

The baseline characteristics were not associated with the expression of PD-L1, neither in TCs nor on TILs.
TILs showed a distinctive cytoplasmic staining in lymphocytes, whereas TCs mostly expressed a membranous pattern of PD-L1 positive staining.
Majority of tumor samples have heterogenous expression of PD-L1 positivity.

Conclusions

- Squamous cell histology is associated with higher expression of PD-L1 on TCs, which could be explained by the high proportion of somatic mutations present in squamous cell carcinomas
- TCs have a prevalent membrane staining, however the distribution of PD-L1 positivity across the tumor is heterogenous.
- Majority of tumors exhibit lymphocytic infiltration irrespective of histology with a high proportion of PD-L1 positivity in TILs

SURVIVAL OF LUNG CANCER PATIENTS INVOLVED OR NOT INTO EARLY PALLIATIVE CARE SETTING - AN OBSERVATIONAL SINGLE INSTITUTION STUDY

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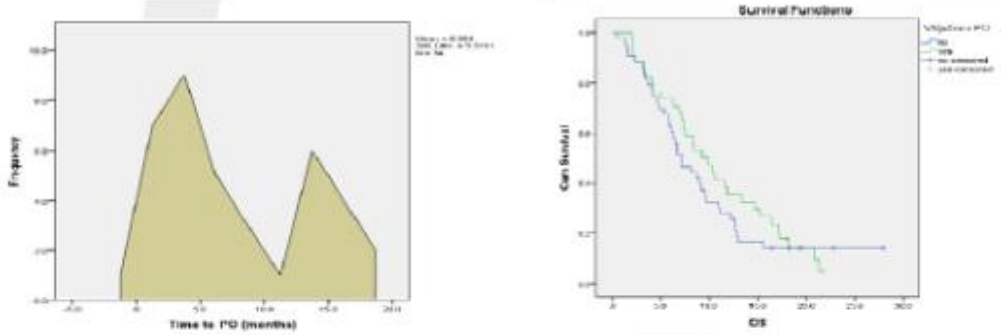
Background

Implementation of early palliative care (EPC) among patients (pts) with metastatic lung cancer (MLC) leads to the improvement of quality of life (QoL), decrease of depression and agressive care at the end of life. In addition, it was found a large prospective trial that EPC added to the standard care significantly improves survival of patients with LC.
The aim of our study was to evaluate the impact of integration of EPC on overall survival, exposure to chemotherapy (Cht) in the last 2 months of life and on the place of death (hospital vs. home) in patients diagnosed with advanced LC treated with standard Cht.

Methods

Pts with advanced lung cancer who started first line ChT in 2013 and followed at a single institution were included in the analysis. Pts with EGFR mutation-positive disease or ALK translocations were not included. All data were collected and obtained from the University Hospital Golnik cancer registry database and from pts records.

Results



77 pts started ChT for advanced LC in 2013, 34/77 (44%) were enrolled in the PC. Among them 6/34 (17,6 %) in the early PC (within 2 months from the beginning of ChT) and 9/34 (26%) pts were enrolled in the last month of life. Median OS for the whole group was 8,3 mo (95%CI:8,5-11,9). No significant difference in mOS was found between the group of pts receiving ChT together with PC and the group receiving standard ChT alone; mOS 9.2 mo (95%CI:8,5-12,5) vs 7.1 mo (95%CI:7,4-12,3) respectively, p= 0,24). 22 out of 68 (32%) pts received ChT in the last two months of life and only 8/22 (36%) of them were integrated into PC. Concerning the place of death, 21/68 (31%) pts died in the hospital, there was no difference among pts integrated or not into PC.

Conclusions

According to our observations no difference in mOS was found among advanced LC pts integrated or not into PC after beginning of treatment with 1st line ChT. But, there is a trend towards better mOS for those included into PC; therefore more rapid access to PC is warranted in future. One third of pts receiving Cht in last two months of life and/or dying in hospital are the rates that are not worrisome but still need to be reduced.

