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Klinisk Biokemi i Norden




Nordisk Forening for Klinisk Kemi

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INDHOLD

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Leder:

Sammenlægning af specialer og/eller speciallægeuddannelsen i de laboratoriemedicinske specialer i Danmark?

Linda Hilsted
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Der har længe verseret rygter om, at Sundhedsstyrelsen i Danmark (Institutionen under Sundhedsministeriet, der bl.a. skal fastlægge regler for uddannelsen af speciallæger og andet sundhedspersonale), har planer om at sammenlægge nogle/flere af de laboratoriemedicinske specialer.

Disse specialer omfatter i Danmark p.t. 5: Klinisk Biokemi; Klinisk Immunologi og Transfusionsmedicin; Klinisk Genetik; Klinisk Mikrobiologi; Patologi og Cytologi. Rygterne har også tilsvarende gået på, at flere af de tilhørende speciallægeuddannelser skulle lægges sammen.

For en ikke-laboratoriemediciner kan dette synes oplagt, og rygterne vil også vide, at den nys afgåede direktør for Sundhedsstyrelsen havde en sådan sammenlægning på agendaen. For der er nu store "analyseautomater" på markedet, der kan lave analyser helt på tværs af specialegrænser; der er andre faggrupper end læger, der udfører en stor del af analysearbejdet (fx bioanalytikere, laboranter m.fl.); det er tiltagende svært at rekruttere kvalificeret personale til de enkelte specialer. Og måske mest foruroligende: specialerne har hidtil ikke formået at arbejde sammen i tilstrækkelig grad, så en administrator trygt kan stole på fremtidssikring i relation til den demografiske udvikling ("ældrebyrde") med deraf stigende behov for vore ydelser – med andre ord "forventningsgabet" der kun bliver større.

Problemet omkring det manglende samarbejde, mange steder i landet sås meget tydeligt i Danmark under CoVid-epidemien (1). Her kom de laboratoriemedicinske specialegrænser/territorier meget tydeligt i spil, hvilket set fra et samfundsmæssigt perspektiv bestemt ikke førte til hensigtsmæssige løsninger, men derimod en beskæmmende mangel på samme. Så der er mange gode argumenter, der kan føre til, at rygterne om sammenlægninger måske kommer til at blive til realiteter.

De yngre læger efterlyser også en større grad af fleksibilitet i deres uddannelsesforløb på vej mod at blive speciallæge – og det gælder også i Laboratoriemedicin. Og de yngre læger vil rigtig gerne netværke med kolleger i de andre specialer, ikke mindst i Laboratoriespecialerne. Så de ser ikke de samme advarselslamper blinke, som vi andre. For en ældre laboratoriemediciner med fast forankring i et af specialerne, in casu Klinisk Biokemi, udgør sammenlægning – selv delvis - et bekymrende perspektiv. I Klinisk Biokemi er vi dog nok knap så bekymrede som i de andre specialer, for Sundhedsstyrelsens udmelding er, at der skal være afdelinger for Klinisk Biokemi på alle akutsygehuse. Det gælder ikke for alle de 4 andre laboratoriemedicinske specialer. Men vi er alle sammen bekymrede for, hvad der kan ske med den specifikke kernefaglighed ved sammenlægninger?

Udviklingen og kravene til vores ekspertviden i specialerne er nærmest eksponentielt stigende. Forventningerne fra de kliniske kolleger, patienterne/borgerne og samfundet ligeså. Hvordan skal vi kunne honorere disse krav, hvis vi sammenlægges? For os kan disse tanker opfattes på linje med, at kirurgi jo lige så godt kunne være ét samlet speciale (hvor svært kan dét lige være!).

Udvides fællesmængden i speciallægeuddannelsen vil behovet for efteruddannelse blive væsentligt større. Dette vil være konsekvensen, i lighed med følgerne af den generalistuddannelse, der blev indført i bacheloruddannelsen for bioanalytikere i Danmark i 2016.

Heldigvis har Sundhedsstyrelsen givet udtryk, for at der ikke vil ske en decideret sammenlægning af vore specialer (om end, der fortsat er mulighed for, at et eller flere kan blive nedlagt…).

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sundhedsøkonomiske udfordringer i de kommende årtier har Sundhedsstyrelsen i 2021 igangsat et større arbejde, der omhandler *hele* speciallægeuddannelsen i Danmark. Og en af de af Sundhedsstyrelsen nedsatte arbejdsgrupper omhandler de Laboratoriemedicinske specialer. Under denne arbejdsgruppe blev der i 2022 nedsat en Underarbejdsgruppe med bl.a. repræsentanter fra hvert af de 5 Lægevidenskabelige Selskaber (Dansk Selskab for Klinisk Biokemi (DSKB), Dansk Selskab for Klinisk Genetik, Dansk Selskab for Klinisk Immunologi, Dansk Selskab for Klinisk Mikrobiologi og Dansk Patologiselskab) – med Sundhedsstyrelsen for bordenden! Tidligt i forløbet meldte Dansk Selskab for Klinisk Genetik og Dansk Patologiselskab ud, at fællesmængden mellem dem og de øvrige 3 specialer var meget lille. De formåede i drøftelserne at skille sig ud, så de ikke var i brændpunktet om et fremtidigt fælles curriculum i speciallægeuddannelserne. På baggrund af arbejdet forelå der så en rapport fra Arbejdsgruppen, med deraf følgende anbefalinger fra Sundhedsstyrelsen, i sommeren 2023. Rapporten med anbefalinger er p.t. i høring "på det politiske niveau".

Jeg har ikke deltaget i arbejdet, og tager derfor kun udgangspunkt i det skriftlige produkt – og hvad der kan læses mellem linjerne. *Arbejdsgruppen* har identificeret betydeligt overlap og fællesmængder i de 3 specialer: Klinisk Biokemi, Klinisk Mikrobiologi og Klinisk Immunologi. Specialerepræsentanterne i *Underarbejdsgruppen* har ikke kunnet blive enige om *omfanget* af en fremtidig fællesmængde. Sundhedsstyrelsen skitserede så flere modeller, som specialerne skulle kommentere på, hvorefter Sundhedsstyrelsen konkluderede.

På baggrund af en samlet vurdering anbefaler Sundhedsstyrelsen i rapporten fra Arbejdsgruppen, at

- der er behov for flere laboratoriemedicinske generalistkompetencer og en styrkelse af de lægefaglige rådgivningsydelser
- der skal etableres en laboratoriemedicinsk funktionsmodel (i speciallægeuddannelsen) for Klinisk Biokemi, Klinisk Immunologi og Klinisk Mikrobiolog, hvori følgende indgår:
  1. *Der udarbejdes et fælles curriculum for henholdsvis introduktionsuddannelse og hoveduddannelsesforløb, som skrives ind i reviderede målbeskrivelser for specialerne*
  2. *Der laves en fælles kursusliste for de laboratoriemedicinske specialer*
  3. *Gennemført introduktionsforløb i et af specialerne i funktionsmodellen giver mulighed for at søge hoveduddannelse i et af de øvrige specialer i funktionsmodellen*

Rapporten har været i høring. Og Dansk Selskab for Klinisk Biokemi har udarbejdet et meget fint høringssvar, der er værd at læse:

https://prodstoragehoeringspo.blob.core.windows.net/160f8bc4-2605-4ad9-b976-9b679971408d/H%C3%B8ringssvar_Dansk%20Selskab%20for%20Klinisk%20Biokemi.pdf

Næste trin er så en revision af de enkelte specialers Specialebeskrivelser og af deres Målbeskrivelser. Det arbejde går i gang NU.

DSKB tog derfor initiativet til et medlemsmøde (9.11.), hvor vi bl.a. skulle tage stilling til de nuværende og fremtidige kernekompetencer i vores speciale. Et meget interessant møde, som førte til gode diskussioner, og et godt output, som vores specialeselskab vil arbejde videre med, og offentliggøre.

Hvad kan vi i Klinisk Biokemi derudover bidrage med/være opmærksomme på? Nedenstående er muligvis banaliteter, men alligevel:

1. Nogle af de andre specialer kæmper for deres identitet og eksistens. Samarbejdet skal foregå i respekt for dette, men selvfølgelig uden at gå på kompromis med, hvad vores speciale kan og skal bidrage med
2. Samarbejde er vejen frem. Hvis ikke vi kan finde ud af det selv, vil myndigheder "hjælpe os" med det
3. Forskning er og skal være en del af laboratoriespecialernes identitet, ikke mindst Klinisk Biokemi. Det skal italesættes vedvarende. Rapporten indeholder meget lidt om den del, og vores erfaring er, at Sundhedsstyrelsen ikke mener, at forskning er en kernekompetence for os "for alle specialer forsker jo"
4. Opgaven er ikke nem – professionsidentitet er en svær størrelse. Men vi skal være meget bevidste om, hvad vores unge kolleger tænker – de udgør jo fremtiden.

1. Jørgensen, PE: Tanker om laboratoriemedicinens fremtidige organisering – med inspiration fra Covid-19 pandemien. Klinisk Biokemi i Norden 2020;3:8-10.

Ordförandespalten

Per Bjellerup
Ordförande i NFKK

Kära KBN-läsare!

Hallå Solen!
Vilken fin höst vi har haft där jag bor. Fin värme hela oktober, lagom med regn, en hel del sol. Men vilken start på november! Bara 0,4 soltimmar så här långt och inte mycket bättring har utlovats. Bra väder för husrenovering, just nu kör jag, hustrun och Harald, vår norske snickare den sista gaveln med tilläggsisolering på den äldre delen av huset och ny yta på fasaden. En norsk ”kust”-variant som Harald föreslagit.

Vad ska NFKK göra då, fortsättning?
Ja, åter några rader om vad NFKK gör och kan göra för att främja nordisk utveckling av vår kära Kliniska Kemi! Vi har genom åren haft olika nordiska arbetsgrupper. Just nu är det ”The Nordic Preanalytical scientific working group” under ledning av Mads Nybo, Odense som NFKK stöttar ekonomiskt under tre år. Vi ser fram mot gruppens presentation på den kommande nordiska kongressen. Redan nu kan jag säga att de har varit mycket produktiva och gör ett gediget arbete.

The XXXIX Nordic Congress in Clinical Chemistry
Ja, nu är hemsidan öppnad och ett första utkast till vetenskapligt program är på plats. Du hittar den på www.nfkk2024.se Den ser fin ut! Det vetenskapliga programmet är mycket intressant! Vår mötespresident Charlotte Gran och hennes medarbetare gör ett fantastiskt fint arbete! Dessutom introducerar de en del uppfriskande nyheter.

- Det finns en ny spännande linje i programmet med fokus på utveckling av laboratoriet och dess medarbete.
- Våra baltiska vänner bidrar med en egen session.
- Postersessionen har blivit två. En för ”scientific” och en för ”laboratory”, i linje med ovan.
- Det blir frukostseminarier med fokus på patientfall och utbildning.

Du kan läsa mer på hemsidan och i detta nummer av KBN.

The NFKK price competition
Vår fina och mångåriga tävling, sedan 1970-talet, ”The Astrup Prize Competition” byter nu skepnad och blir ett nytt nordiskt pris då vi flyttar finansieringen till själva kongressen eftersom det har blivit

Vinbergssnäcka (Helix pomatia). Foto: Henrik Alfthan.

tuffare regler för ren företagssponsring. Jag vill passa på att framför ett stort TACK till Siemens Healthineers som generöst sponsrat priset under de senaste 12 åren. Det har varit mycket värdefullt, det är ett fint och viktigt pris som vi nu tar vidare på lite annat sätt.

Analytisk interferens
I detta nummer av KBN har Nils Bolstad skrivit en lång och inspirerande artikel om immunkemin och analytisk interferens. Fantastiskt roligt att få ta del av Nils gedigna kunskaper och engagemang i detta viktiga ämne! Immunoassaytekniken, framtagen på 1960-talet som RIA av Rosalyn Yalow och Solomon A. Berson med en avgörande publikation 1959, har varit mycket framgångsrik och utvecklat den kliniska kemin enormt. Som alla biokemiska tekniker har den även vissa svagheter som Nils belyser. Artikeln inspirerar oss att utveckla arbetet betydligt mer för att hantera dessa svagheter.

The Quality Hike 2023
I detta nummer kan du även läsa om NFKK:s senaste utbildningskurs arrangerad av våra finska vänner med Anna Linko-Parvinen i spetsen.

The Arctic Experience 2024
Vi ser fram mot nypremiär för denna kurs som våra norska vänner under Anne Vegard Stavelins ledning håller i. Vi har denna gång tre baltiska deltagare anmälda.

Stort TACK till Henrik och Ingunn!!!
Henrik Alfthan och Ingunn Þorsteinsdóttir har varit flitiga och trogna redaktörer i KBN under många år. Men nu är det dags ”to say goodbye”. Ni båda har gjort en fantastiskt fin insats för tidskriften och vi kommer att sakna er i redaktionen. Henrik kommer dock fortsätta att sköta hemsidan ett tag till och säkerligen bidra med en och annan naturbild och mer därtill. Vi hälsar Kristina Hotakainen välkommen som ersättare för Henrik från 2024. Kristina är ansvarig läkare för laboratoriesektorn på Mehiläinen, ett stort privat företag inom vårdsektorn i Finland. Vi har ännu inte fått någon ersättare för Ingunn.

Jag tillönskar dig en fortsatt fin vinter!
Bästa hälsningar Per

Henrik och Ingunn spanar efter bra bilder till KBN vid redaktionsmötet på Svalbard 2008.

XXXIX Nordic Congress
in Clinical Chemistry 2024 in Stockholm

On behalf of Nordic Federation of Clinical Chemistry (NFKK), the Swedish Society for Clinical Chemistry (SFKK), the Swedish Association of Clinical Biochemists (SSKF), the Institute of Biomedical Laboratory Science (IBL)and the Organizing committee, we are delighted to invite you to join us **in Stockholm on 17th-20th September 2024 for the 39th Nordic Congress of Clinical Chemistry**. We have now launched the webpage, https://www.nfkk2024.se/, where you will find updated information on congress.

Program

The scientific program "Preparing for the future" will cover state-of-the-art knowledge in a wide variety of fields of clinical chemistry, aiming to bridge basic research and clinical application. The sessions will present a wide span of areas from practical issues in daily routine to advanced data science. Our invited plenary speakers provide cutting edge updates with an in-depth focus on cardiometabolic disease, coagulation, and neurodegenerative disease. It is our hope that our ambitious program will fulfil the needs of everybody working in and around the exciting field of clinical chemistry. The program will also feature well known scientific competitions, such as the Lorentz Eldjarn Prize Competition for best publication that will be presented in Aula Medica at Karolinska Institutet.

A new theme

A new theme will be introduced in the 2024 congress: "Development and Improvements". This theme will be integrated in the congress program with parallel sessions during all four days of the congress. Sessions on diversity and inclusion for laboratory professions, opportunities for career growth, evolving skill sets (task-shifting), and competencies required for careers in future laboratories will be some of the material presented. An updated program for all sessions can be found under scientific program on the webpage.

