Drug-induced Thrombotic Microangiopathy: Experience of The Oklahoma Registry and The BloodCenter of Wisconsin

Reese J.A. *et al.*

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Many drugs have been reported to cause thrombotic microangiopathy (TMA), often described as thrombotic thrombocytopenic purpura (TTP) or hemolytic-uremic syndrome (HUS). Recently criteria were established to evaluate the evidence for a causal association of a drug with TMA and then all published reports of drug-induced TMA (DITMA) were systematically reviewed to determine the level of evidence supporting a causal association of the suspected drug with TMA. These evaluation criteria were used to assess the Oklahoma TTP-HUS Registry patients who had been previously categorized as drug-induced, 1989–2014. Also, the experience of the BloodCenter of Wisconsin with testing for drug-dependent antibodies reactive with platelets and neutrophils in patients with suspected immune-mediated DITMA, 1988–2014, was reviewed. Among 58 patients in the Oklahoma Registry previously categorized as drug-induced (15 suspected drugs), 21 patients (3 drugs: gemcitabine, pentostatin, and quinine) had evidence supporting a definite association with TMA; 19 (90%) of the 21 patients had quinine-induced TMA. The BloodCenter of Wisconsin tested 40 patients with suspected DITMA (eight drugs); drug-dependent antibodies, supporting a definite association with TMA, were identified in 30 patients (3 drugs: oxaliplatin, quinine, and vancomycin); 28 (93%) of the 30 patients had quinine-induced TMA. Combining the data from these 2 sources, 51 patients (5 drugs) were identified with evidence supporting a definite association with TMA. DITMA was attributed to quinine in 47 (92%) of these 51 patients.

Single-Dose Intravenous Gammaglobulin can Stabilize Neutrophil Mac-1 Activation in Sickle Cell Pain Crisis

Manwani D. *et al.*

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Intravenous immunoglobulin (IVIG) decreases neutrophil adhesion to endothelium and red blood cell–neutrophil interactions in sickle cell mice undergoing vaso-occlusion. In this Phase I clinical trial of sickle cell anemia (SCA) patients admitted with pain crisis, the status of adhesion molecules on neutrophils was evaluated in control and IVIG-treated subjects pre- and post-infusion up to 800 mg/kg, the same dose used in murine studies. Mac-1 function significantly decreased from baseline in the low-dose IVIG (200–400 mg/kg) cohorts. IVIG-related adverse events may have occurred in the high-dose (600–800 mg/kg) cohorts. No significant increases in neutrophil and leukocyte counts were observed, suggesting that IVIG may more selectively inhibit Mac-1 function as opposed to neutrophil adhesion. This study provides the first in-human validation of preclinical murine studies that IVIG can decrease Mac-1 function.

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Intensive Diabetes Therapy and Ocular Surgery in Type 1 Diabetes

The DCCT/EDIC Research Group

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The Diabetes Control and Complications Trial (DCCT) showed a beneficial effect of 6.5 years of intensive glycemic control on retinopathy in patients with type 1 diabetes.

Between 1983 and 1989, a total of 1441 patients with type 1 diabetes in the DCCT were randomly assigned to receive either intensive diabetes therapy or conventional therapy aimed at preventing hyperglycemic symptoms. They were treated and followed up until 1993. Subsequently, 1375 of these patients were followed up in the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study. The self-reported history of ocular surgical procedures was obtained annually. The effect of intensive therapy, compared with conventional therapy, on the incidence and cost of ocular surgery during these two studies was evaluated.

Over a median follow-up of 23 years, 130 ocular operations were performed in 63 of 711 patients assigned to intensive therapy (8.9%) and 189 ocular operations in 98 of 730 patients assigned to conventional therapy (13.4%) ($P < 0.001$). After adjustment for DCCT baseline factors, intensive therapy was associated with a reduction in the risk of any diabetes-related ocular surgery by 48% ($P < 0.001$) and a reduction in the risk of all such ocular procedures by 37% ($P = 0.01$). Forty-two patients who received intensive therapy and 61 who received conventional therapy underwent cataract extraction (adjusted risk reduction with intensive therapy, 48%; $P = 0.002$); 29 patients who received intensive therapy and 50 who received conventional therapy underwent vitrectomy, retinal-detachment surgery, or both ($P = 0.01$). The costs of surgery were 32% lower in the intensive-therapy group. The beneficial effects of intensive therapy were fully attenuated after adjustment for mean glycated hemoglobin levels over the entire follow-up.

