The IXth Makassed Medical Congress

What's New in Medicine for the year 2010?

Movenpick Hotel
Beirut – Lebanon
October 7 – 9, 2010
A Message from the President of the Congress

As part of Makassed Hospital tradition since 1992 and on behalf of Makassed Hospital and the various Makassed Congress committees, we warmly invite you to join us for our IXth congress which will be held in Beirut on October 7 – 9, 2010.

The congress is in joint sponsorship with:
Cleveland Clinic (USA),
The American University of Beirut Medical Center (AUBMC),
and The Saudi Heart Association.

The three - day scientific program includes plenary lectures, multidisciplinary educational interactive sessions, symposia and workshops which will be presented by a number of internationally recognized guest speakers from the United States, Europe, and local and regional speakers. They will address recent updates in various medical fields, including:

Pediatrics, Cardio-Vascular Diseases, Hematology - Oncology and OB-GYN

The IXth Makassed Congress promises to continue the tradition of excellence and to stimulate the interest of its participants from Lebanon and the region.

We look forward to continuing the journey with you this year.

The President
The IXth Makassed Medical Congress

CONGRESS PRESIDENT

Said Sayegh, MD, FACC, FSCAI
Makassed General Hospital.
Beirut, Lebanon.

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**Secretary of the Congress**

Mrs. Ghada Akoum Siblini
The 9th MAKASSED conference offers high standard educational activity for participants. Attendees can enhance their skills, explore practice performance issues, present their own clinical experience, benefit from new and most advanced techniques, participate in sessions addressing specialty and multidisciplinary topics, and interact with renowned local and international experts.

- **Venue:**
The 9th MAKASSED conference will be held at the Movenpick Hotel in Beirut, Lebanon.

- **Objectives:**
After completing this activity, the participant will be able to:

1. Provide current prevention, management and treatment strategies for a broad spectrum of pediatric diseases.
2. Practice current prevention, management and treatment strategies for recent advances and novel techniques in cardiovascular disorders, including ACS, STEMI, acute heart failure, atrial fibrillation in congestive heart failure, and new interventional procedures.
3. Apply current prevention, management and treatment strategies for malignancies of the blood.
4. Use current prevention, management, and treatment strategies for high risk pregnancy and other pregnancy-related issues.

- **Accreditation Statement:**
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The Cleveland Clinic Foundation Center for Continuing Education and American University of Beirut Medical Center. The Cleveland Clinic Foundation Center for Continuing Education is accredited by the ACCME to provide continuing medical education for physicians.

The Cleveland Clinic Foundation Center for Continuing Education designates this educational activity for a maximum of 25.5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Participants claiming CME credit from this activity may submit the credit hours to the American Osteopathic Association Council on Continuing Medical Education for Category 2 credit.

- **Lebanese Order of Physicians Accreditation Statement:**
The Lebanese Order of Physicians designates this educational activity for continuing medical education credits.
• **Target Audience:**
Physicians, Practicing Pediatricians, cardiologists, Obstetricians and Gynecologists, Hematologists and Oncologists, internists, nurses and technicians.

• **GRANTOR ACKNOWLEDGMENT**
The Cleveland Clinic Foundation Center for Continuing Education and the American University of Beirut Medical Center acknowledge educational grants for partial support of this activity from:

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**SOLIFAC SAL**

• **EVALUATION FORM AND CME CERTIFICATE**
The evaluation and CME certificates are available online. In order to receive AMA PRA Category 1 Credit(s)™, please go to [www.ccfcme.org/MyCME](http://www.ccfcme.org/MyCME) to complete the course evaluation and to print your CME Certificate. Once you enter the site, please enter **021213**. The above code is active for 30 days following the symposium.

• **User Instructions:**
If you are a first-time user of “MyCME,” you will need to create a six-digit password comprised of any combination of letters and/or numbers. This will become your permanent log-in for future Cleveland Clinic “MyCME” programs.

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5. Log-in using the information you just provided in the registration form
6. In the “Regularly Scheduled Series” box, enter the code “**021213**”
7. Complete all the fields and hit “submit.”
8. Your official CME certificate will appear. Please print and keep with your permanent files.

**Please note:** Be sure to print your CME certificate and keep for your files. This is your permanent record; no other certificate will be generated.

