Analytical challenges and opportunities of oral fluid
By JW C. Alffenaar

Drug-induced Liver Injury in Haemochromatosis
by M. Neuman

Personalized natalizumab treatment
by Z. van Kempen and J. Killestein

What is new about the exposome?
By N. Venisse

The use of pharmacometric models for COVID-19 treatment
by M. Ahsman, I. Minichmayr and B. de Winter

Who is looking?
Renewed IATDMCT Website!!
by O. Noceti and A. Verstraete

Update on 2020 Congress
We've Gone Virtual!
Dear members,

I hope you are continuing to stay safe and healthy during this challenging time. You may know the very sad news that Professor Roger Jelliffe passed away peacefully on 22 June 2020. Roger was a great pioneer and educator on individualized medicine and pharmacometrics, which are the heart of the IATDMCT. Many members were inspired by his articles, books and lectures. He was also a highly knowledgeable debater and stimulated the discussion at every IATDMCT Congress he attended. The Brisbane Congress was the last time I met him. Indeed, this is a great loss for our community. We wanted to learn more from him. It was so painful to lose two important colleagues of our community during this summer, Roger and Dr. Erik van Maarseveen. It is a difficult time for us, but we will never forget them. Another difficulty is that we are not able to meet in person at the coming Congress at Banff. However, the Congress co-chairs, Drs. David Kinniburgh and Penny Colbourne are working very hard and offering a wonderful virtual opportunity for us. They will be providing a Virtual 2020 Congress via webinar. The scientific sessions will be broadcast live during September 14–16, with plenary lectures and concurrent TDM and Clinical Toxicology streams for 3 hours each day. The virtual Congress is the first experience in our history, and I believe this will be exciting and successful by creating additional values and advantages. I hope to meet you there at the Virtual 2020 Banff Congress. Finally, I take this opportunity to sincerely thank all medical and laboratory professionals for their devoted efforts to contribute to medical service and public health. As I said before, please use your knowledge, skills and accumulated experiences in these difficult times. IATDMCT continues to support members. We may be separated by geography, but we are united by science.

Yusuke Tanigawara, Ph.D.
IATDMCT President

---

**IN THIS ISSUE**

- Message from the President .......................................................... 2
- The use of pharmacometric models for COVID-19 treatment ......................................................... 3
- Increasing global access to therapeutic drug monitoring - Analytical challenges and opportunities of oral fluid .................................... 5
- What is new about the exposome? .............................................. 6
- Clinical Toxicology Assessment in a Drug-induced Liver Injury in Haemochromatosis ..................................................... 7
- Personalized natalizumab treatment in multiple sclerosis .... 8
- Renewed IATDMCT website .......................................................... 10
- Member-Get-a-Member Campaign 2020 ........................................ 15
- Update on 2020 Congress - We’ve gone Virtual! ..................... 15
- Remembering Roger Jelliffe, MD .................................................. 16

---

**IATDMCT COMPASS**

The Compass is published quarterly by the International Association of Therapeutic Drug Monitoring & Clinical Toxicology and distributed to the members by the Association. Letters to the Editor must be signed and should not exceed 200 words in length.

Chairs of Committees are requested to submit announcements and reports of activities.

All IATDMCT members are encouraged to send contributions to the editorial team of COMPASS about professional achievements, new books in relation to the aims of the society, or workshops and symposiums related to TDMCT and held under the auspices of the IATDMCT.

**Deadlines for submission:**

- 1st quarter issue February 7
- 2nd quarter issue May 7
- 3rd quarter issue August 7
- 4th quarter issue November 7

Views and reports appearing in Compass do not necessarily have the endorsement of the Association. Address general communications to the Editor care of the IATDMCT Head Office.

**Editor in Chief:**  Natalia Riva  
nataliarivahg@gmail.com

**Associate Editor:**  Louise Andrews  
LM.andrews@meandermc.nl

**Publication Office:** IATDMCT  
4 Cataraqui St., Suite 310, Kingston ON Canada K7K 1Z7  
Tel: 613-531-8166 / Fax: 1-866-303-0626 / office@iatdmct.org

---

**YUSUKE TANIGAWARA**  
**IATDMCT PRESIDENT**
The use of pharmacometric models for COVID-19 treatment

By Maurice Ahsman, Iris Minichmayr and Brenda de Winter, on behalf of the Pharmacometrics Committee

Over the past few months, increasing experience has been gained regarding the treatment of patients with the Coronavirus disease of 2019 (COVID-19), including pharmacological intervention to either attempt to reduce viral load, or provide supportive care to the patients. Given the urgency of the pandemic and the lack of approved therapies and vaccines, various drugs well-established for other diseases, as well as novel compounds in preclinical and clinical stages of development, have been repurposed for the treatment of COVID-19 (1). In light of the novelty of COVID-19 and therefore the lack of dosing information based on this particular disease and patient population, existing pharmacometric models based on earlier clinical application have been and are being used to enhance the understanding of the time course of drug exposure (pharmacokinetics, PK) and its relationship with drug effects (pharmacodynamics, PD), and to draw inferences about favorable and adverse drug responses in COVID-19 patients. Different pharmacometric model sources have been integrated based on prior knowledge, with the ultimate goal to pivotally aid in designing new clinical studies as well as to shed light on dosing decisions in clinical practice. For example, historic in vitro efficacy data, models on preclinical viral dynamics and clinical pharmacokinetics as well as toxicity data have been united to enhance the understanding of efficacious and safe dosing regimens (2). The power to combine and simultaneously analyze data of different sources (e.g. study sites, biological measurement matrices), even if only sparse, constitutes one of the major strengths of pharmacometric models.

However, the approach also entails some risks. Recently, Venisse et al. (on behalf of the French Society of Pharmacology and Therapeutics, SFPT, Therapeutic Drug Monitoring and Treatment Personalization group) have provided a very useful overview of PK and PD information in literature, specific to COVID-19 treatment(3). They identified sizeable knowledge gaps, but also highlighted ways in which attempts to overcome these gaps, including pharmacometric models and PK/PD information from non-COVID-19 sources, could lead to over- or underdosing. Venisse et al. conclude that ‘available PK and PK-PD studies suffer from severe limitations leading to unreliable conclusions’ regarding the applicability and dose selection of repurposed drugs for the treatment of COVID-19. We concur, and would emphasize that this seems in large part to be the result of an incomplete understanding of critical differences in disease, drug, patient and pharmacometric model characteristics between COVID-19 and the source data and assumptions upon which the earlier pharmacological knowledge had been gained. We would like to bring the paper by Venisse et al. to the attention of the IATDMCT membership, and highlight some issues that require particular consideration due to some common characteristics of COVID-19 patients.