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GOOD CLINICAL PHARMACY PRACTICE IN ONCOLOGY: THE EXPERIENCE FROM UNIVERSITY CLINIC GOLNIK, SLOVENIA

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BACKGROUND

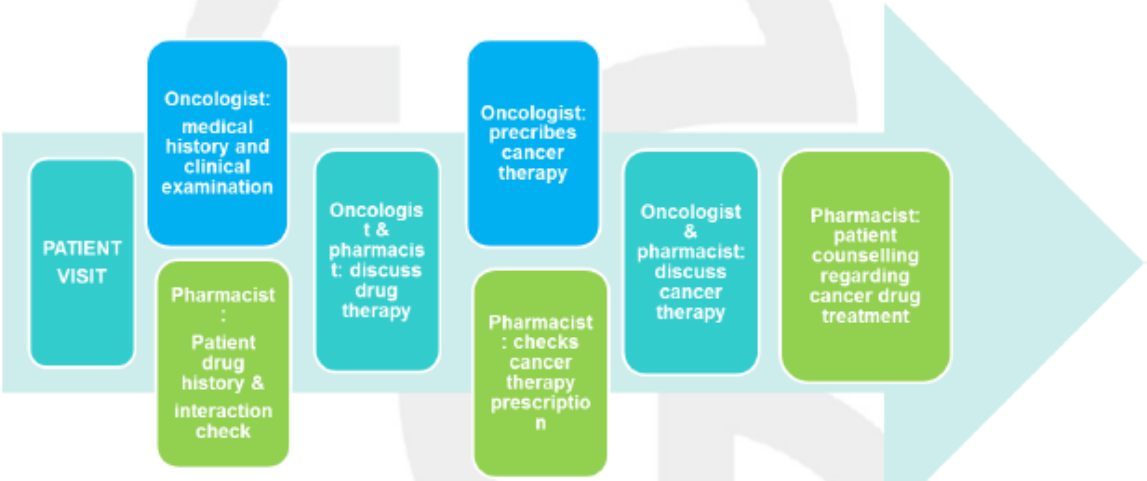
- Anticancer drugs are high risk drug and used regimens are complex: cancer treatment is prone to clinically significant medication errors.
- To safeguard patient safety, multiprofessional collaboration is of paramount importance to reduce such errors.
- Herein, the role of clinical pharmacists in the treatment of oncology patients at the University Clinic Golnik and their contribution to patient safety is presented.

METHODS

- Pharmacists were proactive in looking for possibilities to participate in the treatment of cancer patients with their roles expanding over time.
- To argument the need for pharmacists involvement, pharmacists interventions made during chemotherapy prescription screening and interactions for which a pharmacist's advice was offered, were retrospectively reviewed during a 5-month and a 1-year period.

RESULTS

- **The successful implementation of clinical pharmacy services into routine clinical practice is the most important result.**



- **The contribution of these services to patient care was quantified:**
  - During the screening of 506 chemotherapy prescriptions, pharmacists made 211 interventions: 31% were related to anticancer drugs, and 76% were implemented.
  - Cancer patients were found to be at risk of drug interactions: in 223 patients, 1416 interactions were identified and 52 were judged as clinically important, most of which (41/52) would affect anticancer therapy.

CONCLUSIONS

- **Pharmacists have an important role in the treatment of oncology patients.** The integration of clinical pharmacy services as chemotherapy prescription screening and drug interactions checking were shown to contribute to patient safety.
- Findings from the review of pharmacist intervention during prescription screening served to improve clinical practice.
- The review of drug interactions with cancer treatment emphasize the importance of a correct interpretation of drug interactions to focus all efforts into preventing those clinically relevant.

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DRUG INTERACTIONS IN CANCER TREATMENT:
measures for their identification and prevention in routine clinical practice

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BACKGROUND & AIM

- Anticancer drugs are considered high risk drugs and drug interactions may have important implications for patient safety.
- The presented study evaluates the management of drug interactions with anticancer drug therapy in routine clinical practice.

METHODS

- DRUG INTERACTIONS WERE REVIEWED IN 223 PATIENTS, INITIATED WITH ANTICANCER DRUG THERAPY IN 2012
- AS PART OF ROUTINE CLINICAL PRACTICE, drug interactions were reviewed prospectively by a pharmacist at time of treatment initiation. Drug interactions judged to be clinically important were discussed with the patient's oncologist.
- AS PART OF THE STUDY, drug interactions were reassessed using three different drug interaction databases (Lexi-comp, Stockley's Drug Interaction, Drugs.com) to record all possible interventions.