• **DISCLAIMER**
The information in this educational activity is provided for general medical education purposes only and is not meant to substitute for the independent medical judgment of a physician relative to diagnostic and treatment options of a specific patient’s medical condition. The viewpoints expressed in this CME activity are those of the authors/faculty. They do not represent an endorsement by The Cleveland Clinic Foundation. In no event will The Cleveland Clinic Foundation be liable for any decision made or action taken in reliance upon the information provided through this CME activity.
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International and National Speakers

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The IXth Makassed Medical Congress

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Session 1: Gastroenterology

Moderators: Ziad Naja, MD / Raymond Kamel, MD / Mahmoud Bozo, MD

08:30 - 08:50  Long term outcome of patients with esophageal atresia  
Frederic Gottrand, MD, PhD

08:50 - 09:05  Esophageal and gastric lesions in neonates  
Nahida Rifai, MD

09:05 - 09:20  Congenital Short Bowel Syndrome  
Elie Aramouny, MD

09:20 - 09:35  Constipation in Children: Management & Role of Biofeedback  
Adib Moukarzel, MD

09:35 - 9:45  Discussion

Session 2: Gastroenterology

Moderators: Nahla Khayyat, MD / Bouchra Berro, MD / Maha Abou Alfa, MD

9:45 - 10:00  Updates on Obesity in Children  
Nadine Yazbek, MD

10:00 - 10:20  Evidence Based Guidelines: A Suggested Algorithm for the Diagnostic Workup of Symptomatic and at Risk Children for Celiac disease  
Sibylle Koletzko, MD, PhD

10:20 - 11:00  Eosinophilic Gastroenteropathies: Classification, Diagnosis and Treatment  
Sibylle Koletzko, MD, PhD

Panel Discussion: Pierre Mouawad, MD / Antoine Abi Fadel, MD

11:00 - 11:20  Coffee Break
**Session 3: Intensive Care Neonatology**

**Moderators:** Mariam Rajab, MD / Imad Chokr, MD / Mounzer Cheikh El Haddadine, MD

11:20 – 11:40  Non invasive ventilation in Neonates  
*Laurent Storme, MD, PhD*

11:40 – 12:00  Long term impact of Perinatal environment  
*Laurent Storme, MD, PhD*

12:00 – 12:15  Perinatal Health in Middle East - North Africa  
*Robert Sacy, MD*

12:15 – 12:25  Discussion

**Session 4: Intensive Care Neonatology**

**Moderators:** Ghassan Baassiri, MD / Joumana Alameh, MD / Ali Cheitani, MD

12:25 – 12:40  Survival and Neonatal outcome in Lebanon  
*Khaled Younes, MD*

12:40 – 12:55  Updates in Neonatal infection  
*Joseph Haddad, MD*

12:55 – 13:05  Discussion

13:05 – 14:00  Lunch break

**Session 5: Hepatology / Gastroentorlogy**

**Moderators:** Aziz Koleilat, MD / Maroun Sokhn, MD / Zeina Rida, MD

14:00 – 14:20  Wilson disease in children and adolescents  
*Frederic Gottrand, MD, PhD*

14:20 – 14:40  Updates in viral hepatitis  
*Florence Lacaille, MD*

14:40 – 15:00  Approach to patient with hepatomegaly  
*Florence Lacaille, MD*

15:00 – 15:15  Pediatric Helicopacter Pylori Infection: Overview & Update  
*Firas Semaan, MD*

15:15 – 15:25  Discussion
Session 6: Gastroenterology - Nutrition

Moderators: Zeinat Hijazi, MD / Ziad Bassil, MD / Mouniat Akoum, MD

15:25 - 15:45 Nutrition and Prevention of food allergy
   Dominique Turck, MD, PhD

15:45 - 16:05 Nutrition in patients with inflammatory bowel disease
   Dominique Turck, MD, PhD

16:05 - 16:25 Anti-inflammatory and immunomodulatory effects of n-3 long chain polyunsaturated fatty acids in children
   Frederic Gottrand, MD, PhD

16:25 - 16:45 Nutrition in patients with cystic fibrosis
   Dominique Turck, MD, PhD

16:45 - 17:00 Discussion

17:00 - 17:10 Coffee Break

Session 7: Hematology

Moderators: Ahmad Issa, MD / Rola Farah, MD / Ali Al Matti, MD

17:10 - 17:30 Advances in Pediatric Sickle Cell Disease
   Miguel Abboud, MD

17:30 - 17:50 Update in the management of Idiopathic thrombocytopenic purpura
   Françoise Mazingue, MD