Based on experience treating COVID-19 so far, various (patho) physiological disturbances and further factors pose an obstacle to optimal dosing and risks of complications. These include but are not restricted to obesity, cardiovascular complications (e.g. embolisms), mechanical ventilation and other organ support (e.g. dialysis) or co-medication, including high sedative use(4). Pharmacometrics can help to quantify the impact of patient or viral characteristics on PK and PD, to which extent they can explain variability and their consequences on dosing. We would like to highlight three examples that require particular consideration in COVID-19 patients:

**Obesity**

Obesity (body mass index BMI >30 kg/m2) seems to form a risk factor for increased COVID-19 disease severity and an increased risk of hospital/ICU admission, but also affects PK and PD in a variety of ways(5, 6). Obesity is known to affect the PK of various drugs, resulting from e.g. increased peripheral distribution volumes, altered absorption profiles and/or a change in relative blood flow to different tissues. Treatment of common comorbidities (e.g. diabetes, heart conditions) could also provide more opportunities for drug-drug interactions that could require dose adjustments. The impact of different body weight-related parameters on pharmacokinetics (body weight, BMI, fat-free mass, lean body weight) can be evaluated using model-based covariate analyses, provided there is drug concentration data over a range of body weights and varying degrees of obesity. However, one should be cautious when applying pharmacological information and PK/PD models from non-obese populations.

**Critical illness/ventilation and other organ support**

Treatment of severe cases of COVID-19 includes mechanical respiratory, cardiovascular and/or organ support, via e.g. mechanical ventilation, dialysis or extracorporeal membrane oxygenation (ECMO). These techniques are known to affect PK in various ways including loss of drugs due to adsorption to polymer tubing, an increased distribution volume due to a higher circulating volume or increased capillary permeability, and a change in haemodynamics and organ perfusion resulting in altered clearance. Critical illness in itself is also known to affect PK and PD of many drugs (7). A complicating factor when trying to apply existing PK/PD models for repurposed drugs is the fact that the occurrence and size of any PK changes are dependent on many different characteristics, including the ADME properties and physicochemical properties of the drug (extraction ratio, lipophilicity, protein binding, renal excretion and reabsorption routes), design and settings of the organ support apparatus, and the condition of the patient (including differences in physical condition at steady state versus initial phase of treatment)(8).

This implies that application of existing PK/PD models in the absence of COVID-19 specific data, even when those data were collected in critically ill non-COVID-19 patients, could at most be considered a starting point; careful and cautious dose titration and intensive monitoring (including TDM where useful) may be unavoidable.
Comedication

COVID-19 treatment in severely-affected patients generally includes large sedative doses and a high volume of electrolyte support. These may affect drug clearance (via induction or inhibition of hepatic enzymes, renal transport mechanisms or other types of drug-drug interaction) and the volume of distribution(9). There are physiology-based PK models that may be used to predict some of these interactions for drugs that have not yet been extensively studied(10, 11), but an assessment of the exact effect size and impact of the specific comedication used in individual COVID-19 patients requires dedicated studies. Note that many published pharmacometric models based on post-registration data were not based on data that allow an extensive assessment of potential comedication effects, which could affect applicability to a ‘new’ population.

Venisse et al. stressed the importance of using an adequate model for the target patient population and the clinical situation for which a conclusion shall be drawn. The relevance of this issue has also been demonstrated for the field of therapeutic drug monitoring when performing model-based precision dosing (12). Whereas at the beginning of the COVID-19 pandemic, imperfect pharmacometric models were necessary to get an idea of potential dosing regimens and to generate new hypotheses for unexpected drug behavior, as newly gathered data and clinical studies become available models can be refined. The benefits of pharmacometrics - including the ability to use sparsely sampled data, to assess typical patterns as well as between-subject, between-site and between-occasion variability, to predict PK and PD for different dose regimens and administration routes, to design efficient sampling regimens for new clinical trials, to concomitantly analyze different drugs, metabolites and endpoints, to gain insight into underlying physiological processes via hypothesis testing in mechanism-based models, to include BLQ (Below the Limit of Quantitation) and otherwise censored data, and to evaluate covariate effects - should be taken advantage of while keeping an eye out for unjustified assumptions, applications and extrapolations.

REFERENCES


Erratum

Compass issue II: “The potential of the IATDMCT Scientific Committees”, by Professor Stein Bergan. Dept. of Pharmacology, Oslo University Hospital & Dept of Pharmacy, University of Oslo, Norway. On behalf of the Immunosuppressive Drugs Committee (ISDC).

In last Compass issue from June 2020, Prof. Stein Bergan described that the ISDC has around 40 members. Until now, they all communicate via emails with the ‘reply-to-all’ type, which is not very effective. This sentence was omitted in last Compass Issue:

"Myself I have announced the (not very original) idea to use the Forum already available via the IATDMCT website. Some limitations appeared for this alternative, but hopefully these may be resolved in the near future so that we can take advantage of the obvious benefits from this communication form rather than the ‘reply-to-all’ emails."
Increasing global access to therapeutic drug monitoring - Analytical challenges and opportunities of oral fluid

By Jan-Willem C Alffenaar, Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, the Netherlands, on behalf of the Alternative Sampling Committee

Although we aim to provide optimal care, some patients are not responding to treatment as expected. Pharmacokinetic variability can explain why patients with low drug concentrations do not respond to treatment or why patients with a high drug concentration suffer from adverse drug reactions. Drug concentration guided dose adjustments to optimize treatment, therapeutic drug monitoring (TDM), can have a significant impact on treatment outcome depending on the individual drug and disease. In antimicrobial therapy low drug concentrations are directly linked to poor treatment response and acquired drug resistance.

In order to facilitate TDM, easy to use immunoassays have been developed for commonly used drugs in hospital setting like aminoglycosides and vancomycin. For other antimicrobial drugs laboratories use high performance liquid chromatography-UV/Vis or liquid chromatography coupled to mass spectrometry (LC-MS/MS). In most situations plasma or serum is the preferred matrix.