RESULTS

INCLUDED PATIENTS WERE AT HIGH RISK FOR ADVERSE DRUG EVENTS:
i) were older (median 63 years),
ii) were treated with polypharmacy (in median 4 drugs in drug history + 6 drugs among anticancer & support care drugs),
iii) were treated with high risk drugs.

TABLE 1: Characteristics of drug interactions (DI) reported in DI databases and judged by pharmacists as relevant

DI REPORTED:	IN DI DATABASES (n = 1416)	BY PHARMACIST (n = 52)	P
DI PER PATIENT (RANGE)	5 (0 - 23)	0 (0 - 3)	< 0.01
ANTICANCER DRUG INVOLVED IN DI	249 (18 %)	44 (84 %)	< 0.01
DI AFFECTING CANCER TREATMENT	275 (19 %)	41 (79 %)	< 0.01

THE REVIEW OF DI IN 3 DATABASES REVEALED:
- only 34 % of DI were recorded in all databases
- 74 % of DI were rated as of major clinical importance

CONCLUSIONS:

The large number of possible drug interactions shows the need for their critical appraisal to identify those clinically relevant.
Review of drug interactions at initiation of anticancer drug treatment was successfully implemented into routine clinical practice.

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Poročanje neželenih dogodkov pri zdravljenju z zdravili v Kliniki Golnik

Erika Stariha

Univerzitetna klinika za pljučne bolezni in alergijo Golnik

Uvod

- **Neželeni dogodki pri zdravljenju z zdravili** so **nenamerne napake** pri predpisovanju, izdaji, pripravi, dajanju ali spremljanju učinka zdravil, ki povzročijo nek neželen dogodek pri zdravljenju bolnika. Te dogodke pa se da preprečiti (1,2,).
- **Skorajšnji dogodki (ang. near misses)** so napake, ki so se zgodile v procesu zdravljenja z zdravili, vendar niso dosegle bolnika (3).

- Namen naše analize je kategorizacija napak iz zbranih poročil ter **predlagati izboljšave sistema poročanja in sistemskega ukrepanja.**

Metode

Pregledali smo zbrana poročila od leta 2005 do konca leta 2014. Bolj podrobno smo pregledali poročila za leto 2014, kjer smo napake razvrstili v kategorije in pregledali tudi evidentirane razloge, ki so privedli do napake. Preverili smo tudi popolnost izpolnjenih obrazcev s strani zdravnika. Rezultate smo predstavili na komisiji za kakovost (KZK), medicinskih sestram ter zdravnikom.

Rezultati

- Skupno je bilo v 10 letih zbranih 183 poročil.
- **V letu 2005 je bilo izpolnjenih 5 poročil pri 5436 hospitalizacijah, v letu 2014 pa 52 poročil pri 6843 hospitalnih obravnavah.**
- Od 52ih poročil je bilo **15 poročil o skorajšnjih dogodkih** pri pripravi ali izdaji zdravil iz lekarne, ki tukaj niso podrobneje predstavljeni. Vrste napak pri ostalih 37 neželenih dogodkih in evidentirani razlogi zanje (pri 13 primerih) pri zdravljenju z zdravili so predstavljeni v Tabeli 1 in 2.

Tabela 1: Vrste napak pri neželenih dogodkih pri zdravljenju z zdravili v letu 2014.

VRSTA NAPAKE PRI NEŽELENEM DOGODKU	ŠTEVILO PRIMEROV
Zamenjava odmerka ali poti aplikacije	15/37
Zamenjava bolnika	7/37
Zamenjava zdravila	7/37
Zdravilo ni bilo dano pravočasno	4/37
Zdravilo dano kljub ukinitvi na terapevtskem listu	4/37

Tabela 2: Vzroki za napako za neželen dogodek.

EVIDENTIRAN VZROK ZA NAPAKO	ŠTEVILO PRIMEROV
Nečitljiva pisava	4/13
Moteče okolje	3/13
Slaba predaja službe	3/13
Stiska s časom	2/13
Izolacija bolnika	1/13

- **Klinična pomembnost napake** je bila s strani zdravnika ocenjena pri 30ih poročilih, od tega samo enkrat kot velika klinična pomembnost.
- Velik razpon pomembnosti napak znotraj ocene »majhna klinična pomembnost«.
- Podobne napake pojavljale na različnih oddelkih, vendar sistemske rešitve niso bile razvidne iz poročil.

