



April 13, 2018

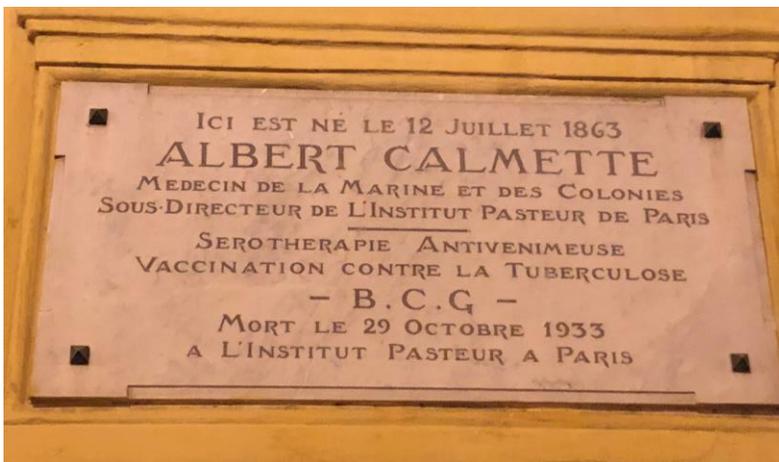
DAILY *Links*

38th Annual Meeting & Scientific Sessions The Acropolis, Nice, France



Review Symposium 14: Old Cells New Tricks: Updates on Transplant Immunology

The 'Natural' Born Killers – Mr. Brightside



Albert Calmette. Born opposite the pub in Nice back in 1863. That's right – the physician who came up with the BCG vaccine for tuberculosis and the first snake antivenom to boot. Immunology was clearly his thing. He would have enjoyed this morning's session entitled "old cells new tricks."

A shoeless Dan Goldstein, MD started by addressing the question as to whether the innate immune system should be manipulated. He showed that innate immune cells are responsible for allorecognition and sterile inflammation but issued caution with respect to infection. He suggested thoracic organs could be pre-treated prior to implantation for therapeutic benefit ameliorating some of the risk. Gregor Warnecke, PhD explored the role of T-reg cells showing a subset with low expression of CD127 to be protective with respect to CLAD development. He finished by presenting novel data from renal transplantation where polyclonal T-reg cells were administered at the time of transplant with encouraging preliminary results. Pilot studies with patients are likely to follow.

'A license to kill'- the double edged role of Natural killer cells was next up (John Greenland, MD, PhD). They may reduce antigen presentation within the graft (good) but have deleterious effects on damaged donor cells and antibody mediated cytotoxicity leading to allograft rejection and injury (bad). The macrophage was next up – specifically its interaction with T-cells. Carla Baan, PhD, demonstrated that T-cells can be stimulated by macrophages with minimal impact by calcineurin pathways. Lori West, MD, D.Phil, suggested that targeting multiple stages in the B-cell development pathways might be an effective strategy in AMR although issued caution - understanding the balance of rejection and tolerance is key! Finally the complex interactions of neutrophils in transplant was explored by Andrew Gelman, PhD. He showed that neutrophils are instrumental in preventing immune tolerance by promoting interactions between T and dendritic cells while stimulating entry of effector lymphocytes into the target organ.

Review Oral Session 15: The Final Frontier? Bleeding in MCS

The Truth Will Set You Free

Free from aspirin? Free from higher INR goals? Free from bleeding events? Maybe so in patients with Heartmate 3 (HM3) devices. Thursday's session on MCS included discussion of reduced intensity antithrombotic strategies in patients with HM3.