Although access to TDM for antimicrobial treatment is improving, it has mainly been restricted to well resourced settings. Lack of funding to buy equipment, absence of highly skilled laboratory scientist to develop and validate assays according to accepted guidelines for bioanalytical method validation, logistical hurdles related to sample transportation and no secure communication of results from the lab to the physician are only a few of the problems in low resourced settings resulting in the fact that patients have no access to TDM.

Affordable point-of-care tests would be ideal to increase access to TDM. Unfortunately, point-of-care tests indicating the presence or absence of a drug, like for drugs of abuse, are not very helpful for optimization of drug dosing. A semi-quantitative scale with subtherapeutic, therapeutic and toxic could be a significant improvement in supporting TDM based clinical decision making TDM.

For an easy to use point-of-care test, a traditional matrix like plasma or serum may not be ideal as it is an invasive procedure requiring well trained staff and sterile materials. In low resourced settings this is another hurdle for implementation of TDM. Oral fluid may be a suitable alternative to plasma and serum. Additional advantage is that it will likely reduce the burden on children and their parents when it can replace traditional blood collection. Oral fluid collection is well accepted by patients and cheaper.

Although saliva may seem ideal there are some limitations and challenges. The physicochemical properties of the drug will determine whether the drug can be found in saliva or not. The drug plasma protein binding, pKa, lipid solubility and molecular mass will determine the oral fluid/plasma ratio. The oral fluid concentration reflects the free drug plasma concentration. Highly protein bound drugs with a subsequent low oral fluid concentration will therefore require a very sensitive assay like LC-MS/MS and will likely be below the lower limit of quantitation of a point-of-care test. Stimulated or passively collected oral fluid may also impact the drug concentration in oral fluid.

As LC-MS/MS is not suitable for point-of-care testing and the commercial interest for developing a point-of-care test for TDM is low, we explored which alternatives were available that could potentially meet the requirements. The currently commercially available microvolume portable UV/Vis spectrophotometers of interest as most drugs can be detected using their unique UV-spectrum. Being a clear liquid, oral fluid can be used for the measurement of the drug concentration using the Lambert-Beer law. Sample preparation of a point-of-care test should be easy. Ideally, a drop of saliva applied on the sensor or cuvette will do the job. With other in house developed assays chromatography would help to separate the compound of interest from other drugs or endogenous compounds in the sample. This would however disqualify its use as a point-of-care test. Direct sample application or an easy sample preparation should be considered. Most important challenge would be to resolve interference with other drugs or endogenous compounds present in oral fluid.

Dr. Hannah Yejin Kim – post doctoral researcher, University of Sydney: “Achieving optimal exposure to voriconazole during treatment of invasive fungal infections is crucial, as sub-therapeutic voriconazole concentrations can cause treatment failure whereas supra-therapeutic concentrations can cause toxicity. Our recent systematic review demonstrates that about 60% of voriconazole in plasma penetrates saliva, and that there is a good correlation between saliva and plasma voriconazole concentrations. Saliva-based voriconazole TDM will be highly beneficial for children as it is non-invasive, and a point-of-care assay will allow prompt dose adjustments and TDM in ambulatory settings.”

Evelien Ruiter – research student, University of Sydney: “At the University of Sydney, we have explored quantifying linezolid in oral fluid by using a mobile UV/Vis spectrophotometer. Because this method does not use chromatography, the main challenge when developing an assay is the separation of the drug of interest with the interfering exogenous and endogenous compounds in saliva, such as amylase. Therefore, exploring the most suitable sample preparation and method for data-analysis are crucial when using the nanophotometer, while keeping in mind the simplicity of a point-of-care test.”

Prof. Dr. Daan Touw – Head of laboratory, University Medical Center Groningen, The Netherlands: “In the Netherlands we have for example developed methods to measure linezolid and rifampicin in oral fluid after a simple filtration step of the sample. To make the method useful for field work and perhaps also for a quick test in outpatient clinics, we redesign the methods to be suitable for nanophotometer detection. At this moment we are testing whether anti-HIV drugs can be tested this way for easy monitoring of drug adherence.”
Dr. Stellah Mpagama – Kibong’oto Infectious Diseases Hospital, Tanzania: “In Tanzania, we have learnt that at least half of our either drug susceptible or multidrug resistant tuberculosis (TB) patients receive sub-optimal serum exposure of one of the key anti-TB medicines making them at risk of acquiring clinically significant drug resistance TB. There is a clear need of administering TDM in a sub-set of TB patients with obvious risks like those with co-morbidities for instance diabetes, and HIV. Also, we have adapted new and repurposed drugs and we observe adverse drug reactions that perhaps management would be guided by TDM. Simplifying the algorithms for TDM including the use of oral fluid (saliva or urine) as an alternate specimen will support field adoption and implementation of TDM where majority of our patients are attended. This will have a considerable contribution in making the END-TB strategy real in high burden settings like Tanzania.”

Erwin Jongedijk – research analyst, University Medical Center Groningen, The Netherlands: “The power of UV/Vis spectrophotometry is the broad range of substances that can be detected. This does make it necessary to focus on selectivity and specificity during method development and validation. In Groningen we developed a method for the quantitation of levofloxacin in saliva, using a mobile microvolume-UVVIS spectrophotometer and derivative spectroscopy. Through extensive validation we have proven that we were able to quantitate levofloxacin, without a clinically significant impact of interferents. The accuracy and precision of laboratory-based LC-MS/MS methods need to comply with FDA/EMA guidelines. With our point-of-care method we were able to comply with the same guidelines.”

Margaritha Sariko - Kibong’oto Infectious Diseases Hospital, Kilimanjaro Clinical Research Institute, Tanzania: “The experience of using saliva and nanophotometer for drug level testing in Tanzania has brought a wide new experience. The use of nanophotometer has increased the knowledge and achieve the goal of levofloxacin testing in the field. This whole new technique improved the clinical knowledge on patient management and also simplifying the drug level testing experience.”

Prof. Dr. Scott Heysell – Infectious diseases physician, University of Virginia, USA: “Personalized dosing of medications, particularly those given for weeks or more, is reflective of broader public health goals to deliver person-centered care to as many people as possible and overcome health inequities driven by access to timely specialized services. Optimization of assays that utilize urine, saliva, or other matrices that do not involve preservation of the cold chain, or analytic strategies that take advantage of mobile device platforms, will bring much needed dose personalization to individuals and communities of need. Dose optimization that improves outcomes from communicable diseases carries both individual and public health benefit.”