The main lecture hall, Aula Medica, will also host the poster and sponsor exhibitions.
Photographer: Henrik Trygg/ mediabank.visitstockholm.com

The program will be continuously updated with more detailed information on sessions and speakers, so make it a habit to check for updates.

Call for abstracts

The abstract committee welcome you to submit your abstract for the congress from 30th of January to 15th of April. There will be two poster prizes of 1000 Euro each for the best poster in the scientific theme and in the development and improvement's theme, so take this opportunity to present your new and exciting result and be a part of the competition.

Social program

The main social activities will include a poster and exhibition mingle on Tuesday 17th of September and a congress dinner on Thursday 19th. The congress dinner will be held at the famous Vasa Museum where you can dine alongside the 17th century ship after exploring the museum.

The congress dinner will be held in the Vasa Museum on Thursday 19th of September. Photographer: Alexander Dokukin/ mediabank.visitstockholm.com

The Organizing committee:

Charlotte Gran, Chair of Organising Committee, President of Congress

Carina Ritzmo, Director of Clinical Chemistry

Uwe Tietge, Chair of Scientific Committee

Marjan Lambert Shafaati, Chair of Improvement and Development committee

Kristina Höög Hammarström, Chair of Sponsor Committee

Daniel Eklund, Chair of Social Committee

Andries Blokzijl, Co-Chair of Abstract Committee

Frida Duell, Co-Chair of Abstract Committee

Hiking with quality

Anna Linko-Parvinen[1], Hanna-Mari Pallari[1], Jonna Pelanti[2]
[1]Clinical Chemistry, Tyks Laboratories, Turku University Hospital, Finland
[2]Labquality, Finland



The very first Quality Hike was organised by the Finnish Society of Clinical Chemistry with the support of the NFKK in Oulanka National Park in 7.-10.9.2023. The idea of the course was to enjoy beautiful hiking trails while discussing various themes around laboratory quality. There were two participants from Denmark, two from Sweden and four from Finland together with three Finnish moderators attending the course.

The course started with a bus transportation from Oulu towards Kuusamo located in Northern Finland. During a three-hour drive, participants from Finland, Sweden and Denmark had a chance to introduce themselves, get to know one another and adapt to the theme. The atmosphere was full of excitement, since we knew that we would have a great opportunity to admire the northern wilderness and pure air in a wonderful weather during the next few days.

Friday started with a short 5 km hike at impressive Kiutaköngäs rapids. We discussed quality indicators and over- and under-use of laboratory tests in two hiking groups. Conversation was active, experiences were exchanged and ideas flowed rapidly. The major conclusions were gathered and summed up later in the evening and shared with all hikers.

After the hike, we had a chance to challenge ourselves and to test our teamwork. abilities in white-river rafting in three rapids, the wildest one being a bumpy class 4 rapid. After that, we enjoyed traditional pot cooked coffee around an open fire in the woods. Those who stayed ashore, tested our trust in each other by collecting mushrooms, which were later prepared to add extra taste for the dinner. All hikers and rafters relaxed in s smoke sauna and a refreshing wilderness lake after the first active day.

Time to catch some breath and enjoy the views during Pieni Karhunkierros (12 km) hike.

Team work skills were tested in white-river rafting. All rafters remained on board and enjoyed the bumpy ride.

The weather on the second hiking day was most beautiful with sunshine and a bright sky. We started the 12 km scenic hike, Pieni Karhunkierros, with lunches packed in our backpacks. This time we had a combined group-discussion and the theme was auto-verification. The discussions went on in smaller and changing groups throughout the hike. Every now and then, we stopped to admire the sceneries for example from hanging bridges over the river Kitkajoki. The topic of the day was discussed and evaluated from different angles, including novel methods in quality assurance and monitoring. Participants represented different organisations, occupations and careers, which resulted in fresh and interesting views on laboratory autoverification procedures. The most important take-home-messages were summed-up and reviewed together in the evening.

Again, we cleared the days dust off in the smoke sauna and clear waters before a dinner in the wilderness in restaurant Kammi. We enjoyed northern delicacies in the exotic atmosphere and living light, and we were happy to have two emeritus professors in clinical chemistry, Pirkko and Reijo Vihko joining us for the dinner. Their strong experience added extra spark to our discussion and their memories of the Nordic collaboration during the decades made us cherish our newly established Nordic contacts.

On Sunday, the bus took us back to Oulu, where some of us had a chance to enjoy the last lunch together and even have a cultural experience in the Oulu art museum. Backpacks filled with wonderful memories and new qualified thoughts we all headed home.

Outi Itkonen, with a major role in all arrangements, and a highly expected moderator, Mads Nybo, had to cancel their participation. All participants thanked and respected Outi's efforts, and we wish that Mads would join us in the future hikes. An experience like this needs to be shared to new colleagues and participants in the years to come. We believe this can be seen also in the reviews given by participants along with some ideas for improvement in the future.

Experiences and thoughts from participants

"The participants praised the initiative and were grateful both to the organizers for the excellent planning including sharing relevant literature, and to the moderators for making the event so successful. The moderators motivated, activated and encouraged all participants to share their past and present quality assurance experiences with specific themes in a friendly atmosphere. This was an excellent way of obtaining useful knowledge on laboratory quality."

"Wonderful setting, organization and company. Very giving discussions regarding lab quality, although I think the course might have benefited from a more structured approach to the content/discussions. Perhaps participants could have been asked to prepare discussion questions around the articles, or presentations on how their labs tackle these subjects?"

Quiet nature and wonderful weather provided nice surroundings for conversation and group work.

The first hike took us to fences used for reindeer round-up. We also spotted several free roaming reindeer in the woods.

Bör rutinmässig immuntypning genomföras vid proteinprofilbedömningar när frågeställningen är polyneuropati?

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Inledning

M-komponentassocierad polyneuropati är en diagnos där det idag finns relativt sparsam information om både patofysiologi, utredning och sjukdomsprevalens och forskning pågår på flera säten i Sverige (1). Vid Akademiska sjukhuset i Uppsala har man sett en ökande trend av önskemål om immuntypning av proteinprofiler även om kapillärelforesen bedöms normal. Hur många kliniskt relevanta M-komponenter kommer immuntypning av normalbedömda elforeser att hitta och är det ekonomiskt och tidsmässigt försvarbart?

Bakgrund M-komponentassocierad polyneuropati

I vårdriktlinjer för utredning av polyneuropatipatienter står det att en proteinprofil ska beställas men ingenstans i svenska riktlinjer om att en rutinmässig immuntypning ska genomföras (2,3,4). Polyneuropati generellt är en relativt vanlig sjukdomsgrupp och prevalensen uppskattas till cirka 1–7% av befolkningen (5). För M-komponentassocierad polyneuropati saknas prevalensuppskattning i Sverige men enligt en norsk studie från 2001 (6) har man sett att det i Norge uppskattas vara 5/100 000 invånare vilket gör att sjukdomen klassas som en sällsynt diagnos (7).

Patofysiologin bakom M-komponentorsakad poly-

neuropati är inte helt klarlagd men man har sett att myelinet bryts ner och ger symtom i form av symmetrisk sensorimotorisk nedsättning i det perifera nervsystemet. M-komponent av IgM-typ är vanligast och cirka hälften av dessa har anti-MAG-antikroppar (myelinassocierat glykoprotein) (8). Idag är det enbart M-komponentassocierad polyneuropati orsakad av IgM-typ som förespråkar behandlingsförsök med särskilda typer av läkemedel, framför allt rituximab. Dock är behandlingsresponsen förhållandevis låg och i många fall är behandlingen mer riskfylld och besvärlig än själva polyneuropatin. Ifall M-komponent av IgG- eller IgA-typ hittas behandlas diagnosen på samma sätt som CIDP (kronisk inflammatorisk demyeliniserande polyneuropati) (9). Således är det för diagnosen idag framför allt relevant att hitta M-komponenter av IgM-typ.

Vad säger forskningen?

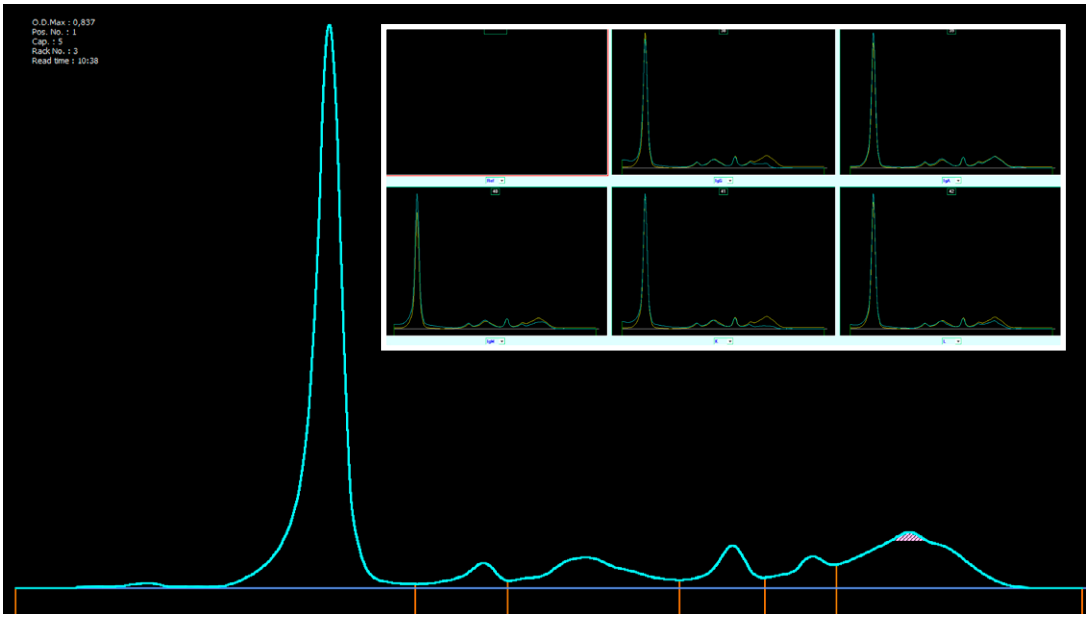
Enligt en artikel från 2021 publicerad i Practical Neurology från BMJ (10) står det att enbart proteinelektrofores i serum inte är tillräckligt känsligt för screening av neurologiska symtom. Det behövs tillägg av immunfixation för att upptäcka de små M-komponenterna (~0,1 g/L), då dessa är avgörande för diagnos och behandling. Denna artikel baseras på en studie från USA på 1 877 patientprov analyserade mellan år 2002 och 2008 genomförda med gelelektrofores (REP; Helena Laboratories) och immunfixation (Hydrasys och Hydragel; Sebia) (11). Där fann man att detektionsgraden för MGUS ökade från 81,9 % till 92,8 % och från 65,9 % till 73,8 % för AL amyloidos efter tillägg av immunfixation.

Vid Akademiska sjukhuset i Uppsala används dock varken gelelektrofores eller immunfixation utan kapillärelektrofores och immunsubtraktion (Capillarys 3; Sebia). Dock använder flera andra laboratorier i Sverige gelelektrofores och upplösningen på de svenska agaroselektroforeserna och kapillärelektroforeserna anses vara högre än motsvarande amerikanska metoder.

Vad visar Akademiska sjukhusets proteinprofilbedömningar?

Vid genomgång av Akademiska sjukhusets besvarade proteinprofilbedömningar i plasma från de senaste två och ett halvt åren (2021-01-01 – 2023-08-31) fann man 321 med frågeställning polyneuropati (av totalt antal 17 089). Utav dessa efterfrågade remittenten sexton gånger immuntypning även om elforesen bedömdes normal. 58 gånger frågade remittenten aktivt om förekomst av M-komponent och resterande 247 gånger beskrevs enbart anamnes på polyneuropati.

Utav alla 321 proteinprofiler med frågeställning



Patologisk kapillärelfores där immunsubtraktion visar en M-komponent av IgM-kappa.

polyneuropati utfördes 47 immunsubtraktioner, 22 gånger på grund av att bedömande läkare sett något avvikande på elektroferogrammet eller i de kvantitativa värdena och 25 gånger enbart på grund av att frågeställningen varit polyneuropati. Ingen gång då immunsubtraktion genomfördes enbart på grund av frågeställningen hittades någon M-komponent.

Avslutning

Det går såklart inte att dra några slutsatser utifrån Akademiska sjukhusets immuntypning på normalbedömda proteinprofiler med polyneuropatifrågeställning från de senaste två och ett halvt åren, de är alldeles får få till antalet. Det vi kan se är dock att antalet frågeställningar med polyneuropati ökar, vilket är helt rätt handlagt enligt vårdriktlinjer, men även efterfrågan från remittenter att det ska utföras immuntypning även om elektroferogrammet och de kvantitativa värdena bedöms normala.

Att genomföra immunsubtraktion på en normalbedömd kapillärelektrofores, jämfört med immunfixation på en normalbedömd gelelektrofores, finns det inte mycket relevant forskning att läsa om idag. Mer forskning behövs för att kunna ta fram riktlinjer om när, eller om, immuntypning vid frågeställning polyneuropati på normalbedömda proteinprofiler på svenska laboratorier (vare sig man använder sig av kapillärelektrofores eller gelelektrofores) ger något mervärde. Ifall immuntypning ska göras på alla polyneuropatifrågeställningar kommer både kostnaden för remittenten och tidsåtgången för laboratoriepersonalen att öka betydligt. Frågan kvarstår då om det är ekonomiskt och tidsmässigt försvarbart då prevalensen av polyneuropati som generellt symtom är relativt hög och diagnosen M-komponentsassocierad polyneuropati relativt låg, och framför allt – skulle fler kliniskt relevanta M-komponenter att upptäckas?

Referenser

1. Socialstyrelsen. M-komponentassocierad polyneuropati. https://www.socialstyrelsen.se/kunskapsstod-och-regler/omraden/sallsynta-halsotillstand/m-komponentassocierad-polyneuropati/ (Hämtad november 2023).
2. Region Stockholm. Polyneuropati. https://viss.nu/kunskapsstod/vardprogram/polyneuropati (Hämtad november 2023).
3. Region Skåne. Polyneuropati. https://vardgivare.skane.se/vardriktlinjer/nervsystemet/ako/polyneuropati/ (Hämtad november 2023).
4. Internetmedicin. Polyneuropati och multipel mononeuropati. https://www.internetmedicin.se/behandlingsoversikter/neurologi/polyneuropati-och-multipel-mononeuropati/ (Hämtad november 2023).
5. Hanewinckel R, van Oijen M, Ikram MA, et al. The epidemiology and risk factors of chronic polyneuropathy. Eur J Epidemiol. 2016; 31: 5-20.
6. Mygland Å, Monstad P. Chronic polyneuropathies in Vest-Agder, Norway. Eur J Neurol. 2001; 8: 157-65.
7. Socialstyrelsen. Socialstyrelsens termbank. https://termbank.socialstyrelsen.se/?TermId=826&SrcLang=sv (Hämtad november 2023).
8. Koike H, Katsuno M. Paraproteinemia and neuropathy. Neurol Sci. 2021; 42: 4489-501.
9. Chaudhry HM, Mauermann ML, Rajkumar SV. Monoclonal Gammopathy–Associated Peripheral Neuropathy: Diagnosis and Management. Mayo Clin Proc. 2017; 5: 838-50.
10. Carroll AS, Lunn MPT. Paraproteinaemic neuropathy: MGUS and beyond. Pract Neurol. 2021; 21: 492-503.
11. Katzmann JA, Kyle RA, Benson J, et al. Screening Panels for Detection of Monoclonal Gammopathies. Clin Chem. 2009; 55: 1517-22.