17:50 - 18:10 Iron Deficiency in Children
   Samar Mouakatt, MD

18:10 - 18:30 Indications of bone marrow transplantation in pediatric age group
   Françoise Mazingue, MD

Panel Discussion: Nabil Yassine, MD / Peter Noun, MD

6:30 p.m Opening ceremony at Movenpick
Friday October 8, 2010

Session 1: Pediatric Intensive Care

**Moderators:** Hassan Fakhoury, MD / Ali Zeitoun, MD / Ali Hammoud, MD

- **08:30 - 08:50** Non invasive mechanical ventilation in children with acute respiratory failure. *François Leclerc, MD*
- **08:50 - 09:10** Update on ARDS *Marianne Majdalani, MD*
- **09:10 - 09:30** Septic shock in children: nine years after the concept of early goal directed therapy *François Leclerc, MD*
- **09:40 - 10:00** Panel Discussion: Ahmad Shatila, MD / Joumana Alameh, MD

Coffee Break

Session 2: Pediatric Intensive Care

**Moderators:** Zouheir Bitar, MD / Kamal Kansou, MD

- **10:00 - 11:30** Workshop on Neonatal Childhood Development *Durriyah Sinno, MD / Lama Charaffedine, MD*
- **Panel Discussion:** Mona Alameh, MD / Mohammad Itani, MD / Oulfat El Tourjuman, MD

Lunch Break

Session 3: Maxillo Facial Surgery

**Moderators:** Salman Mroueh, MD / Ikram Tannir, MD / Bassem Abou Merhi, MD

- **14:00 - 14:20** Meet the expert: Update on Maxillo Facial Surgery in Pediatrics *Selim Bennaceur, MD*
- **14:20 - 14:30** Panel Discussion: Lina Chamseddine fawaz, MD / Jihad Khoury, MD

Session 3: Pediatric Urology - Pediatric Nephrology

**Moderators:** Sami Sanjad, MD / Nabil Daoud, MD / Khaled Sayyed, MD / Khalil Osta, MD

- **14:30 - 14:50** Disorders of Sexual Development (DSD) *Alaa El Ghonaimi, MD*
- **14:50 - 15:10** Management of Posterior urethral valves *Alaa El Ghonaimi, MD*
- **15:10 - 15:50** Nephro Protection in Pediatrics *George Deschenne, MD*
- **15:50 - 16:10** Discussion
- **16:10 - 16:30** Coffee Break
- **19:30 - 20:30** Updates on Human Papilloma Virus *Ghassan Dbaibo, MD*

**Moderators:** Mona Naboulsi, MD / Imad Khayyat, MD
Session I: Hematology – Oncology

Moderators: Ali Taher, MD / Tamima Jisr, MD / Walid Mokadam, MD

14:30 - 15:00 Treatment with anti CD20 Antibody (Mabthera)
   Tadeusz Robak, MD

15:00 - 15:30 New oral anticoagulants
   Ismail El Alamy, MD

15:30 - 16:30 Abnormalities of coagulation: Interactive Session -
   Cases discussion
   Ismail El Alamy, MD

16:30 - 16:45 Coffee Break

Session II: Hematology – Oncology

Moderators: Fadi Farhat, MD / Claudia Khayat, MD / Ghida Moharram, MD

16:45 - 17:15 Advances and Challenges in Pediatrics Oncology
   Rima Jubran, MD

17:15 - 17:45 Recent Advances in the treatment of Metastatic Colon Cancer
   Salah Eddin Al Batran, MD

17:45 - 18:15 Multi Modality Therapy for Gastric Cancer
   Salah Eddin Al Batran, MD

18:15 - 18:30 Screening of Breast Cancer in high risk Women with MRI in combination
   with mammography
   Naji Atallah, MD
### Cardiology Session I: Heart failure I