After the analytical challenges have been overcome and an assay with a suitable linear range with enough accuracy and precision has been validated, it is important to perform a clinical validation study. Comparable to dried blood spots it is important to study level of agreement between the standard procedure i.e. TDM based on a plasma or serum sample quantified on HPLC-UV or LC-MS/MS and the innovative oral fluid assay. Passing-Bablok regression and Bland-Altman analysis can be used to determine whether oral fluid based TDM using the new point-of-care test can replace the traditional TDM. If successful, this could increase global access to TDM which would not have been feasible with traditional TDM.

REFERENCES

What is new about the exposome?

By Nicolas Venisse, Toxicology and Pharmacokinetics Dpt and Clinical Investigation Center, University Hospital, Poitiers, France, on behalf of the Toxicology and Environmental Health Committee

The exposome concept has been first defined in 2005 by Wild1 to describe the environmental counterpart of the genome. The exposome has been proposed as a new paradigm to “encompass life-course environmental exposures (including lifestyle factors), from the prenatal period onwards”. It includes exposure to synthetic chemicals, dietary constituents, psychosocial stressors and physical factors. It has the potential to identify environmental contributors to health and disease but requires the development of reliable exposure assessment tools. Assessing the chemical exposome is a challenging task since the concentrations of environmental pollutants are typically orders of magnitude lower than concentrations of drugs and endogenous chemicals2.

Fifteen years after the introduction of the exposome concept, Vermeulen et al3 have reviewed recent progress in the assessment of the chemical exposome and how it can affect human health. In this review, authors advocate for a coordinated and international effort to provide reliable exposomic data enabling environment-wide association studies to identify
new environmental factors in disease. According to the authors, this effort should rely on the development of large scale non targeted screening methods for chemicals and the development of chemoinformatic and bioinformatic tools. They particularly highlight the prominent role of high resolution mass spectrometry (HRMS) in expanding the analytical window beyond targeted analysis. Several databases providing access to chemical data are available to help in the identification of unknown chemicals. This is the case of the U.S. Environmental Protection Agency’s CompTox Chemistry Dashboard (https://comptox.epa.gov/dashboard) that includes physicochemical, environmental fate and transport, exposure, usage, in vivo toxicity and in vitro bioassay data of nearly 900,000 chemicals. This database also includes an advanced search feature designed to support non-targeted mass-spectrometry research.

In a recent article, Pourchet et al. also made some recommendations for the determination of the human chemical exposome using either large-scale suspect or non-targeted screening methods based on high-resolution mass spectrometry (HRMS). Their approach mainly focuses on liquid chromatography coupled to HRMS, either with Time-of-Flight (ToF) or Orbitrap devices, and their recommendations cover all aspects of the analytical procedure from sample extraction to data processing. For sample preparation of common biological matrices such as blood and urine, they propose simple and non-selective methods in order to cover a wide range of analytes. Recommended methods range from simple “dilute and shoot” to turbulent flow chromatography or online solid-phase extraction. Chromatographic separation could be achieved using a C18 reversed-phase column with a conventional binary gradient (water/methanol or water/acetonitrile) or a ternary gradient (water/methanol/acetonitrile) to take advantage of the specific properties of each solvent. Combined detection in the positive and negative ionization mode is required to provide broader detection capabilities. Combining exact mass measurement with fragment ion information related to the structure of the compound obtained using, for example, data dependent acquisition, increase the level of confidence for identification of target and unknown pollutants. The authors also make recommendations regarding the crucial issue of marker’s identification and call for harmonization in the reporting of screening results especially regarding the confidence level associated with compound annotation. Schymanski et al. have already proposed a 5-level confidence system pertinent to screening methods in environmental sciences: level 1 represents the best situation where the proposed structure has been confirmed using measurement of a reference standard with MS, MS/MS and retention time matching while level 5 represents the situation where solely exact mass is available. Finally, Pourchet et al. propose the development of an extended and qualitatively consolidated European MS reference library. The aforementioned developments and harmonization efforts will be carried out within the framework of the European Human Biomonitoring initiative (HBM4EU, 2017-2021).

The concept of exposome has recently gained increased significant attention. Technological advancements in analytical chemistry through the development of HRMS and data processing will contribute to increase our knowledge on the complex relationships between environmental factors and diseases. Exposomic research is an excellent opportunity to develop multidisciplinary collaborations between exposure scientists, toxicologists, analytical chemists and epidemiologists.

**References**


**Clinical Toxicology Assessment in a Drug-induced Liver Injury in Haemochromatosis**

By Manuela G. Neuman, In Vitro Drug Safety and Biotechnology, Toronto, Canada, on behalf of the Clinical Toxicology and Drugs of Abuse Committee

Patients with haemochromatosis are homozygous for the C282Y mutation of the HFE gene. In the UK about 1 in 150 people will have this genotype although only a minority of these will become seriously ill. Genes, other than HFE, may modify the phenotype of haemochromatosis. It has been suggested that patients with haemochromatosis who have two copies of the ancestral haplotype (a highly conserved region around the HFE gene) may be more severely affected than patients with one or no copies. In order to test this, microsatellite markers around the HFE gene were analyzed in unselected C282Y homozygous first-degree relatives of the probands of two family groups: C282Y homozygotes ascertained by genetic screening of blood donors and haemochromatosis patients.

The ancestral haplotype is defined as D6S265-1, D6S105-8, D6S1260-TS, serum ferritin (sFn) and HFE genotyping. Microsatellite markers around the HFE gene) may be more severely affected than patients with one or no copies. In order to test this, microsatellite markers around the HFE gene were analyzed in unselected C282Y homozygous first-degree relatives of the probands of two family groups: C282Y homozygotes ascertained by genetic screening of blood donors and haemochromatosis patients.