Zaključki

- Prenovljen obrazec, ki zajema vse procese pri zdravljenju z zdravili (ne zgolj zamenjavo zdravila), razširja možnost poročanja vseh zdravstvenih delavcev, ki so vključeni v proces zdravljenja z zdravili, omogoča in spodbuja poročanje skorajšnjih dogodkov **ter kot skrbnika poročanja napak in sistemskega reševanja le-teh postavlja farmacevta** (Slika 1).
- **Skorajšnje dogodke se lahko poroča tudi anonimno saj želimo zmanjšati morebitne zadrške** posameznikov (občutek krivde, strah pred posledicami).
- Razširjena rubrika o oceni klinične pomembnosti, s kratkim opisom, da zdravniku olajša odločitev in hkrati poenoti kriterije (MAJHNA, SREDNJA, VELIKA).
- Rizična zdravila smo pričeli opremljati z nalepkami: »preveri odmerek-nevarnost zamenjave«.
- Pripravili smo plakate, ki bolnike v bolnišnici seznanijo o pomembnosti pravilne identifikacije.

Porast števila poročil je odraz skupnega dela na prepoznavanju napak pri zdravljenju z zdravili in zavedanja, da lahko s poročanjem neželenih dogodkov in skorajšnjih dogodkov bistveno prispevamo k sistemskim rešitvam, ki preprečijo neželene dogodke pri zdravljenju z zdravili v prihodnosti in s tem k večji varnosti in kakovosti zdravljena bolnikov z zdravili v Kliniki Golnik.

Slika 1: Shema spremembe poročanja neželenih dogodkov po procesih pri zdravljenju z zdravili.

Viri:
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2. European medicines agency. http://www.ema.europa.eu/. Dostop: 6-01-2015.
3. Institute for safe medication practice. https://www.ismp.org/. Dostop: 6-01-2015

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SATELITSKI SIMPOZIJI

EGFR mutation type and response to erlotinib treatment

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Disclosure: the lecture is sponsored by the Roche company. The information in this work are intended only for health care professionals. (The content is independent expert opinion of the author and does not necessarily reflect the opinion and position of Roche). Roche supports the use of its products in accordance with the Summary of product characteristics (SmPC).

Activating mutations in *EGFR* are important markers of response to tyrosine kinase inhibitor (TKI) therapy (erlotinib, gefitinib, afatinib) in non-small-cell lung cancer (NSCLC). Since the EGFR TKIs have been discovered, many studies have shown that they significantly prolong progression free survival (PFS) in all patients with advanced NSCLC with EGFR mutations compared to chemotherapy (ChT).

The most common EGFR mutations are in-frame deletions in exon 19 (del19), which represent approx. 45% of all EGFR mutations and the point mutation at codon 858 in exon 21 (L858R), representing approx. 35-45% of all EGFR mutations. Those two mutations are also known as »common mutations« in contrast to other, rare mutations in exon 18-21(G719X, S768I L861Q, resistant mutations as T790M and mutations at exon 20).

Early after developing anti EGFR directed therapy data from different clinical trials showed that response to EGFR TKIs is not the same in all subtypes of EGFR mutations The response to EGFR TKis is much higher in common compared to rare mutations.

OPTIMAL (2) study confirmed a significant PFS benefit in patients with advanced *EGFR* mutation-positive NSCLC in Asian patients who received erlotinib in 1st line setting compared to ChT (HR for PFS is 0.16, $p<0.0001$). Uptadate analysis of PFS according to the type of activating mutations showed a non-significant trend towards improved PFS with exon 19 deletions compared to L858R mutation (PFS 15.3 months vs.12.5 months, $p=0.0567$).