Korsspindel (Araneus diadematus). Foto: Henrik Alfthan.

Immunoassay interference

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Immunoassay technology, pioneered by Yalow and Berson more than 60 years ago *(1)*, has had an enormous impact on modern medicine, both in medical research and clinical management of patients. The early methods were labor intensive and time-consuming, typically relying on incubations spanning days, but modern immunoassays are often fully automated on multi-analysers and provide results in minutes. Monoclonal antibody technology *(2)*, replacing radioactive tracers with fluorophores and chemiluminescent labels, and the invention of monodisperse magnetic beads (Ugelstad/Dynabeads) were all important developments that helped advance and commercialise the immunoassay technology. Today, both in primary care and specialised hospital departments, physicians rely on results from immunoassays to diagnose and manage a range of conditions, such as infections, pregnancies, malignancies and myocardial infarctions. Immunoassays can deliver reliable and rapid information at low cost, but the technology is vulnerable to interference through several mechanisms, which may produce false results and lead to patient harm unless discovered and managed appropriately *(3)*.

I will give a brief overview of immunoassay technology and some important sources of false or confusing results.

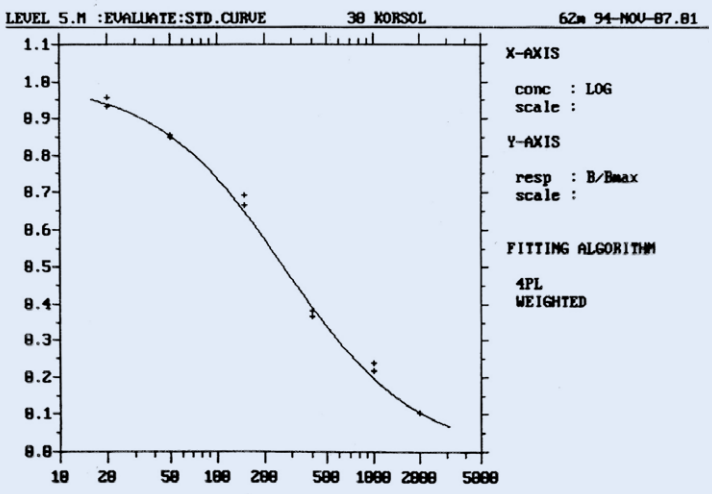
Sällsynt kruskantarell (Pseudocraterellus undulatus) hittad i år! Foto: Henrik Alfthan.

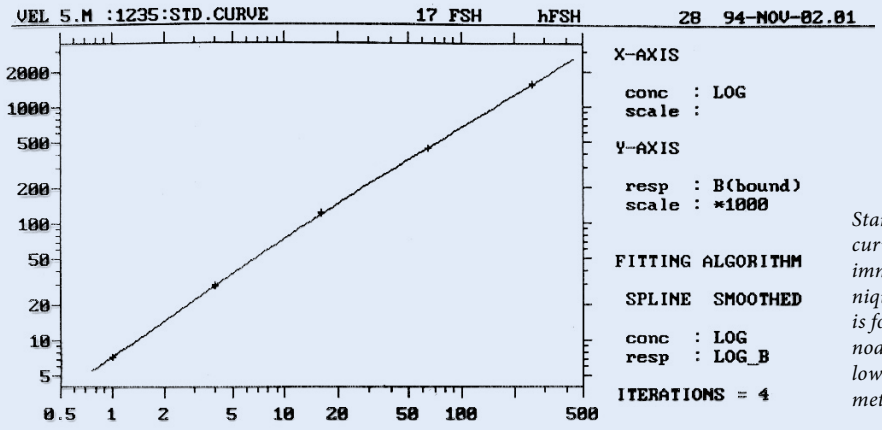
Immunoassay formats

Assay formats

Yalow and Berson used antigen labelled with a radioactive isotope (tracer), hence the name radioimmunoassay, which competed with unlabelled antigen in samples for binding to immobilised antibodies. Similar assays, commonly called ***competitive immunoassays***, are still used today to measure small analytes such as peptide hormones or vitamins. In these assays, the amount of bound labelled antigen is inversely proportional to analyte concentration. Larger analytes are usually measured by using two different antibodies to the antigen, one antibody attached to a solid phase (e.g. well or bead), termed "solid phase antibody", and one antibody labelled with a tracer molecule, termed "tracer antibody". In this assay format, where the two assay antibodies form a sandwich complex with the antigen, the amount of bound labelled antibody is proportional to analyte concentration. While commonly referred to as "sandwich assays", ***immunometric assays*** is the preferred term. While "ELISA", Enzyme-Linked Immuno-Sorbent Assay, is a familiar term often used among medical professionals to refer to any immunoassay, it should be reserved for immunoassays relying on enzymatic processing of substrates to generate signals.

Both competitive and immunometric assays normally rely on one or more wash steps. ***Homogenous immunometric assays***, such as assays performed on the Kryptor immunoassay platform, are assays relying on the relative positioning of assay antibodies to create a quantifiable signal, and do not require wash steps. ***Immunoturbidimetric assays*** do not use traditional labelling of assay antibodies but rather rely on the formation of aggregates of antigen and assay antibodies to quantify an analyte. Increasing aggregation results in decreasing light transmission (increasing turbidity) in the assay well or cuvette. In modern routine diagnostics these assays are usually enhanced by immobilizing the assay antibodies to latex particles or similar entities and can be performed without wash steps.





Standard (dose-response) curves for the two main immunological assay techniques. The upper graph is for a competitive immunoassay (cortisol) and the lower one for an immunometric assay (FSH).

Alla figurer utom den på sida 25: Henrik Alfthan.

Antibody interference in immunoassays

Most immunoassays rely on animal antibodies, or antibody fragments or constructs derived from animal antibodies. Some patients have antibodies in their blood that bind the animal antibodies used in immunoassays, which then may produce false results. The mechanism of antibody interference may vary and depend on assay format and design but is usually either related to cross-linking (in metric assay formats) or blocking/aggregation/consumption (in competitive assay formats) of assay antibodies. In rare cases, such patient antibodies exist because the patients have been exposed to animal antibodies as part of treatment or diagnostic procedures, but in most cases there is no certain exposure in the patient's history to explain such anti-animal antibodies. In the rare cases where exposure to a defined animal immunoglobulin is identified, the patient antibody is usually named after the animal antibody, e.g. a **human anti-mouse antibody (HAMA)** *(4)*. Patient antibodies to animal antibodies are usually called **heterophilic antibodies** when the antigen or exposure is not known. A third category, which is difficult to distinguish from heterophilic antibodies in practice and important to remember as a source of assay interference, is **rheumatoid factor** *(5)*. Rheumatoid factors are autoantibodies that bind the Fc-portion of the patient's own IgG, which sometimes cross-react with animal antibodies used in immunoassays and thus behave like heterophilic antibodies. Patient **anti-bovine antibodies**, which are extremely common in the general population, are likely related to exposure to bovine antibodies through handling and consumption of beef and dairy products. Anti-bovine antibodies, particularly when present in high concentrations, may also cross-react with assay antibodies from other species and create false results in immunoassays *(6)*.

Protecting assays against antibody interference

James T. Sgouris *(7)* and Alfred M. Prince et al. *(8)* both described heterophilic antibody interference in the assay for hepatitis B antigen from Abbott Laboratories as early as 1973. False positive results were caused by patient antibodies reacting with the guinea pig assay antibodies, and results were normalised with the addition of normal guinea pig serum (containing guinea pig antibodies). The addition of animal immunoglobulin to neutralise or block

Antibody interference testing

Reanalysing on the same method to exclude analytical errors such as pipetting inaccuracies, inefficient wash, tracer aggregates or other contaminants, and checking the tube for obvious explanations such as mislabelling or wrong sample material, should be done first.

Reanalysing with different immunoassay or alternative methodology, if possible. Usually, the sample is sent for confirmation to another laboratory which uses a different immunoassay. Particularly difficult patient samples may cause interference in both assays, but even in these rare cases the effects of the interfering antibodies are usually different in the two assays.

Diluting samples, e.g. using the kit diluent, and reanalysing is a common strategy when faced with spurious test results. This approach is available and familiar to most laboratorians, as it is often used to retest all samples with extremely elevated analyte concentrations. In interference testing, dilutions can be useful if the result is sufficiently high. We look for non-linearity upon dilution to indicate interference, but interpretation can be challenging, and it is important to include a sample with analyte in the same range as the test sample as control.

The addition of blocking animal immunoglobulin to the sample prior to reassay is a commonly used strategy to **block interfering antibodies**. If a patient sample contains heterophilic antibodies that cross-link the mouse IgG1 assay antibodies, the addition of mouse IgG1 to the sample can block the heterophilic antibodies and prevent interference. Aggregated antibodies, either heat-treated or chemically aggregated, are more potent blockers than non-aggregated antibodies. As a rule, we let the sample and blocker incubate for 10–15 min prior to reanalysis to allow complete binding of heterophilic antibodies to antibody aggregates. In assays using polyclonal rabbit or goat antibodies, polyclonal rabbit or goat IgG should be added to the sample, but higher concentrations of polyclonal antibody (0.5–1 g/L) are often necessary to achieve efficient blocking compared to monoclonal antibodies

(0.1–0.2 g/L). Immunoassays that combine antibodies from two species, e.g. a mouse monoclonal as the solid phase antibody with rabbit or goat polyclonal as tracer antibody, can be difficult to block. We have had most success blocking with aggregated antibodies similar to the tracer antibodies *(16)*, or by adding blockers mirroring both solid phase and tracer antibodies.

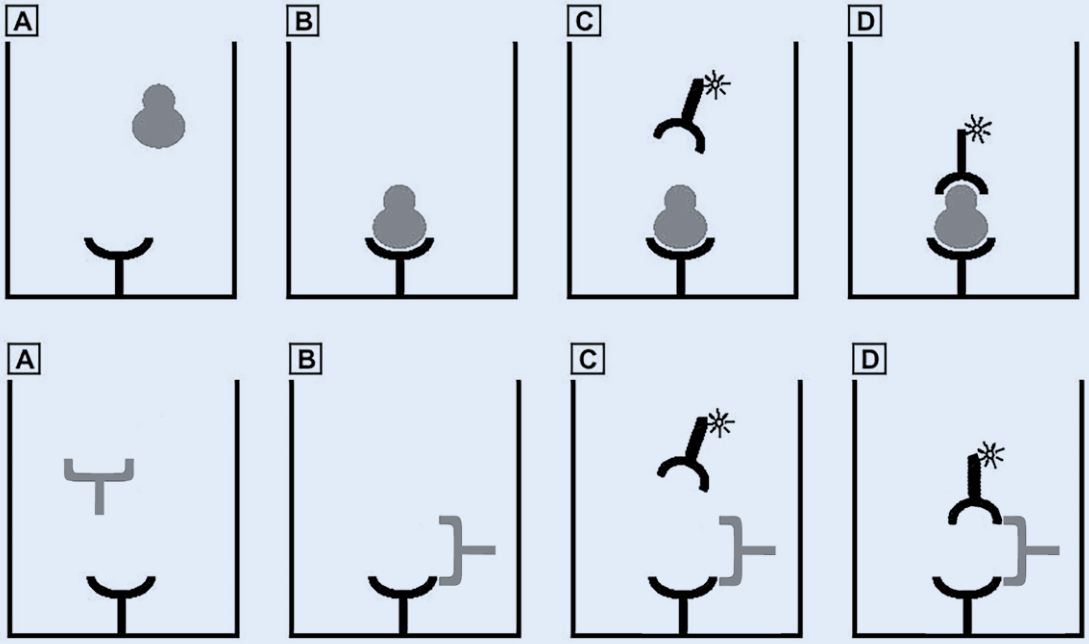
As an alternative to animal immunoglobulin (although to our knowledge, most of these reagents also contain animal immunoglobulin), several **blocking reagents and blocking tubes** are commercially available.

Methods used to **remove interfering antibodies** from samples are usually based on precipitation, affinity extraction or size-exclusion. When antibodies, including interfering antibodies, are removed, the true analyte can be measured in the antibody-free sample. At least in theory. While these methods can be very useful tools, they are demanding and potentially deceptive interference tests *(14)*.

Interference (non-sense) assays are assays where we test if a sample contains antibodies able to cross-link two antibodies that do not form an assay pair *(17)*, e.g. a mouse antibody to AFP and a mouse antibody to CEA. If these antibodies are cross-linked, it is because the sample contains antibodies to mouse antibodies (because AFP-CEA complexes do not exist). While this cannot prove interference, it can be useful to characterize the potential for interference in a sample and help guide further testing.

A. Addition of sample
B. Analyte (top) or heterophilic antibody (bottom) binding to solid phase antibody + wash step
C. Addition of tracer antibody
D. Formation of "sandwich" complex

In the upper panel, the sample contains the molecule you specifically want to measure. In the lower panel, the sample contains only HAMA.
- Two-site immunometric assay
- Effect of HAMA in a immunometric "Sandwich" assay



interference from patient antibodies was the first protective measure against heterophilic antibody interference in widespread use. Meurman and Ziola demonstrated that heat-aggregated IgG effectively (compared to non-aggregated IgG) neutralised interference from rheumatoid factor in 1978 *(9)*, and both Duermeyer et al. and Kato et al. demonstrated that use of Fab' or $F(ab')_2$-fragments in place of intact IgG in immunoassays dramatically reduced interference from rheumatoid factors *(10, 11)*. The effectiveness of using aggregated blocking immunoglobulin and assay antibody fragments were both thoroughly evaluated by Vaidya and Beatty *(12)* and by my supervisors *(13)*, and are arguably still the two most important specific measures against heterophilic antibody interference when designing immunoassays. Because anti-bovine antibodies are so common in patient samples, the addition of high concentrations of blocking bovine immunoglobulin to assay buffers is considered obligatory in assay design.

Detecting antibody interference

The most important step in detecting interference in immunoassays is to suspect it, and this is usually a result of dialogue between clinicians and laboratory staff. Based on my experience, when clinicians question laboratory results, they are usually right. Even if they are not right, and the laboratory result is valid, these investigations are often educative and rewarding for both clinicians and laboratorians. As such, I believe we should always allocate time and resources to cases where laboratory results are questioned. Several strategies can be helpful when examining possible cases of antibody interference. I will briefly introduce some common strategies, with more detailed discussions on the strategies available elsewhere *(14, 15)*.