The ancestral haplotype is defined as D6S265-1, D6S105-8, D6S1260-4. The ancestral haplotype can be identified by microsatellite markers around the HFE gene. Investigations include transferrin saturation (TS), serum ferritin (sFn) and HFE genotyping. Microsatellite markers are used to search for haplotype associations in 54 of the 59 identified C282Y homozygous first-degree relatives. Some of these individuals have two copies of the ancestral haplotype, others carried alleles suggesting the presence of one copy and a small number of individuals lacked markers from the ancestral haplotype. The ancestral haplotype is not associated with higher iron indices, in fact sFn is higher in those lacking alleles associated with the ancestral haplotype (sFn 578 µg/l) compared to those homozygotes with two copies (sFn 208 µg/l). In addition, no association between ancestral haplotype and morbidity (self-reported symptoms, signs, iron removed at venesection or quality of life scores) can be found.
Modifier genes close to the HFE gene do not play an important role in biochemical expression in these families. Possession of the ancestral haemochromatosis haplotype is not associated with an enhanced risk of developing severe iron overload or becoming ill. Generally, sFn > 1000 ug/l is associated with clinically significant overload related disease. In addition to HFE gene, mutations in the genes that encode hemojuvelin, hepcidin, transferrin receptor 2 and ferroportin have been associated with regulation of iron homeostasis and development of hemochromatosis. A 52-year-old heterozygous hemochromatosis patient was referred to a Gastroenterology clinic to explore the significance of hepatic steatosis. The patient initially presented to his family physician for evaluation of chronic fatigue. Further evaluation demonstrated a mildly elevated sFn level of 482 ug/l (limit of normal is 400 ug/l) with normal transferrin saturation. Hemochromatosis HFE genotyping revealed a heterozygous C282Y/H63D mutation. Ultrasound showed features of hepatic steatosis. There was no additional medical or surgical history. The patient had no manifestations of metabolic syndrome (MB) or other endocrinopathies. In particular, he had no pancreatic endocrine insufficiency, cardiomyopathy, arthralgia, or other features of hemochromatosis. The patient had not been taking any prescription medications. He had no prior history of tobacco or recreational drug use. However, he was a frequent alcohol drinker. After an episode of drinking in excess he took 2 acetaminophen pills to prevent a headache.

Enzyme levels were as follows: alanine amino-transferase (ALT) 26 IU/L, aspartate amino-transferase (AST) 84 IU/L, and gamma glutamyl transferase (GGT) 180 IU/L. Since the AST/ALT ratio showed a drug-induced liver injury (DILI) we performed Lymphocyte toxicity Assay (LTA). By exposing the lymphocytes of the person in the presence or absence of microsomes and acetaminophen alone, alcohol and a combination of both acetaminophen and alcohol we mimic the in vivo situation. The LTA showed high toxicity to acetaminophen and a much higher toxicity to the combination of ethanol and acetaminophen.

Elimination of alcohol consumption was advised, along with restriction of Tylenol and ongoing avoidance of any other hepatotoxic medications or iron supplements. The patient was compliant and the fatigue improved.

**Learning points**

1. Hereditary hemochromatosis should be screened using laboratory diagnostic methods, especially in the individuals presenting with chronic fatigue.
2. There is a positive association between C282Y/H63D heterozygosity and development of alcohol-induced liver damage (ALD).
3. Patients with hemochromatosis should be advised not to drink or take medication that induces cytochrome P450 2E1 such as acetaminophen.
4. HFE testing for the main mutations (p.Cys282Tyr and p.His63Asp) should be performed in all patients with primary iron overload and unexplained increased transferrin saturation and/or serum ferritin valus.
5. Lymphocyte toxicity assay can be used to determine a hypersensitivity syndrome to drugs of use (acetaminophen) or misuse (alcohol) and their combination.
6. The toxicological and genetic evaluation of the patients can lead to more adequate and faster treatment.
7. There is the need that laboratory and clinical toxicologist work in concert with the molecular geneticist and internal medicine specialist to help their patients.

**References**


---

**Personalized natalizumab treatment in multiple sclerosis**

By Z. van Kempen and J. Killestein, MS Center Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands, on behalf of the TDM of Biologics Committee

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system and affects over two million people worldwide. As monoclonal antibodies are increasingly used in MS, it is a timely matter to optimize treatment by minimalizing side effects and complications, increasing treatment convenience and decreasing costs. Furthermore, we might be treating our MS patients with a relative overdose of monoclonal antibodies. Personalized treatment by therapeutic drug monitoring could be the answer to all these unmet needs.
Natalizumab was the first monoclonal antibody that was approved for relapsing remitting MS. Natalizumab is a humanized monoclonal IgG4 antibody targeting the 4-1-integrin, which has a vital role in the trafficking of immune cells across the blood brain barrier. A fixed 4-weekly dose of 300 mg was chosen for phase III trials and this monthly dosing schedule was later approved by the FDA/EMA. In this treatment regimen, natalizumab trough concentrations vary widely between patients,[2, 5] underlining the inefficiency of a set treatment dose and interval for all patients.

Significant MS activity returns when the natalizumab receptor saturation falls below 20-40%. Six. Seven Fifty percent receptor saturation relates to 2.5 μg/mL natalizumab concentration,[8] and this concentration could be a safe cut-off used for therapeutic drug monitoring. However, median trough natalizumab concentrations lie between 25-35 μg/mL after a four week interval, indicating the relative overdose of most patients.[2, 5] When considering 2.5 μg/mL as a therapeutic cut-off, >95% of patients could be adequately treated with a lower dose or longer treatment interval.[2]

Treatment with natalizumab is associated with an increased risk of the possibly fatal complication progressive multifocal leukoencephalopathy (PML), caused by reactivation of the JC polyomavirus in immunosuppressed individuals. Interestingly, extended interval dosing, defined as ≤10 infusions per year or ≤18 infusion per 18 months is associated with a drastic reduction of PML risk.[9] Three retrospective studies have shown comparable natalizumab efficacy of extended interval dosing (5 to 8 weeks interval) of natalizumab.[8-10] A recent prospective study performed therapeutic drug monitoring in 61 completely stable MS patients on natalizumab, prolonging the infusion interval when trough concentration exceeded 15μg/mL with an aim of 10μg/mL trough concentration.[3] Forty-eight patients (85%) could prolong the infusion interval to 5-7 weeks. All patients remained without disease activity. Currently, two large prospective studies are ongoing researching extended interval dosing of natalizumab. The first study is the NEXT-MS study (ClinicalTrials.gov Identifier: NCT04225312) applying therapeutic drug monitoring of natalizumab with an aim of 10μg/mL trough concentration.[13] The second study is the NOVA study (ClinicalTrials.gov Identifier: NCT03689972), an international study randomizing patients between four and six week natalizumab interval.