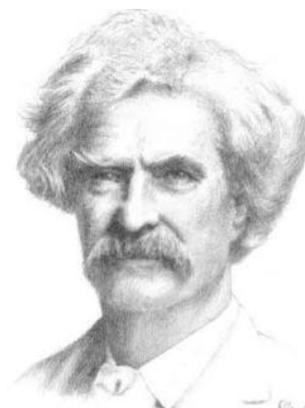
Sern Lim, MD from the University Hospital Birmingham presented a prospective analysis that sought to answer the questions: Is it safe to stop aspirin therapy in patients with HM3 devices? The study investigators chose the strategy of aspirin discontinuation rather than reduction of INR target with warfarin due to the high prevalence of atrial fibrillation (AF) in this patient population. The study sought to enroll 50 consecutive patients implanted with HM3 as a bridge to transplant beginning in November 2015. Seven patients were excluded due to death prior to discharge post-implant. The remaining 43 patients analyzed were initiated on aspirin at a dose of 75 mg and warfarin with an INR goal of 2-3. Aspirin was discontinued if the patient experienced bleeding complications or after three months of dual therapy. Eight patients experienced bleeding and therefore were transitioned to warfarin only, 32 patients had no bleeding and were transitioned to warfarin only after three months of therapy, and finally three patients remained on dual therapy. The eight patients who had bleeding complications on dual therapy were slightly older than patients who did not have bleeding complications however all other baseline characteristics were similar. The dual therapy group had 6 bleeding events (3 GI bleed, 3 epistaxis, 1 fatal intracerebral bleed, 1 retroperitoneal bleed). Only one patient in the warfarin only group had a bleeding event (GI bleed), and this patient had a prior GI bleed while on aspirin + warfarin initially. There were no

differences between thromboembolic events between patients. Dr. Lim concluded that the discontinuation of aspirin may be a reasonable option to minimize bleeding in patients with HM3 devices however this strategy should be tested in a larger randomized controlled trial.

Following Dr. Lim's discussion of a potential reduced antithrombotic strategy, Ivan Netuka, MD, PhD summarized an alternative low intensity anticoagulation strategy that was evaluated in the MAGENTUM 1 Study. This study was a single arm, safety and feasibility of low intensity warfarin in patients with the HM3 device. Patients in this study were bridged with heparin to warfarin (INR 2-3) and started on aspirin 100 mg after device implantation for six weeks. At six weeks, patients who were compliant with their medications and had been stable for discharge home were enrolled. Patients were excluded if they had additional MCS within seven days of implantation, history of thrombotic events, atrial fibrillation without left atrial appendage exclusion, or valve prosthesis (except for bioprosthetic aortic valves). Enrolled patients were changed to a low intensity warfarin protocol (INR 1.5-1.9) and continued on the same dose of aspirin. INRs were monitored weekly using point of care testing and were followed by a clinical pharmacist using a strict anticoagulation protocol. Between November 30, 2016 and September 4, 2017, 15 patients were enrolled. The mean time in therapeutic range (TTR) with a goal INR 1.5-1.9 was 75.3%. Of the enrolled patients, only one patient had a GI bleed. No patients experienced pump thrombosis, stroke, or death. Dr. Netuka concluded that the low intensity strategy may be a safe option for reducing the rate of bleeding events and is feasible due to the high %TTR (higher than previous LVAD demonstrated despite narrower range).*

While the results of these studies are promising, larger studies are needed to confirm their findings. One thing is for sure. The writing is on the wall and low intensity antithrombotic strategies with the improved technology of the HM3 device may be the answer for the future of LVAD associated bleeding.

* View the full results of the MAGENTUM-1 study published online at JHLT on April 11, 2018.



"Tell the truth or 'trump' but get the trick."

"A man is never more truthful than when he acknowledges himself a liar."

"Often the surest way to convey misinformation is to tell the strict truth."

- Mark Twain

Review Symposium 23 – Too Little or Too Much: Controversies in Monitoring After Pediatric Thoracic Transplantation

A Fork in the Fork in the Road: Is There a Best Path or Should We Just Take It?



Transplant cardiologists, Drs. Feingold and Hsu “debating”.