**Moderators:** Nadim Timani, MD / Samir Arnaout, MD / Atika Adhami, MD

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<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>08:45 - 09:05</td>
<td>How to establish a HF program or clinic&lt;br&gt;<em>Hadi Skouri, MD</em></td>
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<td>09:05 - 09:25</td>
<td>Major Co morbidities in Heart Failure:&lt;br&gt;Anemia and Hyponatremia&lt;br&gt;<em>Samer Kabbani, MD</em></td>
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<td>09:25 - 09:45</td>
<td>Bedside assessment and Management of Acute Heart Failure Syndrome&lt;br&gt;<em>Hadi Skouri, MD</em></td>
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<td>09:45 - 10:05</td>
<td>Atrial Fibrillation in HF&lt;br&gt;<em>Samer Nasr, MD</em></td>
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<td>10:05 - 10:25</td>
<td><strong>Panel Discussion:</strong> Hadi Skouri, MD / Samer Kabbani, MD / Samer Nasr, MD</td>
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<td>10:25 - 10:50</td>
<td><strong>Coffee Break</strong></td>
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<tr>
<td>10:50 - 11:10</td>
<td>Echocardiographic criteria in CRT</td>
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<td>11:10 - 11:30</td>
<td>Where, when and how to use ICD-CRT</td>
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<td>11:30 - 11:50</td>
<td>Should we expand CRT to mild Heart Failure?</td>
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<td>11:50 - 12:10</td>
<td>The role of Ablative Therapy in HF</td>
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<td>12:10 - 12:30</td>
<td>Panel Discussion: Elie Chammas, MD / Hassan Mansour, MD / Samer Nasser, MD / Oussama Wazni, MD</td>
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<td>12:30 - 12:50</td>
<td>Left Ventricular Restoration Surgery in Heart Failure</td>
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<td>12:50 - 13:10</td>
<td>LVADs? A bridge or Final Therapy in HF</td>
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<td>13:10 - 13:30</td>
<td>Valve Surgery without Valve Replacement</td>
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<td>13:30 - 15:00</td>
<td>Lunch Break</td>
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Cardiology Session III: Interventional Cardiology

Moderators: Ziad Ghazzal, MD / Samir Alam, MD

15:00 - 15:20 Evolution of Interventional Cardiology
   Spencer King, MD

15:20 - 15:40 TAVI where do we stand in 2010?
   Samir Kapadia, MD

15:40 - 16:00 Multi-Vessel Disease PCI
   Shukri Al - Saif, MD

16:00 - 16:20 Emergent coronary angiogram for graft failure suspicion after CABG:
   The Montreal Heart Institute` s experience
   Gilbert Gosselin, MD

16:20 - 17:00 Meet the experts: Spencer King, MD / Samir Kapadia, MD
   Shukri Al - Saif, MD / Gilbert Gosselin, MD

17:00 - 17:15 Coffee Break

17:15 - 18:30 CD Interactive Session
   Mostafa Youssef, MD

Adjourn
Cardiology Session IV: Clinical and Invasion Cardiology

Moderators: Rabih Azar, MD / Hikmat Khattar, MD / Abdallah Rebeiz, MD

08:00 - 08:20  Optimal anti-platelets therapy in acute coronary syndrome before intervention  
    Gilbert Gosselin, MD

08:20 - 08:40  Treatment of stable IHD  
    Spencer King, MD

08:40 - 09:00  The Radial Approach in PCI  
    Mohammad Zgheib, MD

09:00 - 09:20  Complications in the Cardiac Catheterization Lab  
    Ziad Ghazzal, MD

09:20 - 09:40  Panel Discussion: Gilbert Gosselin, MD / Spencer King, MD / Mohammad Zgheib, MD / Ziad Ghazzal, MD

Cardiology Session V: Cardiac Imaging

Moderators: Georges Ghanem, MD / Bassem Mourany, MD / Habib Dakik, MD

09:40 - 10:00  Role of CCT and CMR in current Cardiology practice  
    Mouaz Al Mallah, MD

10:00 - 10:20  Anatomic vs functional assessment, lessons from FFR  
    Samir Alam, MD

10:20 - 10:40  Routine versus niche indication for IVUS in PCI  
    Samih Lawand, MD

10:40 - 11:00  IVUS in DES failures  
    Lisette Okells Jensen, MD

11:00 - 11:15  Panel Discussion: Mouaz Al Mallah, MD / Samir Alam, MD / Samih Lawand, MD / Lisette Okells Jensen, MD

11:15 - 11:30  Coffee Break
Cardiology Session VI: Interventions in Structural and peripheral Arterial Disease

Moderators: Samer Kabbani, MD / Ismail Khalil, MD / Talal Kassar, MD

11:30 - 11:50  Management of hemopericardium during Mitral Valvuloplasty  
George Ghanem, MD