Since interference tests can be challenging to perform and interpret, I recommend getting comfortable with one or two strategies. A negative interference test does not exclude interference, while a positive interference test, provided it is performed and interpreted correctly, usually indicates interference. If it is not possible to conclude if interference is present or not, based on the tests we have experience with, it is probably better to ask colleagues with experience with other strategies for help, than to try new strategies for the first time. It is also important to include one or two samples with true (preferably comparable) values of the analyte in the interference test, to control the effect of the interference test (dilution, blocking, antibody removal) on the analyte. As an example, PEG-preciptation removes antibodies from the sample, but will often remove some analytes as well. The effect of PEG-precipitation varies between analytes and is not easy to predict, so experience with the PEG used, the precipitation protocol and the analyte is important.

Additional sources of confusing results in immunoassays

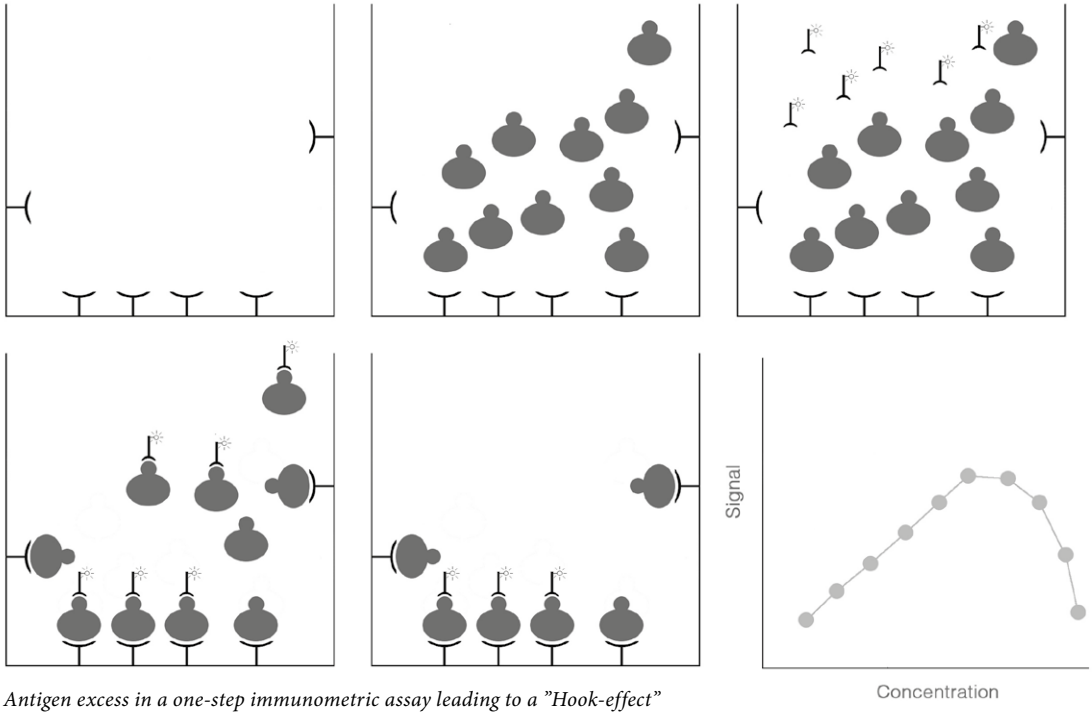
Mislabelling: When sample material is transferred to secondary tubes before transportation or analysis, there is a risk that analysis may be performed in the wrong medium (e.g. EDTA-plasma and not serum) or the wrong sample (due to mistakes in sample transferral or labelling). In such cases, it may be very difficult to identify false results, at least if comparison with previous results is not possible.

Hemolysis, lipemia, icterus or clots in samples may affect assay results, but this is familiar to most laboratorians and will not be discussed further.

Carryover from samples with extremely high concentrations of analyte is a particular concern in our laboratory, since the tumour marker assays we offer can have significant impact on patient care, and because results in many of these assays vary by a factor of millions. Technical issues including carryover, but also mishaps like bubbles, clots or clogged pipettes, can usually be resolved by reanalysis on the same instrument, which should always be the first test we do when we suspect a false result.

High-dose hook effect, antigen excess. False results generated by antigen excess, in immunoassays often referred to as the high-dose hook effect, is still a problem in modern immunoassays (particularly in assays without wash or with only one wash step). The mechanism behind the high-dose hook effect is that the analyte is present in such high concentrations that assay antibodies are fully saturated with analyte, but are bound to separate analyte molecules and are unable to cross-link to form the sandwich complex on which detection is based.

Tracer molecules: In immunoassays using alkaline phosphatase (ALP) to generate signals, and this includes automated immunoassays from major immunoassay producers, endogenous ALP may interfere with analyte quantification. As assays based on



Antigen excess in a one-step immunometric assay leading to a "Hook-effect"

quantification using ALP will always include a wash step before addition of substrate, (barring instrument malfunction) only samples with extreme concentrations of ALP are expected to give false results.

Macro-analytes: In some individuals, endogenous antibodies bind the analyte, altering the plasma clearance and half-life of the analyte to effectively mirror that of the antibody subclass(es) in question. Since antibodies have long half-lives, relative to most analytes, this usually leads to an increased plasma concentration of the analyte. In these cases, plasma concentration of the analyte may increase severalfold without increased production or actual pathology. This phenomenon will be covered in detail in a separate manuscript, but it is worth mentioning here that some of the tests (involving removal of antibodies from the sample) we perform when we suspect antibody involvement cannot distinguish between heterophilic antibody interference and macro-analytes.

Cross-reactivity: Several pharmaceutical drugs are known to give false result in immunoassays. Examples include prednisolone which cross-reacts in assays for cortisol, and furosemide which interferes in some assays for thyroid hormones through an unknown mechanism. Structural similarities in endogenous hormones sometimes create analytical challenges. This used to be a significant problem when steroid hormone analysis was limited to immunoassay technology, and the lack of specificity of certain antibodies used to measure pituitary hormones was less understood. Previously, cross-reactivity in assays for hCG, TSH, LH and FSH created ample confusion in the follow-up of pregnancies and hCG-producing tumours such as testicular cancer and gestational trophoblastic disease.

In addition, some protein variants (e.g. truncated forms) may be detected in some assays but not in others. Important examples are unequal detection of the six major hCG-variants, the varying ability of immunoassays for carcinoembryonal antigen (CEA) to detect the common truncated variant non-specific cross-reacting antigen 2 (NCA-2), and the unpredictable detection of different ACTH-related peptides produced by malignant tumours. In oncology, this may create significant confusion if patients are followed in different medical centres using assays with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different properties, which is common since care for cancer patients is often shared between highly specialised central hospitals and general local hospitals or primary physicians. It is also a source of confusion in interference testing, as different results may be falsely attributed to interference, and could delay or stop further examinations that were called for.

Clearance: Most analytes are removed from the circulation in the liver or kidneys. Hepatic clearance is impaired in patients with hepatic failure, and increased concentration of analytes normally removed by the liver can be found in the circulation, without increased production due to other pathological conditions. Correspondingly, renal clearance is impaired in patients with impaired renal function, and increased concentration of analytes normally removed by the kidneys can be found in the circulation without increased production. This is a general challenge in clinical chemistry and not only to immunoassays.

In addition, membranes used in haemodialysis have varying properties and may treat biomarkers, or variants of biomarkers, differently. In such cases, certain molecular variants are cleared in dialysis while others are retained. If the retained variants, e.g. of a tumour marker like hCG, are measured to give an elevated result, it may create additional challenges in the already complicated care of these patients.

Unknown, genetic: Occasionally we observe aberrant immunoassay results we cannot explain, even after extensive experiments and testing, or unexpected results caused by extremely rare conditions. We have seen patients with grossly elevated levels of CEA or alfa-fetoprotein (AFP), who have been observed for decades without signs of malignant disease. Heterophilic antibody interference has been excluded. We believe they must be related to dysregulated expression of these proteins in non-malignant cells, and not signs of disease. We have also seen patients with clearly elevated hCG, without definitive signs of malignant disease, where extensive testing revealed several family members with similar elevated levels of hCG. This is a rare genetic variant known as familial hCG. Since hCG is actually present in plasma, these patients have increased risk of false diagnosis caused by positive pregnancy tests in both plasma and urine, elevated hCG levels when measured as tumour marker and even possible positive sports doping tests.

When assays are designed using monoclonal antibodies, substitution of one amino acid in the analyte may be sufficient to change the ability of the assay to measure the analyte. Many examples likely exist, but few have been documented. A notable exception is the description of a rare TSH-mutation (a point mutation in the β-chain of TSH) that made TSH undetectable in 4 commercial TSH-assays (Drees JC et al. 2014). The mutation is not expected to affect biological activity of TSH but could certainly complicate care for patients taking levothyroxine supplements.

Monoclonal components, as found in patients with multiple myeloma or Waldenström's macroglobulinemia, may form aggregates or precipitates in certain assays. I believe this is most common in assays involving an acidic dissociation step to separate analytes from binding proteins, such as assays for vitamin D *(18)*. Aggregation or precipitation of monoclonal components in these assays may interfere either by inhibiting binding of analytes to reagents, or by increasing opacity in assay wells and disturbing the quantification step. Analysing in alternative assays, preferably using other methodologies such as mass spectrometry, usually reveal interference.

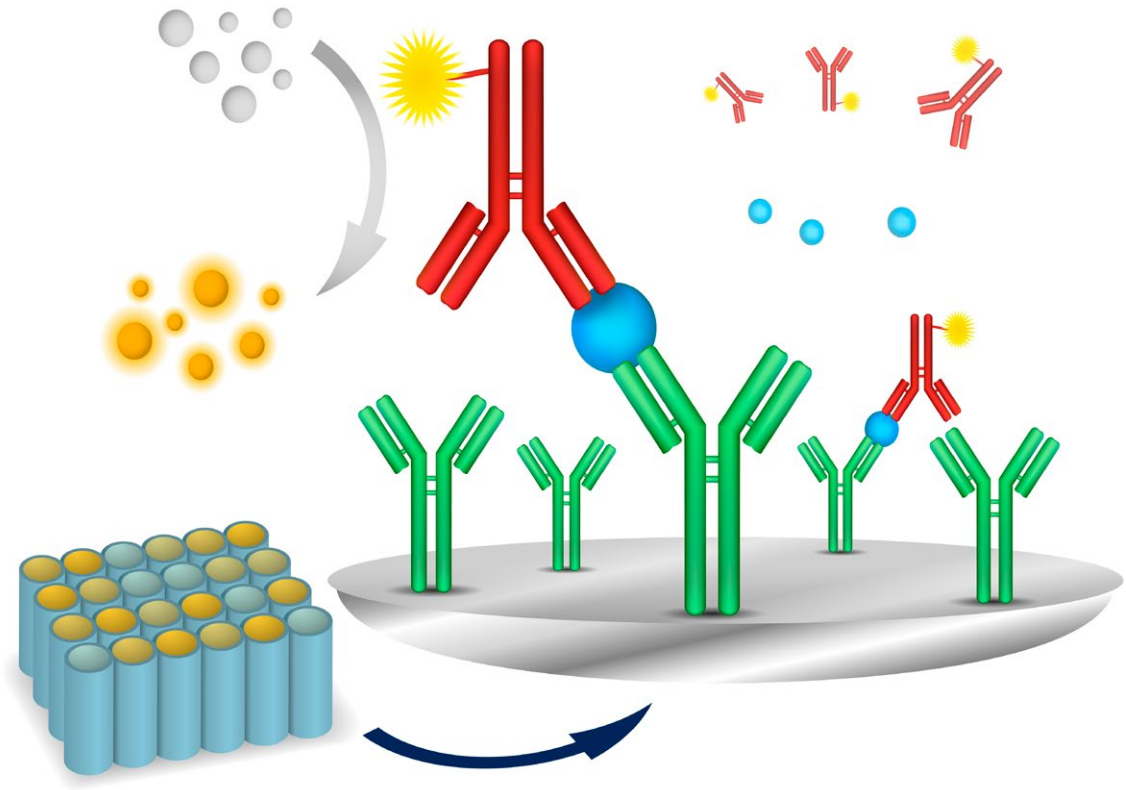
Biotin, anti-streptavidin antibodies and anti-tracer antibodies. Interference from biotin in patient samples is a potentially serious problem in immunoassays. Biotinylation is used by many immunoassay producers to immobilise assay antibodies on streptavidin-coated solid phases (beads or wells). Patients taking high doses of biotin supplements may have sufficient biotin in samples to interfere with the interaction between biotinylated antibodies and streptavidin solid phases necessary for assay performance. Biotin interference can be particularly ominous because it can give false results in several assays, e.g. a falsely elevated thyroxine (FT4)-level and a false low result for thyroid-stimulating hormone (TSH). In addition to people using high dose biotin supplements for alleged cosmetic benefits, two patient groups may take extremely high doses of biotin that could lead to interference: Patients with progressive multiple sclerosis, after reports indicated beneficial effect of biotin, and patients with inborn errors of metabolism, including children with biotinidase/carboxylase deficiencies. Following the death of a patient related to false negative troponin measurements caused by biotin interference, immunoassay producers have

invested significantly to increase assay tolerance to biotin, although the possibility of biotin interference will remain as long as patients take extreme doses and the assays rely on the interaction between biotin and streptavidin. Similar interference is possible if patients have antibodies to streptavidin or anti-tracer antibodies that bind tracer-protein complexes such as antibodies labelled with ruthenium (acting as a hapten). We have seen very few such cases, but I expect they are more common than we presume.

Binding proteins: Some analytes, particularly vitamins and hormones, are normally bound to binding or carrier proteins in plasma. In some cases, high levels of the binding protein may give falsely elevated results in competitive immunoassays through the binding and consumption of tracer, which is usually labelled analyte. Another potential source of false results is incomplete separation of analyte from binding protein, causing the analyte to remain undetectable by the assay.

Final remarks

Immunoassay designers and manufacturers today have the knowledge and tools to make high quality and robust assays, and modern assays from established assay producers are most often well protected against analytical interference. However, proper assay protection increases production costs. Some assays, particularly older assays and assays primarily intended for research, still have inadequate protection *(5, 19)* and should not be used in patient care. It is very difficult to ignore an alarming laboratory result in clinical practice, and one false result can lead to costly interventions and patient harm. Examples include direct costs, such as radiological examinations, surgical interventions and hospital stays, and indirect costs, such as patient anxiety, treatment associated adverse events and distrust towards health care providers *(3, 16, 19, 20)*. These costs are rarely considered in tenders when assay manufacturers are competing for contracts with laboratories.



If we want to reduce patient harm from interference in immunoassays, we must replace the vulnerable assays in our laboratories. Ideally, they should be removed from the market. To achieve this, we have to identify vulnerable assays and document patient harm, and regulatory agencies need to limit market access for poorly protected assays. As academics and specialists in medical biochemistry laboratories, we are trusted to reduce risk of patient harm where we can. If we continue to purchase and offer poorly protected immunoassays, we not only break this trust, but we also relieve assay manufacturers of incentives to invest resources to improve these assays.