Intensive therapy in patients with type 1 diabetes was associated with a substantial reduction in the long-term risk of ocular surgery.

A cluster-randomized trial to reduce cesarean delivery rates in Quebec

Chaillet N. *et al.*

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In Canada, cesarean delivery rates have increased substantially over the past decade. Effective, safe strategies are needed to reduce these rates.

A cluster-randomized, controlled trial of a multifaceted 1.5-year intervention was conducted at 32 hospitals in Quebec. The intervention involved audits of indications for cesarean delivery, provision of feedback to health professionals, and implementation of best practices. The primary outcome was the cesarean delivery rate in the 1-year postintervention period.

Among the 184,952 participants, 53,086 women delivered in the year before the intervention and 52,265 women delivered in the year following the intervention. A significant but small reduction in the rate of cesarean delivery was observed from the preintervention period to the postintervention period in the intervention group compared with the control group ($P = 0.04$). The cesarean delivery rate significantly reduced among women with low-risk pregnancies ($P = 0.03$) but not among

those with high-risk pregnancies (P = 0.35; P = 0.03 for interaction). The intervention group also had a reduction in major neonatal morbidity compared with the control group (P = 0.03) and a smaller increase in minor neonatal morbidity (P < 0.001). Changes in minor and major maternal morbidity did not differ significantly between the groups.

Audits of indications for cesarean delivery, feedback for health professionals, and implementation of best practices, compared with usual care, resulted in a significant but small reduction in the rate of cesarean delivery, without adverse effects on maternal or neonatal outcomes. The benefit was driven by the effect of the intervention in low-risk pregnancies.

Trial of Short-Course Antimicrobial Therapy for Intra-Abdominal Infection

Sawyer R.G. *et al.*

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The successful treatment of intra-abdominal infection requires a combination of anatomical source control and antibiotics. The appropriate duration of antimicrobial therapy remains unclear.

The authors randomly assigned 518 patients with complicated intra-abdominal infection and adequate source control to receive antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus, with a maximum of 10 days of therapy (control group), or to receive a fixed course of antibiotics (experimental group) for 4 ± 1 calendar days. The primary outcome was a composite of surgical-site infection, recurrent intra-abdominal infection, or death within 30 days after the index source-control procedure, according to the treatment group. Secondary outcomes included the duration of therapy and rates of subsequent infections.

Surgical-site infection, recurrent intra-abdominal infection, or death occurred in 56 of 257 patients in the experimental group (21.8%), compared with 58 of 260 patients in the control group (22.3%) (P = 0.92). The median duration of antibiotic therapy was 4.0 days (interquartile range, 4.0–5.0) in the experimental group, compared with 8.0 days (interquartile range, 5.0–10.0) in the control group (P < 0.001). No significant between-group differences were found in the individual rates of the components of the primary outcome or in other secondary outcomes.

In patients with intra-abdominal infections who had undergone an adequate source-control procedure, the outcomes after fixed-duration antibiotic therapy (approximately 4 days) were similar to those after a longer course of antibiotics (approximately 8 days) that extended until after the resolution of physiological abnormalities.

Randomized, Double-Blind, Placebo-Controlled Study of Synbiotic Yogurt Effect on The Health of Children

Ringel-Kulka T. *et al.*

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The aim of this study was to assess the effects of daily consumption of a synbiotic yogurt drink on the health, growth, and quality of life of healthy children, 12-48 months of age, in out-of-home child care.