Before the gloves came off, this session started with a review of emerging biomarkers for allograft rejection and coronary artery vasculopathy. The primary biomarkers discussed were gene expression profiling (AlloMap), donor specific cell free DNA and angiogenesis factors. There was limited data in children, but what was available was promising, with multiple upcoming studies that are mustering much excitement.

After the introductory talk, the bell rang and out came the first debaters to discuss the role of bronchoscopy as the gold standard for monitoring post lung transplantation. As expected, there were very few pediatric studies on this topic, with no current evidence showing a survival benefit when using bronchoscopy. It was evident that bronchoscopy will still be done as it is relatively

safe and can detect rejection and infection, but one can question if it should be done with less frequency to mitigate potential harms. Overall, this debate seemed to be a draw that ended with exciting future directions.

Next out of the tunnel were two pediatric transplant cardiologists to debate the role of catheterization as the gold standard for monitoring of rejection and coronary artery vasculopathy post heart transplantation. After some exciting back and forth, it was clear that much work is being done to find non invasive measurements of rejection and CAV including multiple imaging modalities and serum biomarkers. Until these measures are further refined and perfected, it seems that cardiac catheterization will remain the gold standard, but perhaps, not for long.

Review Symposium 18: It’s Electric! Electrophysiological Management of the LVAD patient.

It’s Been Brewing up a Storm in Nice Today

So it wasn’t only in the skies across Nice this morning that we had electrical storms, but also in this symposium where the many associated electrophysiological complications in the LVAD patient were debated.

Ventricular arrhythmias have long been associated with re-hospitalizations as well as increased morbidity and mortality. How should we best treat these arrhythmias? The answer to this electrifying question was explored in detail during this session. The Chicago cohorts experiences were presented. Intra-operative epicardial voltage mappings are used as a predictive tool to determine those patients who may be most at

risk of developing ventricular arrhythmias post LVAD implantation. The cohort also shared results of their study looking into post ablation reoccurrence, which revealed positive results as well as reduction in numbers receiving long term amiodarone. One reoccurring complication presented today was that of higher rates of VAD pump thrombosis post ablation.

To treat atrial fibrillation or not was then explored, with interesting results from the ENDURANCE trial, suggesting that there is no increase in thrombo-embolic events in patients suffering with AF.

Finally we ended with a fascinating debate on whether cardiac desynchronization therapy is beneficial in LVAD patients post LVAD implantation. Dr. Melana Yuzefpolskaya argued in favor of CRT for reasons such as reduction in hospital readmissions, reoccurrence of ventricular arrhythmias and increased exercise capacity. Dr. Emma Birks rebutted, arguing that no significant improvement to these areas occurs with CRT.

Who wins the argument ? You decide.

How Italy Lost the "French" Riviera...and the 38th Annual Meeting

Excerpts from Links Contributor Luciano Potena, MD, PhD

[Click here](#) to view the full article

Although Nice is the fifth largest French city, it has hotel room availability second only to Paris. Its "grandeur" is in the heart of Nice, with one of the "Nice"-st and most glamorous coastal areas in Europe. You may find yourself jogging in the dreary weather before the morning sessions, perhaps after a brave night, and just west of the Conference Center, you may cross a wide XVIII Century square with a large fountain surmounted by a tall statue of Giuseppe Garibaldi, the Italian hero. Garibaldi, lead a revolutionary red-shirted army of about a thousand people to establish the kingdom of Italy in 1861. Why does this French city give so much emphasis to this Italian Father?

Garibaldi was born in Nice (Nizza or Nissa as it was called back then), when the city was part of Italy. In time, through secret negotiations with Napoleon III, Bonaparte's nephew, Nice came under French control.

Despite it's past, Nice nowadays is happily French, with fond memories of its Italian ancestry.