References

1. Yalow RS, Berson SA. Assay of plasma insulin in human subjects by immunological methods. Nature 1959;184 (Suppl 21):1648-9.
2. Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 1975;256:495-7.
3. Rotmensch S, Cole LA. False diagnosis and needless therapy of presumed malignant disease in women with false-positive human chorionic gonadotropin concentrations. Lancet 2000;355:712-5.
4. Kaplan IV, Levinson SS. When is a heterophile antibody not a heterophile antibody? When it is an antibody against a specific immunogen. Clin Chem 1999;45:616-8.
5. Gehin JE, Klaasen RA, Norli ES, et al. Rheumatoid factor and falsely elevated results in commercial immunoassays: Data from an early arthritis cohort. Rheumatol Int 2021;41:1657-65.
6. Hunter WM, Budd PS. Circulating antibodies to ovine and bovine immunoglobulin in healthy subjects: A hazard for immunoassays. Lancet 1980;2:1136.
7. Sgouris JT. Limitations of the radioimmunoassay for hepatitis B antigen. N Engl J Med 1973;288:160-1.
8. Prince AM, Brotman B, Jass D, et al. Specificity of the direct solid-phase radioimmunoassay for detection of hepatitis-B antigen. Lancet 1973;1:1346-50.
9. Meurman OH, Ziola BR. IgM-class rheumatoid factor interference in the solid-phase radioimmunoassay of rubella-specific IgM antibodies. Clin Pathol 1978;31:483-7.
10. Kato K, Umeda U, Suzuki F, et al. Use of antibody Fab' fragments to remove interference by rheumatoid factors with the enzyme-linked sandwich immunoassay. FEBS Lett 1979;102:253-6.
11. Duermeyer W, Wielaard F, van der Veen J. A new principle for the detection of specific IgM antibodies applied in an ELISA for hepatitis A.
12. Vaidya HC, Beatty BG. Eliminating interference from heterophilic antibodies in a two-site immunoassay for creatine kinase MB by using F(ab')2 conjugate and polyclonal mouse IgG.
13. Bjerner J, Nustad K, Norum LF, et al. Immunometric assay interference: Incidence and prevention. Clin Chem 2002;48:613-21.
14. Bolstad N, Warren DJ, Nustad K. Heterophilic antibody interference in immunometric assays. Best Pract Res Clin Endocrinol Metab 2013;27:647-61.
15. Ismail AA. On the interpretation of affirmative follow-up tests in immunoassays: What must not be done? Ann Clin Biochem 2006;43:249-51.
16. Bolstad N, Kazaryan AM, Revheim ME, et al. A man with abdominal pain: Enough evidence for surgery? Clin Chem 2012;58:1187-90.
17. Boscato LM, Stuart MC. Incidence and specificity of interference in two-site immunoassays. Clin Chem 1986;32:1491-5.
18. Hager HB, Bolstad N, Warren DJ, et al. Falsely markedly elevated 25-hydroxyvitamin D in patients with monoclonal gammopathies. Clin Chem Lab Med 2021;59:663-9.
19. Bolstad N, Warren DJ, Bjerner J, et al. Heterophilic antibody interference in commercial immunoassays; a screening study using paired native and pre-blocked sera. Clin Chem Lab Med 2011;49:2001-6.
20. Cole LA, Rinne KM, Shahabi S, et al. False-positive hcg assay results leading to unnecessary surgery and chemotherapy and needless occurrences of diabetes and coma. Clin Chem 1999;45:313-4.

Persontilpassede beslutningsgrenser

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Hva er den beste beslutningsgrensen for en diagnostisk test? Laboratoriene tilstreber å anbefale den samme og beste beslutningsgrensen for samme kliniske tilstand. Men det kan ikke eksistere én riktig beslutningsgrense for alle pasienter under utredning for samme tilstand. Her viser vi hvorfor.

Hvis et prøvesvar over eller under en viss grense utløser en bestemt klinisk handling, kalles grenseverdien på norsk for en beslutningsgrense. Eksempler er 48 mmol/mol som beslutningsgrense for b-HbA1c, og 20 µg/L for p-ferritin. Disse beslutningsgrensene brukes som hjelp til å stille diagnoser, henholdsvis diabetes mellitus og jernmangel. Grensene er ikke referansegrenser. De fastsettes vanligvis ikke som persentiler i en referansepopulasjon, men ut fra vurderinger av hva som er klinisk mest nyttig. Det forhindrer ikke at referansegrenser blir brukt som beslutningsgrenser, antakelig uten at det har blitt gjort noen formell nytteanalyse av valget.

Hvordan kan vi gjøre en slik nytteanalyse? Først må vi definere *behandlingsterskelen*. Uttrykket er direkte oversatt fra det engelske uttrykket «treatment threshold». Det er den laveste sannsynligheten for sykdom som tilsier at pasienten bør få behandling [1]. I denne sammenheng betyr «behandling" ikke bare et visst legemiddel eller et bestemt operativt inngrep, men ethvert tiltak som er mer nyttig enn skadelig for pasienten. Det kan for eksempel være en beslutning om videre utredning. Skal vi kunne estimere en behandlingsterskel, må vi ha kjennskap til nytten (N) av et visst tiltak for en pasient dersom pasienten *har* en gitt tilstand, og kostnaden (K) av feilaktig å utføre tiltaket dersom pasienten *ikke har* tilstanden. Nytte og kostnad må være på samme måleskala, for eksempel antall friske levedager. Data om nytte og kostnad er mangelvare, og man kunne tro at pasientens lege ikke hadde noe slikt grunnlag for å ta beslutning i de fleste tilfeller. Men det stemmer ikke med virkeligheten. Ofte kan vi klare oss med et anslag av *forholdet* mellom nytte og kostnad (N/K-ratio). Mange medisinske tiltak har en relativt høy N/K-ratio, for eksempel kirurgisk behandling av akutt appendicitt [1]. Antibiotikabehandling av sepsis har sikkert enda høyere N/K-ratio, kanskje 100 eller mer. Andre tiltak, som en medisinsk behandling med tvilsom effekt og mange bivirkninger, kan ha en N/K-ratio på 1 eller lavere. N/K-ratio under 1 betyr at feilaktig å behandle en pasient som ikke har en gitt tilstand er mer skadelig enn nettoeffekten er gunstig hvis pasienten likevel har tilstanden. Hvordan en bestemt lege tenker i et konkret tilfelle, er ikke godt å vite. Likevel - i de fleste tilfeller må en lege ha en følelse, basert på egne og andre sine erfaringer, om det aktuelle tiltaket er over eller under behandlingsterskelen, selv om legen ikke kan uttrykke behandlingsterskelen med et tall.

Det kan vises at [1,2]:
behandlingsterskel = 1 / (1 + N/K)

Funksjonen er grafisk framstilt i figur 1, som viser at behandlingsterskelen ligger under 0,1 (10 %) hvis N/K-ratio er over 9. Med andre ord, dersom N/K-ratio er større enn 9, trenger sannsynligheten for sykdom bare å være 10 % for at behandlingsterskelen oversti-

ges. Ved NK-ratio på 50 er behandlingsterskelen 1/51 x 100 % = 2 % og ved N/K-ratio på 100 er den 1/101 x 100 % = 1 %. Vi kan ha problemer med å forestille oss så lave sannsynligheter.

Det vi også trenger for å gjøre nytteanalysen, er en funksjon som viser sammenhengen mellom prøvesvaret og prøvesvarets sannsynlighetsratio [2]. I sin tur krever det kjennskap til fordeling av prøvesvar hos syke og ikke-syke. Det burde vi laboratoriespesialister ha, men også slike data mangler for de fleste analytter og diagnoser. Men hvis vi hadde data, kunne vi bruke for eksempel logistisk regresjon til å finne funksjonen for sannsynlighetsratio [3], som angir sannsynligheten for å få et gitt prøvesvar hos syke dividert med sannsynligheten for å få det samme prøvesvaret hos ikke-syke [2, 4]. For vel 30 år siden publiserte Guyatt og medarbeidere en funksjon for sannsynlighetsratio for diagnostikk av jernmangel gitt p-ferritin hos pasienter uten inflammasjon [5]:

$$\text{sannsynlighetsratio} = e^{[6{,}5429 - 1{,}6985 \ln(\text{p-ferritin})]}$$

Det vil vi bruke som eksempel. Med kjennskap til pretestsannsynlighet (pre) og sannsynlighetsratio (S) kan vi regne ut posttestsannsynlighet:

$$\text{posttestsannsynlighet} = S \times \text{pre} / (S \times \text{pre} + 1 - \text{pre})$$

Dermed kan vi regne ut optimal sannsynlighetsratio (Soptimal), som må være den sannsynlighetsratio som gir posttestsannsynlighet lik behandlingsterskelen:

$$\text{posttestsannsynlighet} = \text{behandlingsterskel}$$

eller

$$S_{optimal} \times \text{pre} / (S_{optimal} \times \text{pre} + 1 - \text{pre}) = 1 / (1 + N/K)$$

eller

$$S_{optimal} = [(1\text{-pre}) / \text{pre}] / (N/K)$$

Det prøvesvaret som tilsvarer $S_{optimal}$ er den grenseverdien vi søker, for prøvesvar som er mer patologiske enn det, bringer posttestsannsynlighet over behandlingsterskelen, og prøvesvar som er mindre patologiske gir posttestsannsynlighet under behandlingsterskelen [2]. Figur 2 viser noen mulige optimale beslutningsgrenser for p-ferritin i diagnostikk av jernmangel (y-aksen), gitt funksjonen for sannsynlighetsratio [5], pretestsannsynlighet og to ulike eksempler på N/K-ratio.

Vi ser nå at det ikke finnes én felles optimal beslutningsgrense for p-ferritin, fordi hver pasient har en personlig pretestsannsynlighet og en personlig N/K-ratio. En kvinne i 20-årsalderen har større pretestsannsynlighet for jernmangel enn en kvinne i 60-årsalderen. Til gjengjeld kan den eldre kvinnen ha en langt høyere N/K-ratio enn den yngre, fordi jernmangel i 60-årsalder kan være forårsaket av kreft, mens jernmangel i 20-årsalder mest sannsynlig er forårsaket av ukompensert jern-tap via menstruasjon og svangerskap. Tiltakene kan være anbefaling av peroralt jerntilskudd til den yngre og videre utredning av den eldre. I figur 2 er det vist eksempel på to mulige N/K-ratio, henholdsvis 5 og 25, som kanskje kan passe i de to tilfellene. Merk at jo høyere N/K-ratio er, og jo høyere pretestsannsynlighet er, desto høyere er optimal beslutningsgrense i eksemplet med ferritin. Ulike N/K-ratio kan også føre til samme beslutningsgrense hvis pretestsannsynlighet er ulik.

Huskeregel: Jo mer nyttig behandlingen (tiltaket) er i forhold til kostnaden (høyere N/K-ratio) og jo mer sannsynlig det er at pasienten har tilstanden og trenger behandling (høyere pretestsannsynlighet), desto større bør sannsynligheten være for at behandling blir utfallet. For p-ferritin, der lave verdier indikerer patologi, betyr det høyere beslutningsgrense. For andre analytter, der høye verdier indikerer patologi, betyr det lavere beslutningsgrense. I begge tilfeller betyr det høyere sensitivitet og lavere spesifisitet ved beslutningsgrensen.

Konklusjon: Persontilpasset diagnostikk krever persontilpassede beslutningsgrenser. Det er pasientens lege som må foreta slike vanskelige vurderinger. Laboratoriets rolle må være å skaffe data om sannsynlighetsratio for ulike prøvesvar. Det burde ikke være *så* vanskelig.

Oppgavefordeling

Pasientens lege

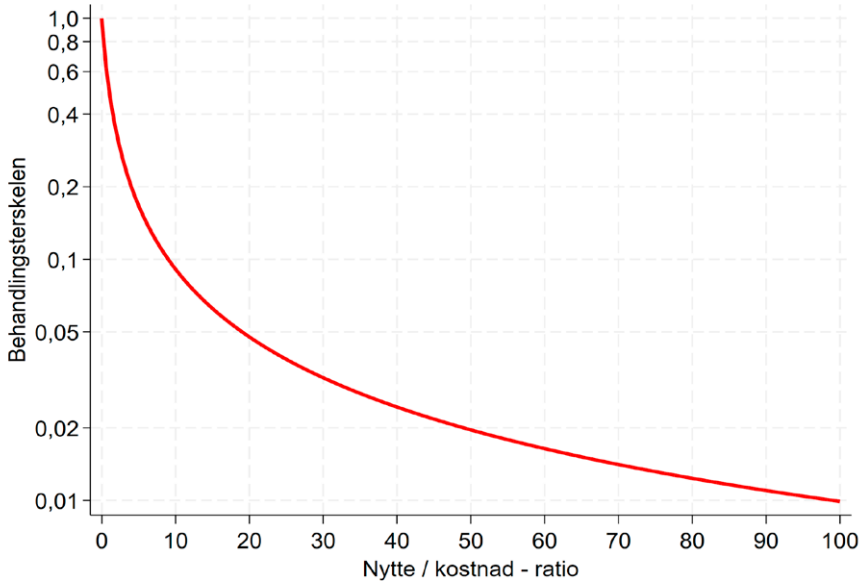
- Ta stilling til N/K-ratio for tiltaket
- Basert på N/K-ratio, vurdere hvor stor sannsynligheten må være for at tiltaket skal iverksettes (behandlingsterskelen)
- Vurdere om posttestsannsynlighet er større enn behandlingsterskelen

Laboratoriet

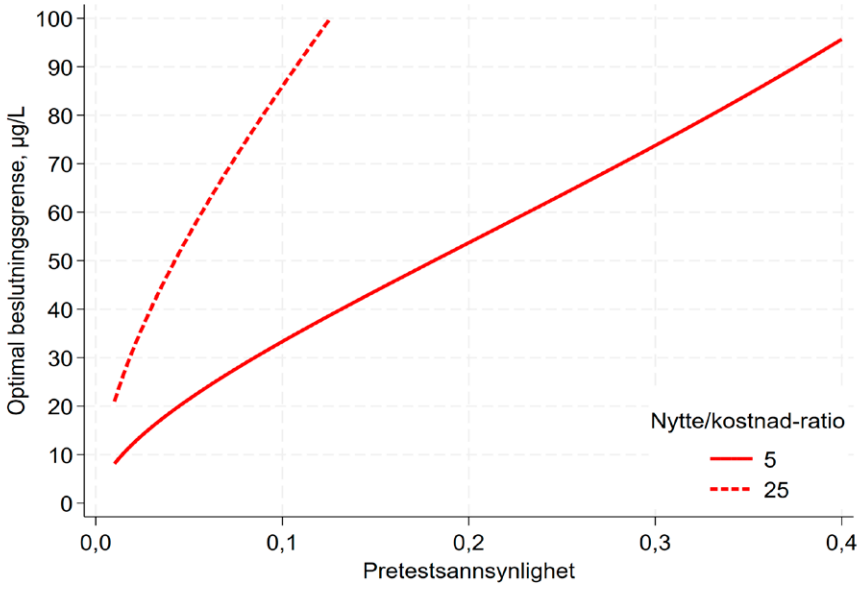
- Levere prøveresultatet
- Kunne angi prøvesvarets sannsynlighetsratio for en gitt tilstand i en viss klinisk situasjon

Litteratur

1. Pauker SG, Kassirer JP. Therapeutic decision making: a cost-benefit analysis. N Engl J Med 1975;293:229-34.
2. Åsberg A, Bolann BJ. Hva betyr prøvesvaret? Rasjonell tolking av svar på medisinske analyser. Oslo: Cappelen Damm, 2022: 31-72.
3. Albert A. On the use and computation of likelihood ratios in clinical chemistry. Clin Chem 1982;28:1113-9.
4. Grimes DA, Schulz KF. Refining clinical diagnosis with likelihood ratios. Lancet 2005;365:1500-5.
5. Guyatt GH, Oxman AD, Ali M, et al. Laboratory diagnosis of iron-deficiency anemia: an overview. J Gen Intern Med 1992;7:145-53. Erratum in: J Gen Intern Med 1992;7:423.