11:50 - 12:10  Mitral clip EVEREST did it reach the peak?  
Samir Kapadia, MD

12:10 - 12:30  Update on TEVAR  
Fadi Haddad, MD

12:30 - 12:45  CTO in PAD  
Mohammad Zgheib, MD

12:45 - 14:00  CD Interactive Session  
Ziad Ghazzal, MD

Adjourn
## Session I: GYN-Oncology

**Moderators:** Joseph Abboud, MD / Faysal El Kak, MD / Daved Atallah, MD / Janah El Hassan, MD

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<tr>
<td>8:40</td>
<td>Update on guidelines for cancer screening.</td>
<td>Adnan Munkarah, MD</td>
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<tr>
<td>9:00</td>
<td>A review of malignant ovarian germ cell tumors.</td>
<td>Adnan Munkarah, MD</td>
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<tr>
<td>9:20</td>
<td>Update on gynecological cancer in Lebanon.</td>
<td>Muhieddine Seoud, MD</td>
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<td>9:40</td>
<td>Surgical staging of endometrial cancer.</td>
<td>Adnan Munkara, MD</td>
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<td>10:00</td>
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## Session II: High Risk Pregnancy

**Moderators:** Zulfikar Hashash, MD / Said Mikawi, MD / Ihab Usta, MD

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<tr>
<td>10:40</td>
<td>Recent French guidelines for twin gestation.</td>
<td>Phillipe Deruelle, MD</td>
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<tr>
<td>11:00</td>
<td>Delayed interval delivery: our case series at MGH.</td>
<td>Mohammad Ramadan, MD</td>
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<td>11:20</td>
<td>A Sonographic short cervix: clinical significance and treatment.</td>
<td>Sonia Hassan, MD</td>
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<td>11:40</td>
<td>Discussion</td>
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<td>12:00</td>
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## Session III: High Risk Pregnancy

**Moderators:** Toufic Eid, MD / Abdallah Adra, MD / Rabih Chahin, MD

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<td>12:20</td>
<td>Preterm birth examination of the uterine cervix: Diagnosis and pitfalls</td>
<td>Sonia Hassan, MD</td>
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<tr>
<td>12:40</td>
<td>Timing and delivery for the pregnant with gestational diabetes.</td>
<td>Phillipe Deruelle, MD</td>
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<td>13:00</td>
<td>Preterm birth prevention: What is progesterone and how does it work?</td>
<td>Sonia Hassan, MD</td>
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<td>13:20</td>
<td>Discussion</td>
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**Cardiology Symposia (NON-CME)**

**Friday, 8 October, 2010**

13:30-14:30  **The Therapeutic imperative for optimal LDL-c and comprehensive lipid management in high risk patients**  
*Sponsored by MSD*  
Sami Kabbani, MD

18:30-19:30  **DRI: A Novel in the Management of Hypertension**  
*Sponsored by Novartis*  
Samir Mallat, MD

Current and future perspectives in the management of hypertension and cardiovascular diseases  
Said Sayegh, MD

20:00-20:30  **Ant platelet therapy in ACS: Where do we stand?**  
*Sponsored by Algorithm*  
Rabih Azar, MD

**Saturday, 9 October, 2010**

13:30-14:30  **Dual antiplatelet therapy-An “Evergreen” in clinical cardiology**  
*Sponsored by Sanofi Aventis*  
Hans-Jürgen Rupprecht, MD
OESOPHAGEAL ATRESIA: RECENT ADVANCES AND LONG TERM OUTCOME

Frederic Gottrand MD, PhD

Oesophageal atresia is a rare malformation with an incidence of 1/3000. Recent advances in surgery and neonatal care have provided a better prognosis, the survival rate of infants born with oesophageal atresia has dramatically improved over the last decade increasing from 80% to more than 95%. However oesophageal atresia is definitively not only a neonatal surgical issue but a long lasting disease through adulthood since many problems (growth, respiratory, digestive, feeding difficulties) persist on the long term. At long term follow-up very few patients are free of any digestive symptoms, the most frequent manifestations being dysphagia and gastro-oesophageal reflux disease. Recent data have shown that the quality of life of these patients is lower than in healthy controls. Many questions remain about the future of these patients since several cases of Barrett oesophagus and oesophageal adenocarcinoma have been reported in young adults with oesophageal atresia. The high frequency of late sequelae in oesophageal atresia justifies regular and multidisciplinary follow-up through adulthood.