In summary, personalized and extended dosing of natalizumab in MS is receiving increasing attention over the last years. We feel that personalized dosing of natalizumab is the way to move forward as it could bring major benefits for patients and health care.

References
RENEWED IATDMCT WEBSITE

By Alain Verstraete, on behalf of the Communications Committee

During the last few months, the IATDMCT website has undergone a thorough renovation. All the pages were critically evaluated and updated. The home page (Figure 1) has been modified, with links to a new COVID-19 resource page and an announcement for the virtual Congress.

The pages about the scientific committees have been harmonized and updated, with the help of the committees. This is currently being finalized. The page with the resources for the members has been simplified, and it now contains links to presentations, guidelines, e-books, software tools and target databases.

For example, the resources area contains many video presentations from different congresses ranging from 2013 in Salt Lake City to Foz do Iguacu in 2019. It also contains presentations from regional meetings and from other congresses with IATDMCT participation (Figure 2). In all, more than 100 presentations are available to the membership, with 54 presentations that were recorded during the last Congress (Figure 3).

The archives of the Compass, from 2005 onwards, are also available for the members on the website.

I am very grateful to doctor Ofelia Noceti, vice-chair of the communications committee for driving this forward and to Pam and Megan in the office and for quickly implementing all the changes.

We encourage you to visit the website and explore the resources and look forward to your comments and suggestions.
IATDMCT WEBSITE: WHO IS LOOKING?

By Ofelia Noceti, on behalf of the Communications Committee

As part of the initiative of restructuring and enhancing our website, from the Communications Committee we understood that it is critical to better comprehend and fulfill the expectations of our members. Therefore, we have decided to use Google Analytics to monitor traffic to the IATDMCT site, to identify our target population and to define future strategies.

Here we present the first results obtained in July of this year. This constitutes our baseline to start analyzing the data and set new objectives.

Below we show how many visits our website received during the month on a daily basis. We had 1300 sessions by 964 users, with an average of 2 minutes and 29 seconds per visit; 38.1% knew the site and went directly, while 51.1% found it while making searches through Google, Bing or similar engines, the other 10.7% derived from social media, emails…

Figure 1. Summarized report

Figure 2. Main traffic channels
Where are our visitors located?
Figure 3. Map of the countries with the most visitors.

The middle of the month and mid-week are the main moments our website is visited. Our audience mainly accesses the site from desktop devices; however there is 21% from mobile devices. Figure 5. Devices category.
Figure 6. Top 10 ranking of site visits by location. In the top-3 we find the United States, India and Japan.

<table>
<thead>
<tr>
<th>País</th>
<th>Usuarios</th>
<th>Usuaries nuevos</th>
<th>Sesiones</th>
<th>Porcentaje de visitas</th>
<th>Páginas vistas</th>
<th>Duración media de la sesión</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. United States</td>
<td>241 (24.99%)</td>
<td>229 (22.68%)</td>
<td>202 (20.02%)</td>
<td>71.37 %</td>
<td>61.22 %</td>
<td>00:02:20</td>
</tr>
<tr>
<td>2. India</td>
<td>127 (12.68%)</td>
<td>118 (11.96%)</td>
<td>156 (15.72%)</td>
<td>51.97 %</td>
<td>54.12 %</td>
<td>00:03:02</td>
</tr>
<tr>
<td>3. Japan</td>
<td>71 (7.26%)</td>
<td>59 (5.91%)</td>
<td>88 (8.84%)</td>
<td>62.50 %</td>
<td>65.17 %</td>
<td>00:01:41</td>
</tr>
<tr>
<td>4. Netherlands</td>
<td>57 (5.86%)</td>
<td>50 (5.01%)</td>
<td>60 (6.04%)</td>
<td>71.00 %</td>
<td>72.20 %</td>
<td>00:00:29</td>
</tr>
<tr>
<td>5. Canada</td>
<td>53 (5.41%)</td>
<td>40 (4.01%)</td>
<td>108 (10.94%)</td>
<td>51.93 %</td>
<td>54.93 %</td>
<td>00:07:33</td>
</tr>
<tr>
<td>6. France</td>
<td>44 (4.58%)</td>
<td>34 (3.41%)</td>
<td>61 (6.14%)</td>
<td>52.46 %</td>
<td>55.46 %</td>
<td>00:01:40</td>
</tr>
<tr>
<td>7. Australia</td>
<td>28 (2.90%)</td>
<td>25 (2.51%)</td>
<td>37 (3.72%)</td>
<td>62.16 %</td>
<td>64.16 %</td>
<td>00:00:47</td>
</tr>
<tr>
<td>8. Brazil</td>
<td>28 (2.90%)</td>
<td>22 (2.21%)</td>
<td>51 (5.11%)</td>
<td>51.98 %</td>
<td>54.98 %</td>
<td>00:03:20</td>
</tr>
<tr>
<td>9. Germany</td>
<td>28 (2.90%)</td>
<td>23 (2.31%)</td>
<td>52 (5.21%)</td>
<td>61.98 %</td>
<td>64.98 %</td>
<td>00:02:38</td>
</tr>
<tr>
<td>10. China</td>
<td>25 (2.59%)</td>
<td>24 (2.41%)</td>
<td>42 (4.22%)</td>
<td>86.95 %</td>
<td>89.95 %</td>
<td>00:02:24</td>
</tr>
</tbody>
</table>

Figure 7. Demographic data. Male and female access is mostly balanced. Age analysis points out that highest bar corresponds to visitors mostly belong to the range of 25 to 34 years.

Focusing on Social Media links, as we show below, Twitter brings the most visitors, exhibiting the same trend as for its own channel. Figure 8. Social Media Channels traffics.

<table>
<thead>
<tr>
<th>Red social</th>
<th>Sesiones</th>
<th>% Sesiones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twitter</td>
<td>23</td>
<td>74.19 %</td>
</tr>
<tr>
<td>LinkedIn</td>
<td>6</td>
<td>19.35 %</td>
</tr>
<tr>
<td>Facebook</td>
<td>2</td>
<td>6.45 %</td>
</tr>
</tbody>
</table>
The flow from social media channels analyzed is as follows. It can be clearly inferred that the blog related to how COVID-19 affected young scientist lives well captured the attention of a fraction of our audience.

Figure 9. Social Media Channels flow inside the website.