Figur 1. *Behandlingsterskel som funksjon av nytte/kostnad-ratio. Merk at y-aksen er logaritmisk.*



Figur 2. *Optimal beslutningsgrense for p-ferritin i diagnostikk av jernmangel, gitt pretestsannsynlighet og to verdier av nytte/kostnad-ratio.*

Lipoprotein(a) – en kort oversikt over målemetoder, indikasjoner og kliniske beslutningsgrenser

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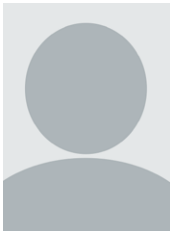


Hva er Lp(a) og hvordan bør det måles?

Lipoprotein(a), forkortet Lp(a) er et LDL-lignende lipoprotein først karakterisert av den norske legen og genetikeren Kåre Berg på begynnelsen av 60-tallet (1). Det har lenge vært kjent at Lp(a) er en risikofaktor for aterosklerotisk hjertesykdom, men det er først i nyere tid at det har kommet overbevisende evidens for at Lp(a) også har en kausal rolle (1-5). Lp(a) består av en kjerne av kolesterol, triglyserider og fosfolipider (figur 1). Kjernen er omringet av apolipoproteinene apo(a) og apoB, der førstnevnte kan foreligge i en rekke isoformer. Antall repetisjoner av det såkalte kringle-IV-2-domenet (KIV2) til apo(a) kan variere fra 1 til > 40 i antall, noe som medfører en betydelig variasjon av massen til Lp(a)-partiklene (2). Denne KIV2-polymorfismen i tillegg til andre genetiske apo(a)-variasjoner samt post-translasjonelle modifikasjoner vanskeliggjør målingen av Lp(a) (6).

Det er tilgjengelig flere kommersielle metoder (immunoassays) som kan benyttes på en rekke klinisk kjemisk instrument. Dette inkluderer metoder til Roche Cobas™, Siemens Atellica™/ Advia Chemistry™, Beckman Coulter AU™ og Abbott Alinity™ / Architect™ for å nevne et utvalg av vanlige brukte plattformer i Norden. Men det

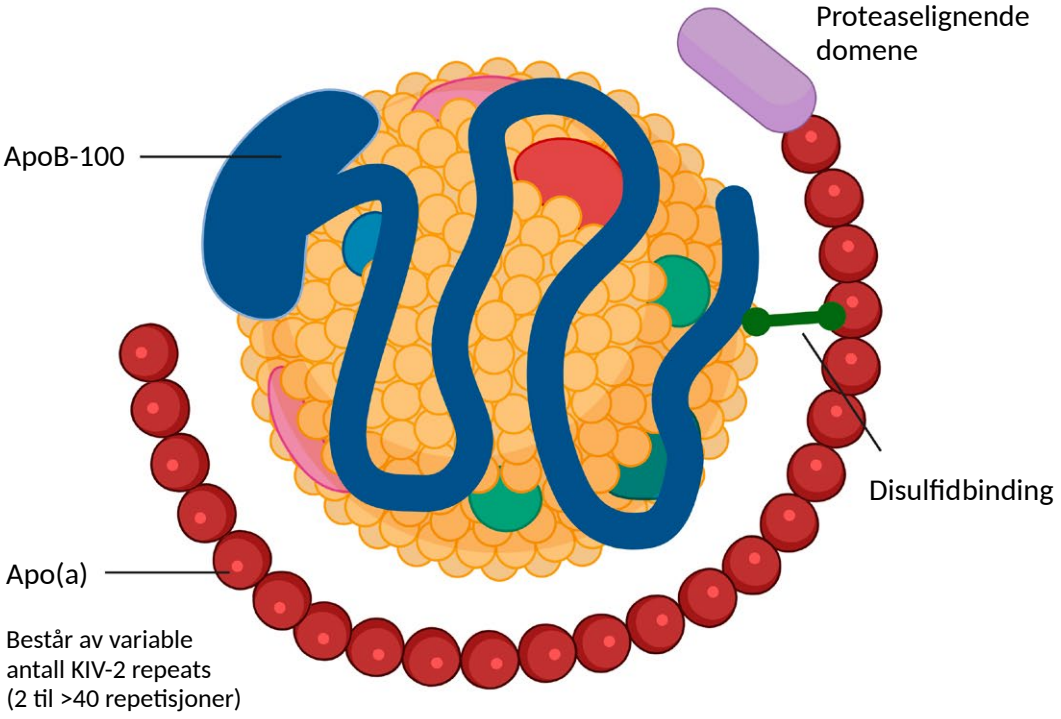
Solnedgang over Puddefjorden, Bergen. Foto: Erik Vinnes.

påpekes at det foreligger en betydelig variasjon i riktigheten (*trueness*) mellom metodene (6, 7). SRM2B referansematerialet for Lp(a) har vært i bruk siden 90-tallet, imidlertid har dette referansematerialet nylig blitt brukt opp (rundt ca. 2021 - 22) noe som har gitt IVD-produsentene ytterligere utfordringer (6, 8). Det er derfor særlig viktig at det utvikles et nytt referansemateriale og det er nedsatt en arbeidsgruppe i regi av IFCC som har som oppgave å etablere et nytt referansemateriale (https://ifcc.org/ifcc-scientific-division/sd-working-groups/wg-apo-ms/). Tilnærmingen er å fastsette dette ved bruk av massespektroskopi som vil medføre en rekke fordeler i arbeidet med å sikre den metrologiske sporbarheten til Lp(a) (6, 8). Arbeidet er pågående, men forventes ferdigstilt i løpet av 2024.

Når er undersøkelse for Lp(a) indisert?

Det har de siste årene kommet flere internasjonale retningslinjer for måling og tolkning av Lp(a) (oppsummert i tabell 1). Retningslinjene har gjennomgående lignende anbefalinger, men det foreligger noen variasjoner for foreslåtte indikasjoner og kliniske beslutningsgrenser. Norske nasjonal faglige retningslinjer for forebygging av hjerte- og karsykdom (faglig oppdatert i 2022) angir foreløpig sparsomme anbefalinger, men oppsummerer klokt ved å angi at: "*Måling av lipoprotein(a) kan gjøres hos pasienter med økt forekomst av hjerte- og karsykdom i familien, der indikasjonen for bruk av legemiddelbehandling er usikker*" (9).

Siden Lp(a) i stor grad er genetisk bestemt (10), anbefaler flere forfattere at «kaskade-screening» kan være en fornuftig tilnærming (2, 11). Kaskadescreening innebærer at førstegradsslektninger til individer som får påvist forhøyet nivå av Lp(a), også vurderes for måling av Lp(a). Av samme grunn er det sjeldent nødvendig å utføre repeterte målinger av Lp(a)



Figur 1. *Lipoprotein(a) består av en kjerne dekket av et apoB-apoprotein og et apo(a) bundet med en kovalent disulfidbinding. KIV-2 domenet til apo(a) foreligger i et variabelt antall fra 1 til >40 repetisjoner (1, 3). Lp(a) finnes derfor i en rekke isoformer med en molekylærvekt fra ≈ 250 til 800 kDa. Figuren er tegnet ved hjelp av biorender.com.*

	AHA / ACC 2018 (20)	The National Lipid Association (NLA) 2019 (11)	UK Heart 2019 (14)	Canadian Cardiovascular Society Guidelines 2021 (12)
Foreslått indikasjon(er) for Lp(a)	Ved familiær opphopning av prematur AHKS. Ved prematur AHKS hos pasienter ikke forklart av andre risikofaktorer.	1. Hos individer med førstegradsslektninger med prematur hjerte- og karsykdom 2. Hos individer med prematur hjerte- og karsykdom 3. Hos individer med alvorlig hyperkolesterolemi (LDL-kolesterol >190 mg/dL) eller mistenkt FH 4. Hos individer med betydelig forhøyet risiko for hjerte- og karsykdom (for å vurdere om det foreligger indikasjon for behandling med PCSK9-hemmere)	1. Ved personlig eller familiær historikk for prematur AHKS (< 60 års alder) 2. Ved førstegradslektninger med Lp(a) > 200 nmol/L 3. Hos individer med FH, andre genetiske dyslipidemier eller kalsifisert aortastenose 4. Hos pasienter med borderline økt (men < 15%) 10-års risiko for en kardiovaskulær hendelse	Screening en gang ila. voksen alder som ledd i et initialt lipidpanel.
Foreslåtte kliniske beslutningsgrenser	Lp(a) > 125 nmol/L eller 500 mg/L vurderes som en risikoforsterkende faktor	Lp (a) ≥ 100 nmol/L eller ≥ 500 mg/L	Foreslått risikostratifisering: Lav: 32 – 90 nmol/L Moderat: 90 – 200 nmol/L Høy: 200 – 400 nmol/L Veldig høy: > 400 nmol/L Hos pasienter med økte nivåer av Lp(a) (> 90 nmol/L) er det ønskelig med non-HDL kolesterol < 2.5 mmol/L	Lp(a) > 100 nmol/L eller 500 mg/L

Tabell 1. *Oppsummering av foreslåtte indikasjoner for måling av Lp(a) og kliniske beslutningsgrenser fra ledende internasjonale retningslinjer. AHKS: Aterosklerotisk hjerte-og karsykdom. FH: Familiær hyperkolesterolemi.*

hos samme pasient (2, 12). Distribusjonen av Lp(a) nivå varierer mellom forskjellige etnisiteter. Av den grunn foreslår noen forfattere en lavere klinisk beslutningsgrense for individer av afrikansk herkomst, men det er behov for ytterligere arbeid for å etablere etnisitetsspesifikke beslutningsgrenser (13, 14). Retningslinjene angir ingen kjønnsspesifikke kliniske beslutningsgrenser da forskjellen i nivået mellom menn og kvinner er forholdsvis liten (14). Avslutningsvis er det viktig å være klar over at Lp(a) oppfører seg som en akuttfasereaktant. I forbindelse med akutt myokardielt infarkt eller etter en større kirurgisk prosedyre kan man forvente opp til en dobling av Lp(a) nivået i plasma (15). Måling av Lp(a) bør derfor ikke utføres i en akuttfase (2).

Oppsummering

Lp(a) har de siste årene fått en mer sentral rolle i risikostratifisering av aterosklerotisk hjertesykdom, og ledende internasjonale retningslinjer anbefaler i økende grad måling av Lp(a) (tabell 1). Imidlertid foreligger det ikke en fullstendig enighet om

European Atherosclerosis Society 2022 (19)	Norske nasjonal faglige retningslinjer for forebygging av hjerte- og karsykdom 2022 (9)
Foreslått screening en gang ila. voksen alder, for å identifisere individer med arvelig svært forhøyet Lp(a) nivåer. Hos individer med familiær opphopning av prematur AHKS eller familiær historikk av forhøyet Lp(a).	Måling kan gjøres hos pasienter med økt forekomst av hjerte- og karsykdom i familien, der indikasjonen for bruk av legemiddelbehandling er usikker.
Foreslåtte beslutningsgrenser for å vurdere Lp(a) som tilleggsrisikofaktor for AHKS: Rule-out: 75 nmol/L eller < 300 mg/L Grå-sone: 75 – 125 nmol/L eller 300 – 500 mg/L Rule-in: 125 nmol/L eller ≥ 500 mg/L	Ikke angitt.

indikasjoner og kliniske beslutningsgrenser. Det finnes per i dag ingen effektiv Lp(a)-reduserende behandling, utover lipidaferese som er ressurskrevende og lite brukt (færre enn 5 pasienter får per skrivende stund behandling av høyt Lp(a) nivå med afarese i Norge). Behandlingen bør derfor stadig primært være rettet mot optimalisering av andre modifiserbare risikofaktorer som hypertensjon, diabetes, røyking og ugunstig HDL/LDL profil (3). Det pågår imidlertid fase 3-studier som undersøker effekten av selektive Lp(a) senkende medikamenter på kardiovaskulære hendelser (16) og resultater fra disse forventes i løpet av de neste årene.

Laboratorier bør tilby analysen på en metode som er sporbar til WHO/IFCC referansematerialet og som rapporterer prøvesvaret i molarkonsentrasjon (nmol/L) (1, 17), noe som er en gjennomgående anbefaling i litteraturen (1-4, 11, 12). For videre fordypning kan de nylige publiserte oversiktsartiklene til Svilaas et al. (18), Ruscica et al. (3) og Consensus statement fra European Atherosclerosis Society (EAS) særlig anbefales (19). For ytterligere drøfting omkring de målemessige utfordringene og det pågående arbeidet med å etablere et nytt referansemateriale anbefales artikkelen til Ruhaak et al. https://clinlabint.com/next-generation-apoa-standardization-why-when-and-how/ som leder arbeidsgruppen i regi av IFCC.

Referanser

1. Cegla J, France M, Marcovina SM, et al. Lp(a): When and how to measure it. Ann Clin Biochem. 2021;58(1):16-21.
2. Virani SS, Koschinsky ML, Maher L, et al. Global think tank on the clinical considerations and management of lipoprotein(a): The top questions and answers regarding what clinicians need to know. Prog Cardiovasc Dis. 2022.
3. Ruscica M, Sirtori CR, Corsini A, et al. Lipoprotein(a): Knowns, unknowns and uncertainties. Pharmacol Res. 2021;173:105812.
4. Reyes-Soffer G, Ginsberg HN, Berglund L, et al. Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association. Arteriosclerosis, Arterioscler Thromb Vasc Biol. 2022;42(1):e48-e60.
5. Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. J Lipid Res. 2016;57(11):1953-75.
6. Ruhaak LR, Cobbaert CM. Next-generation apo(a) standardization: why, when and how? Clin Lab Int 2023(3):6 - 8.
7. Labquality - Lipids and Lipoprotein. External Quality Assessment Scheme. Product no 2000, 2202. 2023.
8. Ruhaak L. Apolipoproteins by Mass Spectrometry (WG-APO MS) - Transitioning to a new RMS for apolipoproteins https://ifcc.org/

ifcc-scientific-division/sd-working-groups/wg-apo-ms/: The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC); 2023 [lest 27. sept 2023].
9. Helsedirektoratet. Nasjonal faglig retningslinje for forebygging av hjerte- og karsykdom. [lest 27. sept 2023]. 2022.
10. Boerwinkle E, Leffert CC, Lin J, et al. Apolipoprotein (a) gene accounts for greater than 90% of the variation in plasma lipoprotein (a) concentrations. J Clin Invest. 1992;90(1):52-60.
11. Wilson DP, Jacobson TA, Jones PH, et al. Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. J Clin Lipidol. 2019. 2019;13(3):374-92.
12. Pearson GJ, Thanassoulis G, Anderson TJ, et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. Can J Cardiol. 2021;37(8):1129-50.
13. Guan W, Cao J, Steffen BT, et al. Race is a key variable in assigning lipoprotein(a) cutoff values for coronary heart disease risk assessment: the Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol. 2015;35(4):996-1001.
14. Cegla J, Neely RDG, France M, et al. HEART UK consensus statement on Lipoprotein(a): A call to action. Atherosclerosis. 2019;291:62-70.
15. Maeda S, Abe A, Seishima M, et al. Transient changes of serum lipoprotein(a) as an acute phase protein. Atherosclerosis. 1989;78(2):145-50.
16. Langsted A, Nordestgaard BG. Antisense Oligonucleotides Targeting Lipoprotein(a). Curr Atheroscler Rep. 2019;21(8):30.
17. Tsimikas S, Fazio S, Ferdinand KC, et al. NHLBI Working Group Recommendations to Reduce Lipoprotein(a)-Mediated Risk of Cardiovascular Disease and Aortic Stenosis. J Am Coll Cardiol. 2018;71(2):177-92.
18. Svilaas T, Klemsdal TO, Bogsrud MP, et al. Høyt nivå av lipoprotein (a)–utredning og behandling. Tidsskr Nor Laegeforen. 2022.
19. Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement Eur Heart J. 2022;43(39):3925-46.
20. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1046-e81.