WILSON DISEASE

FREDERIC Gottrand MD, PhD

Wilson disease (WD) is an autosomal recessive disease with a prevalence of 30 affected individuals per million due to mutation of ATP7B gene, that encodes a metal-transporting P-type adenosine triphosphatase (ATPase), which is expressed mainly in hepatocytes and functions in the transmembrane transport of copper within hepatocytes. Absent or reduced function of ATP7B protein leads to decreased hepatocellular excretion of copper into bile. This results in hepatic copper accumulation and injury. Eventually, copper is released into the bloodstream and deposited in other organs, notably the brain, kidneys, and cornea. Failure to incorporate copper into ceruloplasmin is an additional consequence of the loss of functional ATP7B protein. The hepatic production and secretion of the ceruloplasmin protein without copper, apoceruloplasmin, result in the decreased blood level of ceruloplasmin found in most patients with WD due to the reduced half-life of apoceruloplasmin.

For the pediatric hepatologist, WD is often a diagnosis challenge, since clinical features are usually polymorphic and non specific. Children may be entirely asymptomatic, with hepatic enlargement or abnormal serum aminotransferases found only incidentally. Some patients have a brief clinical illness resembling an acute viral hepatitis, and others may present with features indistinguishable from autoimmune hepatitis. Some present with only biochemical abnormalities or histologic findings of steatosis on liver biopsy. Many patients present with signs of chronic liver disease and evidence of cirrhosis, either compensated or decompensated. Patients may present with isolated splenomegaly due to clinically inapparent cirrhosis with portal hypertension. WD may also present as acute liver failure with an associated Coombs-negative hemolytic anemia and acute renal failure. Some patients have transient episodes of jaundice due to hemolysis. Low-grade hemolysis may be associated with WD when liver disease is not clinically evident. Extrahepatic manifestations (ie neurological, psychiatric, renal manifestations) present later than the liver disease and are rarely observed during childhood.
The age at which WD may present is younger than generally appreciated, though the majority present between ages 5 and 35. WD is increasingly diagnosed in children younger than 5 years old, the youngest case reported being 2 year-old, and cirrhosis reported in a 3-year-old child.

A combination of clinical findings and biochemical testing is usually necessary to establish the diagnosis of WD. Kayser-Fleischer rings represent deposition of copper in Descemet’s membrane of the cornea and required a slit-lamp examination by an experienced observer to be identified. They are not entirely specific for WD, because they may be found in patients with chronic cholestatic diseases and are usually absent in children with hepatic presentation. Serum ceruloplasmin is usually decreased in patients with WD but can be elevated by inflammation. Low ceruloplasminemia can be observed in renal or enteric protein loss, in severe end-stage liver disease as well as in Menkes disease and aceruloplasminemia. Although a disease of copper overload, the total serum copper (which includes copper incorporated in ceruloplasmin) in WD is usually decreased in proportion to the decreased ceruloplasmin in the circulation. Increased 24-hour urinary excretion of copper is probably the best non invasive diagnosis tool for the diagnosis of WD and should be obtained in all the patients. Elevated urinary copper excretion has been reported in autoimmune hepatitis and in heterozygotes. In these cases or when WD is suspected and urinary copper excretion is normal, urinary copper excretion with D-penicillamine administration may be a useful diagnostic adjunctive test. Hepatic copper content ≥250 µg/g dry weight remains the best biochemical evidence for WD, but required liver biopsy that is an invasive procedure. It however allows obtaining histopathological information for both diagnosis (steatosis and excluding other etiologies) and prognosis (fibrosis, cirrhosis). Molecular genetic studies are becoming available for clinical use. Pedigree analysis using haplotypes based on polymorphisms surrounding the WD gene requires the identification of a patient within the family (the proband) by clinical and biochemical studies. After the mutation or haplotype, based on the pattern of dinucleotide and trinucleotide repeats around ATP7B, is determined in the proband, the same specific regions of the DNA from first-degree relatives can be tested to determine whether they are unaffected, heterozygous, or indeed patients. Direct mutation analysis is feasible but interpretation of results can sometimes be difficult because most patients are compound heterozygotes with a different mutation on each allele. Currently, more than 300 mutations of ATP7B have been identified, but not all gene changes have been established as causing disease.