Healthy children attending child care centers were enrolled in a prospective, double-blind, placebo-controlled clinical trial. The intervention was a yogurt drink containing Streptococcus thermophilus, Lactobacillus bulgaricus, and Bifidobacterium animalis subspecies lactis (BB-12), and 1 g of inulin (synbiotic group) vs a similar nonsynbiotic-containing acidified milk drink (placebo group) once daily for 16 weeks. The endpoints were days of diarrhea, fever,

vomiting, symptoms of upper respiratory tract infection, use of antibiotics, physician visits, child care absenteeism, parental work absenteeism, and quality of life.

Compared with placebo (n = 73), children receiving synbiotic (n = 76) had significantly fewer days of reported fever, significant improvement in social functioning, and school functioning. More days with ≥3 loose/watery stools were reported in the synbiotic group ($P < 0.05$).

Daily supplementation of children's diet with yogurt containing probiotic bacteria BB-12 and inulin significantly reduced days of fever and improved social and school functioning. The increased frequency of bowel movements may be explained by an accelerating effect of BB-12 and inulin on intestinal transit. Further research on the possible benefits of synbiotics on children's health is advised.

A NICE delivery: The Cross-Atlantic Divide Over Treatment Intensity in Childbirth

Shah N. *et al.*

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For generations, both British and American mothers have assumed that the safest way to give birth is to spend many hours, if not days, in a hospital bed under the supervision of an obstetrician. Now, new guidelines are challenging these deeply held beliefs.

After completing an evidence-based review, the United Kingdom's National Institute for Health and Care Excellence (NICE) concluded that healthy women with straightforward pregnancies are safer giving birth at home or in a midwife-led unit than in a hospital under the supervision of an obstetrician.1 Across the pond, eyebrows went up. The New York Times editorial board (and others) wondered, "Are midwives safer than doctors?" How can homes be safer than hospitals? And what implications will the British guidelines have for the United States?one

Currently, 9 out of 10 babies born in the United Kingdom are delivered in physician-led hospital maternity units (in the United States, the rate is closer to 99 out of 100). NICE does not dictate a clinician type or birth setting and makes it clear that women should have freedom to make choices consistent with their needs and preferences. Yet Britain's National Health Service believes that when the new guidelines are implemented, these preferences may change. Thousands more British women per year are expected to avoid hospitals willingly at least in part out of concern for their own safety and with the expectation that their babies will be no worse off.

The safety argument against physician-led hospital birth is simple and compelling: obstetricians, who are trained to use scalpels and are surrounded by operating rooms, are much more likely than midwives to pick up those scalpels and use them. For women giving birth, the many interventions that have become commonplace during childbirth are unpleasant and may lead to complications, including hospital-acquired infections. For babies, the interventions rarely appear to be helpful.

Ombitasvir Plus Paritaprevir Plus Ritonavir with or without Ribavirin in Treatment-Naive and Treatment-Experienced Patients with Genotype 4 Chronic Hepatitis C Virus Infection (Pearl-I): A Randomized, Open-Label Trial

Hézode C. *et al.*

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Hepatitis C virus (HCV) genotype 4 accounts for about 13% of global HCV infections. Because interferon-containing treatments for genotype 4 infection have low efficacy and poor tolerability, an unmet need exists for effective all-oral regimens. The authors examined the efficacy and safety of an all-oral interferon-free regimen of ombitasvir, an NS5A inhibitor, and paritaprevir (ABT-450), an NS3/4A protease inhibitor dosed with ritonavir (ombitasvir plus paritaprevir plus ritonavir), given with or without ribavirin.

In this multicenter ongoing phase 2b, randomized, open-label combination trial (PEARL-I), patients were recruited from academic, public, and private hospitals and clinics in France, Hungary, Italy, Poland, Romania, Spain, Turkey, and the USA. Eligible participants were aged 18-70 years with noncirrhotic, chronic HCV genotype 4 infection (documented ≥6 months before screening) and plasma HCV RNA levels higher than 10,000 IU/mL. Previously untreated (treatment-naive) patients were randomly assigned (1:1) using computer-generated randomization lists to receive once-daily ombitasvir (25 mg) plus paritaprevir (150 mg) plus ritonavir (100 mg) with or without weight-based ribavirin for 12 weeks. Previously treated (treatment-experienced) patients who had received pegylated interferon plus ribavirin all received the ribavirin-containing regimen. The primary endpoint was a sustained virological response (HCV RNA <25 IU/mL) 12 weeks after the end of treatment (SVR12). The analysis was by intention to treat.