Fyren på Kynö (estn. Kihnu) i Estland. Foto: Henrik Alfthan.

Interessekonflikter

KR har mottatt honorar for foredrag fra Amgen (produsent av PCSK9-hemmeren evolokumab), Bayer, Novartis (produsent av antisense-oligonukleotidet pelacarsen) og Sanofi (produsent av PCSK9-hemmeren alirokumab). EWV og RR oppgir ingen interessekonflikter.

PhD thesis

Effect of thrombopoietin receptor agonists on coagulation and fibrinolysis in patients with immune thrombocytopenia

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Akershus University Hospital

Introduction

Primary immune thrombocytopenia (ITP) is an autoimmune bleeding disorder characterized by isolated thrombocytopenia (platelet count < $100{\cdot}10^9$/L) in the absence of underlying disease (1). ITP is caused by immune-mediated increased platelet destruction and impaired production (2). The pathophysiology involves both B cell and T cell abnormalities where the production of autoantibodies against platelets is central. Primary ITP has an incidence of approximately 2-6/100 000 adults per year (3, 4).

Despite being a condition with low platelets, ITP is a prothrombotic disorder (5). Thrombopoietin receptor agonists (TPO-RAs) are used to increase platelet count in patients who fail to achieve adequate response to steroids or other immunosuppressant, and act by binding to the thrombopoietin receptor c-MPL and stimulating megakaryocyte differentiation, proliferation and platelet production. There is a strong indication that TPO-RAs are associated with increased risk of thromboembolism where long-term treatment safety reports have shown thromboembolic event rates of 6% during a 2-year follow up (6, 7).

Thesis aims

The overall objectives were to investigate the presence of a procoagulant state in ITP patients and evaluate if TPO-RA-treatment leads to a more hypercoagulable state and thus greater thrombotic risk.

The specific aims were:

I. To study markers of coagulation activation, platelet activation and fibrinolysis, measure thrombin generation in ITP patients before the initiation and after TPO-RA-treatment to evaluate the short- and long-term effect of treatment on these markers.

II. To assess the procoagulant activity of microvesicles (MVs), both phosphatidylserine (PS)- and tissue factor (TF)-dependent procoagulant activity in the plasma of ITP patients, and study the capacity of isolated MVs and plasma to generate thrombin in a phospholipid-dependent manner before and after TPO-RA-treatment, and evaluate the effect of this treatment on the procoagulant activity of MVs.

III. To study markers of endothelial cell activation and neutrophil extracellular trap (NET) formation in ITP patients before and after TPO-RA-treatment to explore whether these mechanisms contribute to the procoagulant state in ITP and study the effect of TPO-RA-treatment on these markers.

Study design and study population

ITP patients who were planned to be treated with a TPO-RA were prospectively recruited in cohort 1 (n= 39). Blood samples were obtained before treatment initiation, and two, six and twelve weeks after treatment. ITP patients who had been on TPO-RA-treatment for more than one year were recruited in cohort 2 (n=18), and blood samples were obtained at inclusion. Hospital employees (n=35) without a history of ITP were recruited as controls.

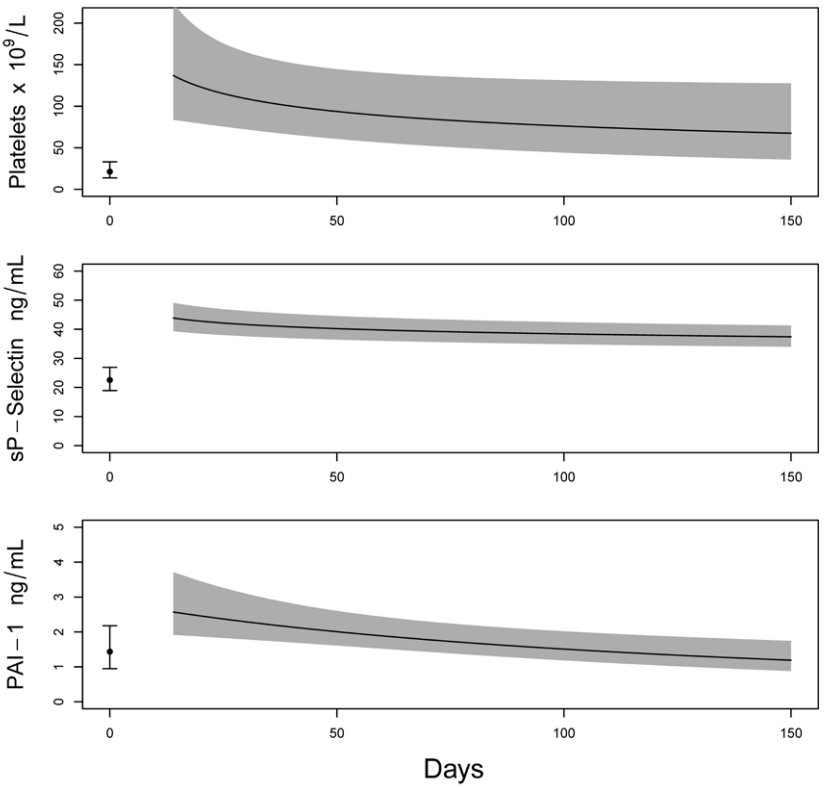

Figure 1: Effect of TPO-RA treatment and time on platelet count (upper panel); sP-selectin concentration (middle panel) and plasminogen activator inhibitor-1 (PAI-1) (lower panel). *0-time represents pre-treatment estimated mean values with 95% confidence interval. The black line represents the estimated mean value while the grey area represents the 95% confidence bands.*

Short summary and discussion of the main findings
Effect of Thrombopoietin Receptor Agonists on Markers of Coagulation and P-selectin in Patients with Immune Thrombocytopenia (8).

In this study, we showed that ITP patients had higher levels of prothrombin fragment 1+2 (F_{1+2}), D-dimer and plasminogen activator inhibitor-1 (PAI-1) activity than controls; and that TPO-RA-treatment was associated with an increase in soluble P-selectin (sP-selectin) and a further increase in PAI-1 activity (Figure 1). We also found that the expression of the P-selectin gene (SELP) was upregulated after treatment. No significant difference in the parameters of thrombin generation was found between ITP patients prior to the initiation TPO-RA-treatment compared with controls, nor did we find significant changes in thrombin generation parameters after the initiation of with TPO-RA-treatment.

Elevated levels of F1+2 and D-dimer before initiation of TPO-RA-treatment reflect the presence of coagulation activation and fibrinolysis. However, TPO-RA-treatment did not result in significant elevation of F1+2 or D-dimer. Higher PAI-1 activity in ITP patients before initiating TPO-RA-treatment and the further increase after TPO-RA-treatment reflects reduced fibrinolysis. Reduced fibrinolysis is a risk factor for both venous and arterial thrombosis. Furthermore, the increase in the levels of sP-selectin in ITP patients after initiating TPO-RA-treatment reflects increased platelet activation.

Both increased coagulation activation and impaired fibrinolysis before the initiation of TPO-RA-treatment support that the disease is prothrombotic, and the further impairment in fibrinolysis and increased platelet activation after the initiation of TPO-RA-treatment may contribute to a more hypercoagulable state and thus further increase in the thrombotic risk.

Increased Microvesicle-associated Thrombin Generation in Patients with Immune Thrombocytopenia after Initiation of Thrombopoietin Receptor Agonists (9).

We measured MV-associated TF activity and MV-associated PS activity in plasma before and after the

initiation of TPO-RA-treatment. In addition, we measured the capacity of MVs to generate thrombin by two approaches that differed from the assay performed in the study described above: the first by using isolated MVs from the plasma of ITP patients (MV-associated thrombin generation) and the second by using a reagent with no/only a minimal amount of phospholipid, which makes the measured generated thrombin in the plasma dependent on amount of phospholipid in the patient´s plasma (phospholipid-dependent thrombin generation in plasma).

We found no significant differences in the MV-associated PS activity/ TF activity or in the parameters of thrombin generation by the two methods between ITP patients before TPO-RA-treatment compared with controls. After TPO-RA-treatment, ITP patients had higher MV-associated PS activity and phospholipid-dependent thrombin generation in plasma (higher Peak and velocity index) than controls. MV-associated thrombin generation showed an increase in patients two weeks after the initiation of TPO-RA compared with pre-treatment levels as well as with the levels in controls.

This study showed that TPO-RA-treatment was associated with increased phospholipid-dependent procoagulant activity of MVs leading to more thrombin generation.

Markers of Endothelial Cell Activation and Neutrophil Extracellular Traps Are Elevated in Immune Thrombocytopenia but Are not Enhanced by Thrombopoietin Receptor Agonists (10).

We aimed to evaluate whether patients with ITP have increased endothelial cell activation and NET formation and to study the effect of TPO-RA-treatment on these potential contributors to the procoagulant state in ITP patients. We measured markers of endothelial cell activation (intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin and thrombomodulin; and markers of

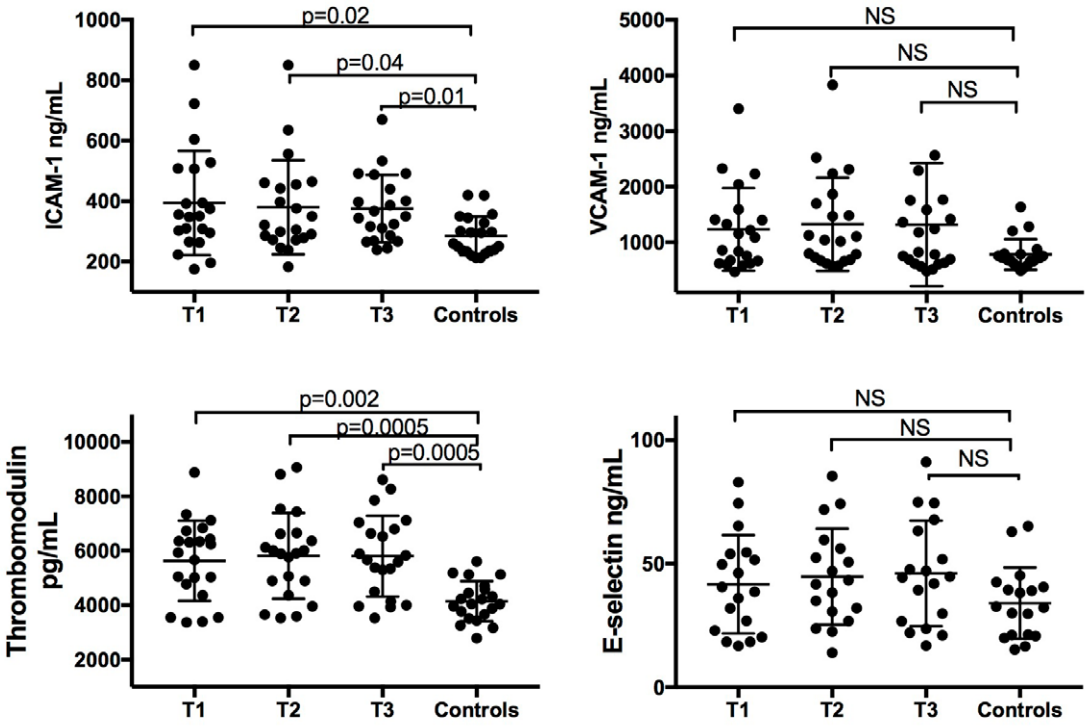

Figure 2: Markers of endothelial cell activation.
Measurements of ICAM-1, VCAM-1, thrombomodulin and E-selectin before (T1), two weeks (T2) and six weeks (T3) after initiation of TPO-RA treatment in ITP patients, and in controls. NS (not significant; $p \geq 0.05$).

NET formation (citrullinated histone 3-DNA (H3Cit-DNA) and cell free DNA) before the initiation and after TPO-RA-treatment.

We found that ITP patients, both before and after the initiation of TPO-RA treatment, had elevated levels of ICAM-1 and thrombomodulin compared with controls (Figure 2). In addition, ITP patients had elevated levels of H3Cit-DNA compared with controls. Treatment with TPO-RAs was not associated with an increase in those markers.

This study showed that endothelial cell activation and NET formation were increased in ITP patients before initiating TPO-RA-treatment compared with controls, suggesting that these two mechanisms may contribute to the increased thrombotic propensity in ITP patients. Treatment with TPO-RAs was not associated with significant changes in markers of endothelial cell activation or NET formation.

Conclusions

Overall, our studies show that ITP patients have increased coagulation activation and impaired fibrinolysis as well as increased endothelial cell activation and NET formation. The results of this thesis support the presence of a hypercoagulable state in ITP patients and demonstrate that the cause of this state is multifactorial, where platelets, endothelial cells, neutrophils and procoagulant MVs play important roles through different mechanisms and therefore lead to increased arterial and venous thrombosis (Figure 3). The work of this thesis also shows that treatment with TPO-RAs may potentiate this hypercoagulable state, as this treatment was associated with increased levels of sP-selectin, indicating increased platelet activation, and increased PAI-1 activity, leading to impaired fibrinolysis, as well as increased phospholipid-dependent procoagulant activity of the MVs.