First-degree relatives of any patient newly diagnosed with WD must be screened for WD. Assessment should include: physical examination; serum copper, ceruloplasmin, liver function tests including aminotransferases, albumin, and conjugated and unconjugated bilirubin; slit-lamp examination of the eyes for Kayser-Fleischer rings; and basal 24-hour urinary copper. Molecular testing for ATP7B mutations or haplotype studies should be obtained and may be used as primary screening. Treatment should be initiated for all individuals greater than 3 years old identified as patients by family screening.

Treatment for WD is a lifelong pharmacologic therapy; liver transplantation, which corrects the underlying hepatic defect in WD, is reserved for severe or resistant cases. Failure to comply with therapy – as observed in some adolescents- lead to significant progression of liver disease and liver failure in 1-12 months following discontinuation of treatment, resulting in death or necessitating liver transplantation. The approach to treatment is dependent on whether there is clinically-evident disease or laboratory or histological evidence of aggressive inflammatory injury, whether neurologic or hepatic, or whether the patient is identified prior to the onset of
clinical symptoms. D-penicillamine is a chelating agent, and remains the first line treatment of WD. Treatment should be increased progressively and tolerance carefully monitored since many side effects have been reported (including early sensitivity reactions, nephrotoxicity, lupus-like syndrome, thrombocytopenia or total aplasia, dermatological manifestations. Trientine (triethylene tetramine dihydrochloride) is also a chelator effective in the treatment for WD and is indicated especially in patients who are intolerant of penicillamine. Trientine has few side effects. Zinc interferes with the uptake of copper from the gastrointestinal tract. Zinc has very few side effects. Although zinc is currently reserved for maintenance treatment, it has been used as first-line therapy, most commonly for asymptomatic or presymptomatic patients where it appears to be equally effective as penicillamine but much better tolerated. Foods with very high concentrations of copper (shellfish, nuts, chocolate, mushrooms, and organ meats) generally should be avoided, at least in the first year of treatment.

Children with acute liver failure due to WD require liver transplantation, which is life-saving. A scoring system help determine which patients with acute hepatic presentations will not survive without liver transplantation, including serum bilirubin, serum aspartate aminotransferase, and prolongation of prothrombin time above normal. Until transplantation can be performed, plasmapheresis and hemofiltration and exchange transfusion or hemofiltration or dialysis may protect the kidneys from copper-mediated tubular damage. Albumin dialysis and Molecular Adsorbents Recirculating System ultrafiltration device can stabilize patients with acute liver failure due to WD and delay, but not eliminate, the need for transplantation.[

RECENT ADVANCES AND PERSPECTIVES:
Neurologic manifestations present most often in the third decade of life, but earlier subtle findings may appear in pediatric patients, including changes in behavior, deterioration in schoolwork, or inability to perform activities requiring good hand-eye coordination. Recent recommendations highlight the need of systematic neurological evaluation in childhood including eventually brain imaging procedure (computerized tomography and/or resonance magnetic imaging).

Direct assessment of serum non-ceruloplasmin bound copper concentration is a promising tool both for diagnosis and monitoring treatment of WD. Non invasive tests for assessing liver fibrosis (fibrotest, fibroscan…) are promising tools to monitor evolution of liver disease. 


1. WD should be considered in any individual between the ages of 3 and 55 years with liver abnormalities of uncertain cause. Age alone should not be the basis for eliminating a diagnosis of WD (Class I, Level B).
2. WD must be excluded in any patient with unexplained liver disease along with neurological or neuropsychiatric disorder (Class I, Level B).
3. In a patient in whom WD is suspected, Kayser-Fleischer rings should be sought by slit-lamp examination by a skilled examiner. The absence of Kayser-Fleischer rings does not exclude the diagnosis of WD, even in patients with predominantly neurological disease (Class I, Level B).
4. An extremely low serum ceruloplasmin level (<50 mg/L or <5 mg/dL) should be taken as strong evidence for the diagnosis of WD. Modestly subnormal levels suggest further evaluation is necessary. Serum ceruloplasmin within the normal range does not exclude the diagnosis (Class I, Level B).
5. Basal 24-hour urinary excretion of copper should be obtained in all patients in whom the diagnosis of WD is being considered. The amount of copper excreted in the 24-hour period is typically >100 μg (1.6 μmol) in symptomatic patients, but finding >40 μg (>0.6 μmol or >600 nmol) may indicate WD and requires further investigation (Class I, Level B).