Home section is our main window to communicate and attract new visitors and members. The events section promoting activities and congresses is also frequently explored. Member resources area is valuable for our affiliates. The work and initiatives of IATDMCT Scientific Committees are particularly important to gather professionals with similar interests and to help in building networks and knowledge to guide better practices. Guidelines, standards of practice and consensus documents are the results of the hard work of these Committees of experts. Membership section informs about membership conditions and benefits and our member directory allows quickly access to professional contact information.

Figure 10. Most frequently visited pages.

From the Communications Committee we would like to thank you IATDMCT Board for their support to make this initiative a reality, and in particular to Dr. María Shipkova, that accompanied us during the whole process for her enthusiastic encouragement and contributions; to Pam Lyons and Megan Howes for their professionalism, well disposition and execution, and to Professor Alain Verstraete for his commitment and support.

We invite our members to make suggestions and comments as well as to contribute keeping our site updated sending materials: i.e. presentations, webinar opportunities, articles, education courses and job offers.
Dear IATDMCT Members,

As you all know, due to the COVID pandemic and concern for everyone’s safety, we made the difficult decision to cancel the in-person congress that was to have been held in Banff, Alberta, Canada this September. Our Organizing Committee and contributing members put in a lot of work to organize an excellent program and a memorable experience for everyone. Fortunately, we are going to be able to offer you much of the excellent program, but you will have to wait for another year to experience Banff National Park and our Alberta hospitality.

We will be providing a Virtual Banff 2020 Congress via webinar. The scientific sessions will be broadcast live from September 14 – 16, with plenary lectures and simultaneous TDM and Clinical Toxicology streams for 3 hours each day. Recorded sessions will also be available for viewing at individual convenience.

Posters and short presentations from authors will also be available, with a link to contact the authors for more information. Best TDM and Best Tox Poster awards will be presented. Our sponsors will be providing a series of informative sessions highlighting their latest innovations and technology, starting on September 23, 2020.

The congress program is available on our website and delegates can register now as well. We are excited to be able to bring our members this exciting series of TDM/Toxicology presentations even though we cannot meet in person. We hope that you will plan to take advantage of this Virtual Banff 2020 Congress.

Penny Colbourne and David Kinniburgh
Co-Chairs Banff 2020
On behalf of the Organizing Committee

MEMBER-GET-A-MEMBER CAMPAIGN 2020 UPDATE

Invite Your Friends and Colleagues!

Dear Colleagues,

The “Member-get-a-member” Campaign has already more than 10 years of successful history in IATDMCT. Initiated by Dr. Don LeGatt, the campaign is traditionally led by the IATDMCT Secretary with the purpose of encouraging current members to recruit colleagues to our Association. Now I am looking back respectfully and proudly at the many campaign editions that attracted a lot of new members for IATDMCT and helped the Association to grow.

This year’s Campaign started in January and I am delighted to report that up to May 11 new members were recruited by 11 established members.

Well done to all who participated!

As usual the prize for this year’s Campaign was a free registration for the upcoming IATDMCT Congress! Although, sadly, due to the pandemic situation the Congress 2020 had to be cancelled, the achievement of the current participants is of course highly appreciated and it counts.

“Member-get-a-member” 2020 continues and becomes “Member-get-a-member” 2020/2021.

The Campaign rules and the participation procedure remain the same, but the deadline and the prize change.

NEW CAMPAIGN DEADLINE: AUGUST 30, 2021

THE TOP TWO "RECRUITERS" WILL RECEIVE FREE REGISTRATION FOR THE ROME CONGRESS 2021!

Campaign Rules

• To receive credit for each new referral, the application form must include the name of the member who recommended them, and the application must be approved.

• The referral must be a paying member and must be enrolled for membership in order for the recruiter to be eligible for the prize of one free registration fee for the Rome Congress 2021.

How Do You Participate?

• Know your IATDMCT Member benefits.

• Contact potential members. Share how IATDMCT has benefited you, give them the IATDMCT Membership Application Form or direct them to Join IATDMCT on our website at http://iatdmct.org/member-join. The application form has a section for the new member to place your name as the person who recommended them for membership.

• Send an email to the IATDMCT Office with the potential member’s name and email address and the IATDMCT office staff will follow up with them personally.

• When the new member’s application arrives with appropriate payment and is approved, you will be advised by email.

Visit the IATDMCT webpage for complete participation details!

Be active for IATDMCT, take part in this campaign and win the prize!

Respectfully submitted,
Maria Shipkova
IATDMCT Secretary

UPDATE ON 2020 CONGRESS
WE’VE GONE VIRTUAL!

Dear IATDMCT Members,

As you all know, due to the COVID pandemic and concern for everyone's safety, we made the difficult decision to cancel the in-person congress that was to have been held in Banff, Alberta, Canada this September. Our Organizing Committee and contributing members put in a lot of work to organize an excellent program and a memorable experience for everyone. Fortunately, we are going to be able to offer you much of the excellent program, but you will have to wait for another year to experience Banff National Park and our Alberta hospitality.

We will be providing a Virtual Banff 2020 Congress via webinar. The scientific sessions will be broadcast live from September 14 – 16, with plenary lectures and simultaneous TDM and Clinical Toxicology streams for 3 hours each day. Recorded sessions will also be available for viewing at individual convenience.

Posters and short presentations from authors will also be available, with a link to contact the authors for more information. Best TDM and Best Tox Poster awards will be presented. Our sponsors will be providing a series of informative sessions highlighting their latest innovations and technology, starting on September 23, 2020.

The congress program is available on our website and delegates can register now as well. We are excited to be able to bring our members this exciting series of TDM/Toxicology presentations even though we cannot meet in person. We hope that you will plan to take advantage of this Virtual Banff 2020 Congress.

Penny Colbourne and David Kinniburgh
Co-Chairs Banff 2020
On behalf of the Organizing Committee
REMEMBERING ROGER JELLIFFE, MD

By Michael Neely MD, Alan Schumitzky PhD, and George Drusano MD

On June 22, 2020, Roger Jelliffe MD, FCP, FAAPS, passed away peacefully in Pasadena, California at the age of 91, with family at his bedside, appropriately masked in the middle of the COVID-19 pandemic. He did not have the virus, and although his body was done, his mind was fighting until the end. It was that fighting spirit that for decades made him such a champion of individualized therapy and what has come to be known as model informed precision dosing. Here, three of us who knew him well over a combined total of almost 100 years share some recollections of our friend and mentor.