Between August 14, 2012, and November 19, 2013, 467 patients with HCV infection were screened, of whom 174 were infected with genotype 4. A total of 135 patients were randomly assigned to treatment and received at least 1 dose of study medication; 86 patients were treatment-naive, of whom 44 received ombitasvir plus paritaprevir plus ritonavir and 42 received ombitasvir plus paritaprevir plus ritonavir with ribavirin, and 49 treatment-experienced patients received the ribavirin-containing regimen. In previously untreated patients, SVR12 rates were 100% in the ribavirin-containing regimen and 90•9% in the ribavirin-free regimen. No statistically significant differences in SVR12 rates were noted between the treatment-naive groups (P = 0•086). All treatment-experienced patients achieved SVR12. In the ribavirin-free group, 2 (5%) of 42 treatment-naive patients had virological relapse, and 1 (2%) of 44 had virological breakthrough; no virological failures were recorded in the ribavirin-containing regimen. The most common adverse event was headache (14 [29%] of 49 treatment-experienced patients and 14 [33%] of 42 treatment-naive patients). No adverse event-related discontinuations or dose interruptions of study medications, including ribavirin, were noted, and only 4 patients (4%) of 91 receiving ribavirin required dose modification for hemoglobin less than 100 g/L or anemia.

An interferon-free regimen of ombitasvir plus paritaprevir plus ritonavir with or without ribavirin achieved high sustained virological response rates at 12 weeks after the end of treatment and was generally well tolerated, with low rates of anemia and treatment discontinuation in noncirrhotic previously untreated and previously treated patients with HCV genotype 4 infection.

Immediate Delivery Versus Expectant Monitoring for Hypertensive Disorders of Pregnancy between 34 and 37 Weeks of Gestation (HYPITAT-II): An Open-Label, Randomized Controlled Trial

Broekhuijsen K. *et al.*

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Little evidence is available to guide the management of women with hypertensive disorders in late preterm pregnancy. The authors investigated the effect of immediate delivery versus expectant monitoring on maternal and neonatal outcomes in such women.

An open-label, randomized controlled trial was conducted in 7 academic hospitals and 44 nonacademic hospitals in the Netherlands. Women with nonsevere hypertensive disorders of pregnancy between 34 and 37 weeks of gestation were randomly allocated to either induction of labor or caesarean section within 24 h (immediate delivery) or a strategy aimed at prolonging pregnancy until 37 weeks of gestation (expectant monitoring). The primary outcomes were a composite of adverse maternal outcomes (thromboembolic disease, pulmonary oedema, eclampsia, HELLP (H: hemolysis; EL: elevated liver enzymes; LP: low platelet count) syndrome, placental abruption, or maternal death), and neonatal respiratory distress syndrome, both analyzed by intention-to-treat.

Between March 1, 2009, and February 21, 2013, 897 women were invited to participate, of whom 703 were enrolled and randomly assigned to immediate delivery (n = 352) or expectant monitoring (n = 351). The composite adverse maternal outcome occurred in 4 (1.1%) of 352 women allocated to immediate delivery versus 11 (3.1%) of 351 women allocated to expectant monitoring (P = 0•069). Respiratory distress syndrome was diagnosed in 20 (5.7%) of 352 neonates in the immediate delivery group versus 6 (1.7%) of 351 neonates in the expectant monitoring group (P = 0•005). No maternal or perinatal deaths occurred.

For women with nonsevere hypertensive disorders at 34–37 weeks of gestation, immediate delivery might reduce the already small risk of adverse maternal outcomes. However, it significantly increases the risk of neonatal respiratory distress syndrome; therefore, routine immediate delivery does not seem justified and a strategy of expectant monitoring until the clinical situation deteriorates can be considered.