*Is that Dr. Glanville?
How on 'Earth' did that
Alien become so
radiant?*



COMING ATTRACTIONS

Preview Symposium 27: DCD lungs – Expanding Utilization

A Polarizing Issue

Believers and non-believers. There can be no doubt that DCD organs can have a substantial effect on expanding the donor pool, but at what cost? One would think warm ischemia adversely affects an allograft, but how can this be assessed, and is this important? And with the resources involved! Donor organ retrieval is a costly business both in terms of human time and dollars spent. All well and good if the transplant proceeds. All aspects of DCD will be explored in this symposium: from the nuts and bolts of starting a program to predicting a successful retrieval outcome, and even pushing the boundaries with uncontrolled DCD!

Preview Oral Session 39: All is Not Lost: Improving Outcomes in Children with a Failing Heart

Can We Get a Passing Grade on a Failing Heart?

This may be one of the highlight sessions for those interested in pediatric heart failure. An elite group of presenters will be discussing a variety of large studies from various databases and consortiums. This will include Dr. Dipchand discussing the first analysis from the international pediatric heart failure registry. Dr. Peng will review the Pedimacs registry and the outcomes of children with congenital heart disease who were implanted with a VAD. This will tie in nicely *from Nice* with a discussion from Dr. Butto on the impact of pre-implant illness severity on outcomes of pediatric VAD patients and Dr. Cantor discussing trends in pediatric mechanical support. Finally, Dr. Lasa will discuss a report from the pediatric critical care consortium regarding acute decompensated heart failure in children and Dr. Schubert will discuss pediatric myocarditis with 3 year outcome data from the German multi-center Prospective Myocarditis Registry (MYKKE). This is a very exciting set of studies with relatively large numbers for pediatric studies and should ensure you turn to your neighbor at the end of these talks and say, "**Orange** you glad you stayed for this amazing session!"



Orange trees in full bloom in rainy Nice.

Preview Oral Session 27: How sick is too sick? The impact of frailty and cognitive function in LVADs

To VAD or not to VAD that is the Question. Whether 'tis Nobler in the Mind to Suffer...

We are very familiar with the dilemmas facing us with the frail heart failure patient. Chronic de-conditioning leads not only to physical deterioration in health but also neurological and psychological functioning, but when is a sick patient too sick to receive an implantable VAD?

Does frailty really affect outcomes such as prolonged ICU stay, hospital readmissions and hospital stay as well as overall survival? If we are brave, or nobler, enough to embark on this sea of troubles, will we really improve patient's lives or are we hastily pushing them off this mortal coil.

This oral session aims to answer some of these questions, as well as present us with data to show us how cognitive and functional capacity and physical frailty maybe improved by choosing the VAD pathway, whilst reminding us to, on occasion, exercise caution in our decision making with the grunts and sweats under a weary life.

Preview: Oral Session 30: Infection: Achilles Heel of Mechanical Circulatory Support

The Search for Answers for a Pesky Problem



Friday's oral session entitled "Infection: Achilles Heel of Mechanical Circulatory Support" is sure to generate new ideas regarding the pesky problem of chronic infection in LVAD patient. The speakers have sought to answer questions not well described in the literature. To begin the session, Anton Peleg, PhD, MPH, FRACP will discuss microbial film formation and the use of in vitro models to character the biofilm formation of various pathogens along the driveline. Next, Mustafa Toma, MD will review the results of a meta-analysis looking at the impact of LVAD related infections on post-transplant outcomes. Andrewas Kyvernitakis, MD will then report the results of a retrospective review of 212 patients evaluating the impact of blood stream infection on time to transplant and mortality in LVAD patients awaiting transplant. Nils Reiss will present a study on the use of telemonitoring of driveline sites to detect and aid in the diagnosis of driveline site infection. Next Sarah Schubert, MD will discuss a study looking at infection rates associated with two different perioperative antibiotic prophylaxis regimens. Finally, Sabarivinoth Rangasamy, MD will discuss an evaluation of Hepatitis C antibody testing pre- & post-LVAD and post heart transplant to determine the prevalence of false positive testing as well as the duration of HCV Ab reactivity. If you find yourself getting frustrated with those pesky LVAD infections, you won't want to miss this informative session.

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