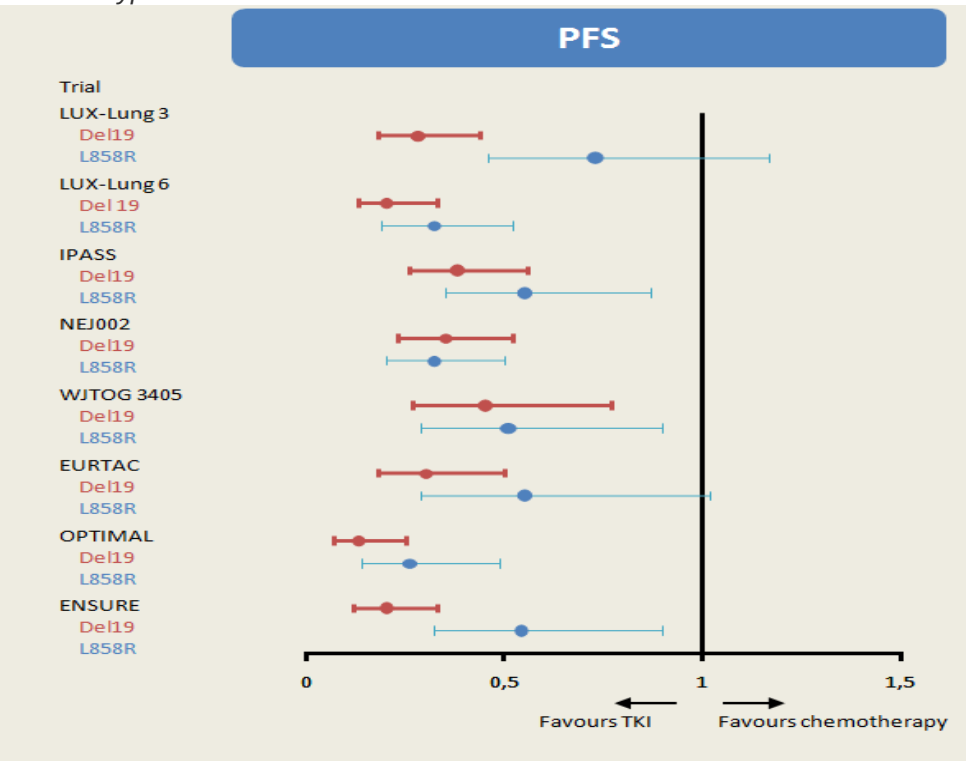
After that, some studies suggested that there is a greater efficacy of EGFR TKIs in exon 19 deletions than in L858R mutations, but those findings were not consistently observed in other studies.

In June 2015 an interesting metaanalysis (3) was published to answer the question, whether the PFS on 1st line EGFR TKI vs. ChT is affected by EGFR mutation type. 1649 patients were included, data was collected from 7 phase 3 studies for 3 different EGFR TKI inhibitors – gefitinib, erlotinib and afatinib (NEJ002, WJTOG, OPTIMAL, EURTAC, LUX LUNG 3 and 6 and ENSURE). In all trials EGFR TKIs compared to ChT significantly prolonged PFS overall. 94.5% of patients had common mutations. In the subgroup with exon 19 deletions the pooled HR for PFS was 0.24 (95%CI, 0.20-0-29, $p<0.001$). In the exon 21 L858R substitution subgroup, the pooled HR for PFS was 0.48 (95%CI, 0.39 to 0.58; $p<0.001$). Compared to ChT treatment with EGFR TKIs demonstrated 50% greater benefit in exon 19 deletions than in exon 21 L858R substitution.

The mechanism of the different response to EGFR TKIs not entirely clear, but may be connected to different biological activity of EGFR mutations.

In conclusion EGFR TKIs significantly prolong PFS in all patients with advanced EGFR mutated NSCLC compared to ChT and the greatest benefit was shown in patients with exon 19 deletions.There are more potential uses of those findings: Exon 19 deletions and L858R mutations have different prognostic and predictive roles and can be used as stratification factor in future clinical trials. Further drug development of newer generations of EGFR TkIs is needed to enhance antitumor activity for tumors with exon 21 L858R mutation.

Figure1: Forest plot of the effect of treatment on PFS in subgroups of patients according to EGFR mutation type



Literature

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3. Lee CK, et al. Impact of Specific Epidermal Growth Factor Receptor (EGFR) Mutations and Clinical Characteristics on Outcomes After Treatment With EGFR Tyrosine Kinase Inhibitors Versus Chemotherapy in EGFR-Mutant Lung Cancer: A Meta-Analysis. J Clin Oncol. 2015 Jun 10;33(17):1958-65.