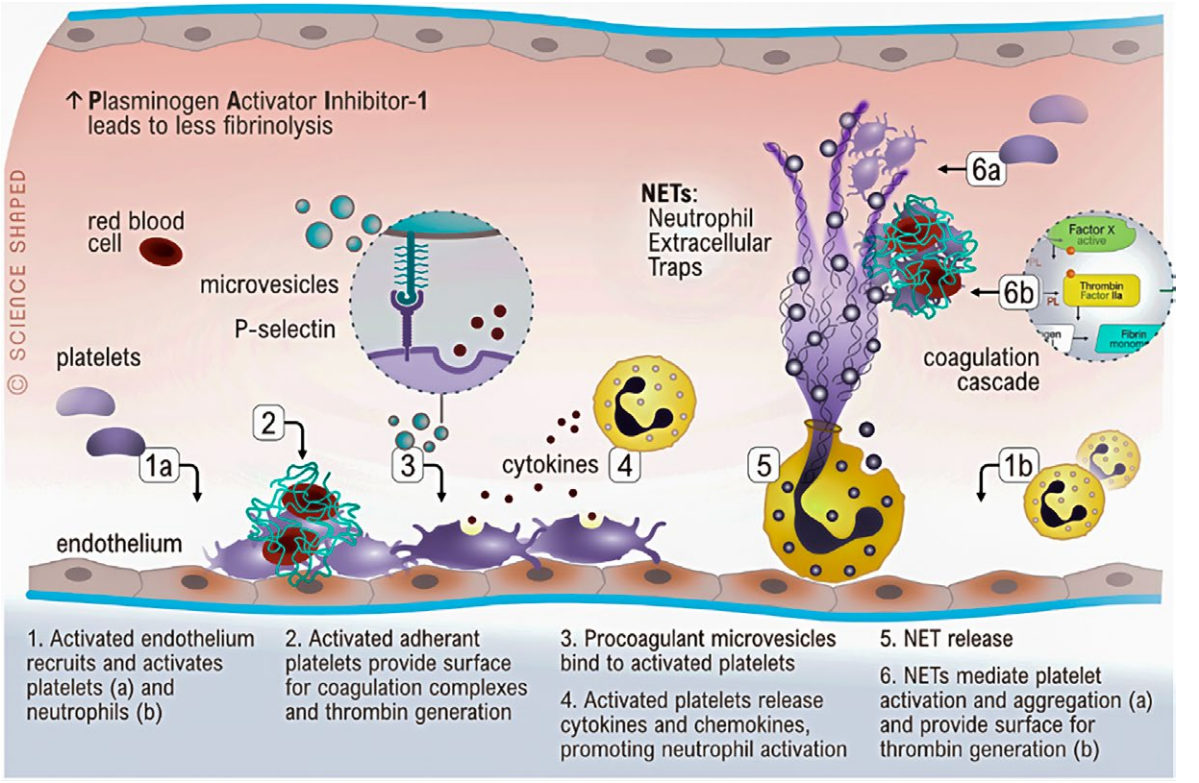

Figure 3: Potential mechanisms promoting thrombosis in ITP

Referances

1. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113:2386-93.
2. Ballem PJ, Segal GM, Stratton JR, et al. Mechanisms of thrombocytopenia in chronic autoimmune thrombocytopenic purpura. Evidence of both impaired platelet production and increased platelet clearance. J Clin Invest. 1987;80:33-40.
3. Terrell DR, Beebe LA, Vesely SK, et al.. The incidence of immune thrombocytopenic purpura in children and adults: A critical review of published reports. Am J Hematol. 2010;85:174-80.
4. Christiansen CF, Bahmanyar S, Ghanima W, et al. Chronic immune thrombocytopenia in Denmark, Sweden and Norway: The Nordic Country Patient Registry for Romiplostim. EClinicalMedicine. 2019;14:80-7.
5. Langeberg WJ, Schoonen WM, Eisen M, et al. Thromboembolism in patients with immune thrombocytopenia (ITP): a meta-analysis of observational studies. Int J Hematol. 2016;103:655-64.
6. Kuter DJ, Bussel JB, Newland A, et al. Long-term treatment with romiplostim in patients with chronic immune thrombocytopenia: safety and efficacy. Br J Haematol. 2013;161:411-23.
7. Wong RSM, Saleh MN, Khelif A, et al. Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND study. Blood. 2017;130:2527-36.
8. Garabet L, Ghanima W, Monceyron Jonassen C, et al. Effect of thombopoietin receptor agonists on markers of coagulation and P-selectin in patients with immune thrombocytopenia. Platelets. 2019;30:206-12.
9. Garabet L, Ghanima W, Hellum M, et al. Increased microvesicle-associated thrombin generation in patients with immune thrombocytopenia after initiation of thrombopoietin receptor agonists, Platelets 2020;31:322-8.
10. Garabet L, Henriksson CE, Lozano ML, et al. Markers of endothelial cell activation and neutrophil extracellular traps are elevated in immune thrombocytopenia but are not enhanced by thrombopoietin receptor agonists. Thromb Res. 2020;185:119-24.

Martorn (Eryngium maritimum). Foto: Henrik Alfthan.

Svenska Folkhälsomyndighetens undersökning av förekomsten av anti-covid-19 antikroppar

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Sedan början av pandemin har Folkhälsomyndigheten i Sverige som en del i den nationella övervakningen av covid-19 genomfört undersökningar av antikroppsförekomsten mot SARS-CoV-2, viruset som orsakar covid-19. I undersökningarna skattar man hur stor andel av befolkningen som har antikroppar mot viruset. Antikropparna bildas normalt inom två veckor efter infektion och kan mätas genom laboratorieanalys av blodprov. De vacciner mot covid-19 som används i Sverige är baserade på ytproteinet hos SARS-CoV-2, och de antikroppar som bildas efter vaccination är riktade mot detta protein.

Antikropparna fungerar som en markör för genomgången infektion eller vaccination. De utgör också en del i det immunsvar som skyddar mot allvarlig sjukdom. Resultaten av undersökningarna har använts som underlag för modelleringar av scenarier för smittspridning och som stöd för beslut om smittskyddsåtgärder, t ex rekommendationer för vaccination.

Den 11-25 september 2023 gjordes den senaste undersökningen. Totalt 1964 överblivna och avidentifierade blodprover från öppenvården samlades in i åtta regioner/landsting och förekomsten av antikroppar mot SARS-CoV-2 undersöktes.

Totalt hade 96,7% av de testade individerna antikroppar mot SARS-CoV-2. Antikroppsförekomsten

Kön	Analyserade prover	Seroprevalens (procent)	95 procent KI
Totalt	1 964	96,7	(95,1-97,9)
Kvinnor	1 089	97,0	(95,2-98,5)
Män	875	96,4	(94,2-98,2)

Tabell 1. *Andelen provgivare 0-95 år (födda 1928-2023) i öppenvården i åtta regioner under perioden 11-25 september 2023 med påvisade antikroppar mot SARS-CoV-2, fördelat på kön.*

Ålder (a)	Antal analyserade prover	Seroprevalens (%)	95 procent KI
0-13 år	786	89,6	(87,1-91,9)
14-18 år	229	100,0	(97,8-100,0)
19-49 år	201	97,2	(93,3-99,7)
50-64 år	213	98,4	(94,9-100,0)
65-79 år	355	97,8	(95,1-99,6)
80-95 år	180	98,2	(94,0-100,0)

Tabell 2. *Andelen provgivare 0-95 år (födda 1928-2023) i öppenvården i åtta regioner under perioden 11-25 september 2023 med påvisade antikroppar mot SARS-CoV-2, fördelat på åldersgrupper.*

var hög hos ungdomar och vuxna (14-95 år), från 97,2 procent (19-49 år) till 100 procent (14-18 år). Dessa åldersgrupper har rekommenderats vaccination mot SARS-CoV-2.

Även hos barn 0-13 år, där mycket få har vaccinerats, var antikroppsförekomsten hög, 89,6 procent.

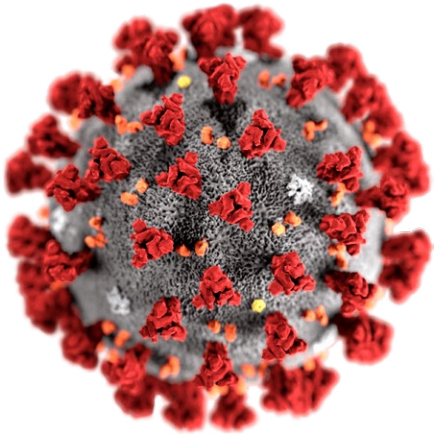
I alla åtta deltagande regioner var den totala antikroppsförekomsten hög, mellan 90,7 procent och 98,2 procent.

Sammantaget visar resultaten i denna undersökning att en hög andel av befolkningen i alla åldersgrupper och i alla de åtta undersökta regionerna i september 2023 hade antikroppar mot SARS-CoV-2. Dessa antikroppar, som uppkommit genom infektion och/eller vaccination, är i många fall kopplade till skydd mot allvarlig covid-19. Det är inte känt hur varaktigt detta skydd är och det är viktigt att fortsatt följa rekommendationerna för vaccination.

Laboratorieanalys

Proverna analyserades vid Folkhälsomyndighetens laboratorium i Solna för antikroppar mot SARS-CoV-2 ytprotein (spike). Analyserna utfördes med V-PLEX SARS-CoV-2 Panel 2 (IgG) Kit (Meso Scale Discovery, USA) enligt tillverkarens instruktion.

Källa: https://www.folkhalsomyndigheten.se/publikationer-och-material/publikationsarkiv/f/forekomsten-av-antikroppar-mot-sars-cov-2-i-sverige-11-25-september-2023/



SARS-CoV-2 virus. This illustration, created at the Centers for Disease Control and Prevention (CDC), part of the United States Department of Health and Human Services, reveals ultrastructural morphology exhibited by coronaviruses. By CDC/ Alissa Eckert, MS; Dan Higgins, MAM/ Public domain.

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2. Fiechtner M, Ramp J, England B, et al. Affinity binding assay of glycohemoglobin by two-dimensional centrifugation referenced to hemoglobin Alc. Clin Chem 1992;38:2372–9.

Abstrakt:

3. Hortin GL, King C, Kopp J. Quantification of rhesus monkey albumin with assays for human microalbumin [Abstract]. Clin Chem 2000;46:A140-1.

Bok kapitler:

4. Rifai N, Warnick GR. Lipids, lipoproteins, apolipoproteins, and other cardiovascular risk factors. In: Burtis CA, Ashwood ER, Bruns DE, eds. Tietz textbook of clinical chemistry and molecular diagnostics. 4th Ed. St. Louis: Elsevier Saunders 2006:903-81.

PhD teser:

5. Haughton MA. Immunonephelometric measurement of vitamin D binding protein [MAppSci thesis]. Sydney, Australia: University of Technology, 1989:87pp.

On-line publisert artikkel som ennå ikke er trykt:

6. Milbury CA, Li J, Makrigiorgos GM. PCR-based methods for the enrichment of minority alleles and mutations. [Epub ahead of print] Clin Chem February 6, 2009 as doi:10.1373/clinchem.2008.113035.

Supplement:

7. Castelli WP. Lipids, risk factors and ischaemic heart disease. Atherosclerosis 1996;124 Suppl:S1-9.

Internett kilde:

8. American Association for Clinical Chemistry. AACC continuing education. https://www.aacc.org/education-and-career/continuing-education (Tilgjengelig april 2020).

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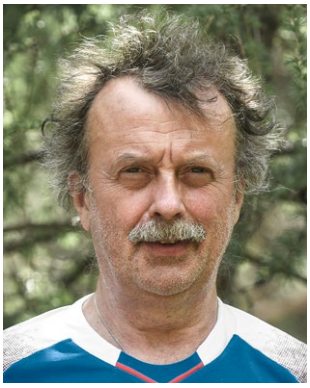

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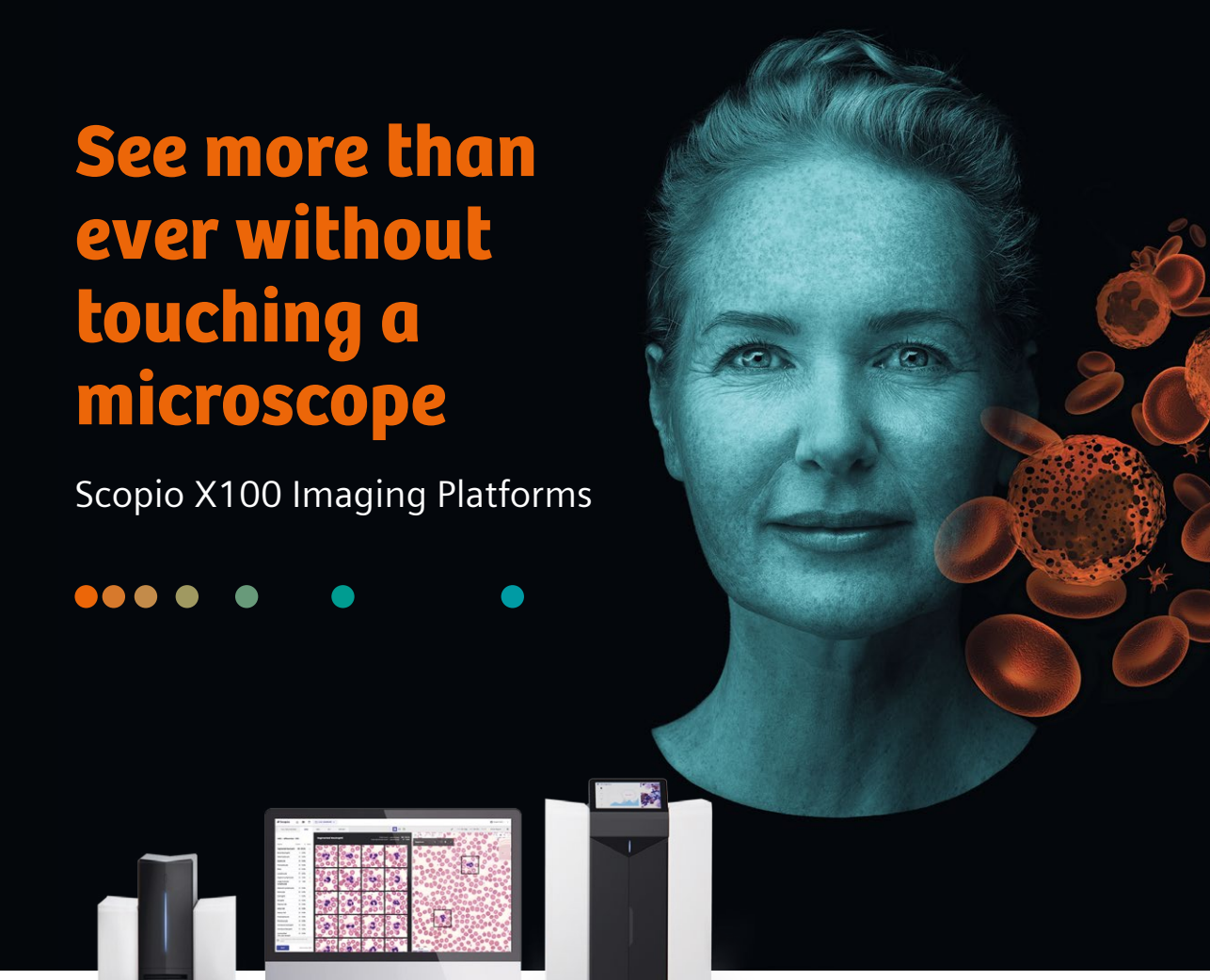

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