Michael Neely: In 2001, I recall nearing the end of my physician subspecialty training in pediatric infectious diseases and clinical pharmacology at Rainbow Babies’ and Children’s Hospital in Cleveland, Ohio. As I searched the internet for academic positions, I stumbled across the website of the Laboratory of Applied Pharmacokinetics (LAPK) at the University of Southern California (USC). Roger had founded LAPK in 1973, when I was just 4 years old. He was offering one of his famous workshops in Washington, DC that September, promising to introduce me to the arts of population modeling, especially from the nonparametric statistical perspective, and even more importantly, how to use the models to benefit my patients.

I attended the workshop, and although I understood only half of what I heard, Roger’s passion and skill captivated me. Despite being nearly trapped in DC from the horrific events of September 11, 2001, just two days after that workshop, with the generous support of many, I began my career with Roger and LAPK at USC, where I work to this day, almost 20 years later. Roger’s Monday night lab meetings introduced me to a world of colleagues, mathematicians, statisticians, and possibilities to enhance my use of therapeutic medications. Those nights and days in the lab profoundly altered how I viewed a prescription pad, changing it from something to be completed from memory or a reference, to a living document supported by evidence and mathematics tailored to each patient. Because of Roger and LAPK, I have had therapeutic successes arise from great uncertainties more times than I can recall, especially as a pediatrician prescribing medications that often had few to no dosing recommendations. Without a doubt, I remember Roger as one of the most influential people in my life, and I will miss him.

Alan Schumitzky: Roger Jelliffe was a true renaissance man in Medicine, Science, Art, Music, Languages, and Mathematics. I first met Roger in 1975. At the time I was supervising a PhD student in Applied Mathematics who had an interest in mathematical problems in Pharmacokinetics. This was a relatively new area of research at that time. We happily discovered there was an expert in this area at the USC Medical School, namely Roger Jelliffe. We made an appointment to see him, which began for me a 45-year history of collaboration.

Roger’s interest in mathematics was deep. To learn about this subject he went back to school. I will never forget hour-long telephone conversations with him about his course in Multivariate Calculus (eg, Green’s Theorem and Stokes’ Theorem). This is difficult mathematics. Somehow, we survived this course and Roger went on to learn all the mathematics and statistics that we subsequently used in our research work together in LAPK.

I was not the only mathematical influence on Roger. He also developed a close relationship with the famous mathematician Richard Bellman. Dr. Bellman was the founding editor of the journal Mathematical Biosciences. In all of Roger’s many scientific papers he was most proud of his paper with his daughter Susan on estimating creatinine clearance.

Roger was an accomplished pianist (he took piano lessons all his life) and classical guitarist. He was a linguist fluent in French and Spanish and was famous for his language tapes in Russian that he played in his minivan. Whenever he developed a professional relationship with a foreign scientist, he would begin to learn their language. Finally, Roger was a devoted husband and father. He will be sorely missed by me and by too many to count.

George Drusano: Roger Woodham Jelliffe was a friend of mine. He was a remarkable man. I can remember well the first time we met. In 1986 I was visiting Carl Peck, who later headed the US Food and Drug Administration Center for Drug Evaluation and Research (CDER) among many other accomplishments. With me on that visit was another friend, Alan Forrest, a fellow faculty member at the University of Maryland, who had his own long and productive career in clinical pharmacology until his untimely death in 2018. As it turned out, Roger was also visiting Carl. He was carrying a computer terminal with a telephone modem (remember them?). He used it to connect with his USC*PACK clinical modeling and dosing software that was housed on a mainframe at the University of Southern California. Alan and I spent a very entertaining hour watching Roger play (there is no other word that fits) with that PK program. His enthusiasm was infectious.

This was the start of a multi-decade friendship. Over the years, I watched Roger go from city to city all over the world to give seminars. First, it was about USC*PACK, later about LAPK’s Nonparametric Adaptive Grid (NPAG) algorithm and then what was originally MM-USC*PACK and came to be BestDose. I got tired just thinking about his travels. His indefatigable journeys served a much larger purpose. Roger knew in his brain, but much more importantly in his heart that knowledge of a drug’s pharmacokinetics would allow a physician to make better therapeutic decisions, generating better therapeutic outcomes with less concentration-driven toxicity. Indeed, in the later years of our friendship, Roger would rat at the pharmaceutical companies because they marketed an agent (in many classes) without sufficient attention to the pharmacokinetics and pharmacodynamics. He equally blamed the regulatory agencies for failing to demand more.

So, how did a cardiologist become one of the first quantitative pharmacologists? Interestingly, Roger took a course at Oak Ridge National Laboratories to learn about radioactive decay. The mathematical bug bit him and changed him forever (with consequent good outcomes for patients).

I watched Roger pull together a truly remarkable research team. There are so many names and I fear that I will cause offense by leaving an important name out. Nonetheless, here are some of Roger’s friends and colleagues:

Alan Schumitzky, a professor of mathematics at USC, the rock of the Laboratory of Applied Pharmacokinetics, developer of the nonparametric expectation maximization (NPEM) algorithm and one of the smartest men I have ever met;

Michael van Guilder, the gentleman who turned ideas into Fortran code and who could unravel all the bugs in the programs;

David Bayard, a control engineer employed by the NASA Jet Propulsion Lab (JPL) who worked with Mark Millman, also from JPL. Together, they were the prime drivers of the algorithms that power BestDose, LAPK’s dosing software. They brought optimal control and multiple-model design to LAPK and broke from the rest of the clinical pharmacology world, which still uses single-model, MAP-Bayesian methods;

Bob Leary, a scientist at the University of California, San Diego at the time, who developed NPAG with the other LAPK members, and is regarded as one of the smartest pharmacokineticians around;

Michael Neely, a physician trained in pediatric infectious diseases and clinical pharmacology who has picked up Roger’s mantle and leads LAPK (now LAPKB). He has engulfed NPAG in the R package, which has markedly improved its utility and, perhaps most importantly has shown in multiple NIH grants how important stochastic control is clinically.

Roger is gone now. I miss him dearly. He has left behind a great legacy of first-class work, and, perhaps most importantly, he honored his Hippocratic Oath in many ways. Most significantly his scientific endeavors have added to patient care, the careers of innumerable others, and most definitely to my own career.