6. Penicillamine challenge studies may be performed for the purpose of obtaining further evidence for the diagnosis of WD in symptomatic children if basal urinary copper excretion is <100 μg/24 hours (1.6 μmol/24 hours). Values for the penicillamine challenge test of >1600 μg copper/24 hours (>25 μmol/24 hours) following the administration of 500 mg of D-penicillamine at the beginning and again 12 hours later during the 24-hour urine collection are found in patients with Wilson disease. (Class I, Level B).

7. Mutation analysis by whole-gene sequencing is possible and should be performed on individuals in whom the diagnosis is difficult to establish by clinical and biochemical testing. Haplotype analysis or specific testing for known mutations can be used for family screening of first-degree relatives of patients with WD. A clinical geneticist may be required to interpret the results (Class I, Level B).

8. WD should be considered in the differential diagnosis of patients presenting with nonalcoholic fatty liver disease or have pathologic findings of nonalcoholic steatohepatitis (Class IIb, Level C).

9. WD should be suspected in any patient presenting with acute hepatic failure with Coombs-negative intravascular hemolysis, modest elevations in serum aminotransferases, or low serum alkaline phosphatase and ratio of alkaline phosphatase to bilirubin of <2 (Class I, Level B).

10. First-degree relatives of any patient newly diagnosed with WD must be screened for WD (Class I, Level A).

11. Initial treatment for symptomatic patients should include a chelating agent (D-penicillamine or trientine). Trientine may be better tolerated (Class I, Level B).

12. Patients should avoid intake of foods and water with high concentrations of copper, especially during the first year of treatment (Class I, Level C).

13. Treatment of presymptomatic patients or those on maintenance therapy can be accomplished with a chelating agent or with zinc. Trientine may be better tolerated (Class I, Level B).

14. Patients with acute liver failure due to WD should be referred for and treated with liver transplantation immediately (Class I, Level B).

15. Patients with decompensated cirrhosis unresponsive to chelation treatment should be evaluated promptly for liver transplantation (Class I, Level B).

16. Treatment is lifelong and should not be discontinued, unless a liver transplant has been performed (Class I, Level B).

17. For routine monitoring, serum copper and ceruloplasmin, liver biochemistries and international normalized ratio, complete blood count and urinalysis (especially for those on chelation therapy), and physical examination should be performed regularly, at least twice annually. Patients receiving chelation therapy require a complete blood count and urinalysis regularly, no matter how long they have been on treatment (Class I, Level C).

18. The 24-hour urinary excretion of copper while on medication should be measured yearly, or more frequently if there are questions on compliance or if dosage of medications is adjusted. The estimated serum non-ceruloplasmin bound copper may be elevated in situations of nonadherence and extremely low in situations of overtreatment (Class I, Level C).
LONG CHAIN POLUNSATURATED FATTY ACIDS AND INFLAMMATION

FREDERIC GOTTRAND MD, PHD

Inserm U995, IMPRT/IFR 114, Faculty of Medicine and University Lille 2, Lille, France

Department of Pediatrics, Jeanne de Flandre University Hospital, Place de Verdun, 59037 Lille, France.

(n-3) LCPUFA exerts their immunomodulatory activities at different levels. (n-3) LCPUFA metabolites induce eicosanoid and docosanoid production, alter gene expression and modify lipid raft composition altering T cell signalling all contribute to immunological functional changes. However the respective part of these mechanisms and the type of T or other immunological cells involved remain unclear at present. Moreover effect of (n-3) LCPUFA on immune system may vary according to dose, time of exposure, and profile of the immune system (T-helper Th1/Th2). Biological effects of (n-3) LCPUFA are also mediated through their direct anti-inflammatory properties. Most of the interventional studies have been performed for prevention of allergy (in infants) and prevention/modulation of several infectious and inflammatory diseases (ie dermatologic, digestive, rheumatologic, as well as in immunocompromised patients). They all confirmed influence on T cell function and cytokine profiles but clinical beneficial effects are more conflicting.

Mechanism of action and biological functions of LCPUFA

Several molecular mechanisms whereby (n-3) LCPUFA act in the modulation of many biological functions, have been demonstrated. These mechanisms include i) alteration of cell membrane fluidity, ii) alteration of the raft lipid composition, iii) effects on eicosanoids, and iv) modification of transcription factor activity.

Cell membrane properties

The major LCPUFA in cell membranes is AA. LCPUFA play an important role in membrane structure and modification in the ratio (n-6)/(n-3) can thus affect membrane protein function. FA composition of membranes affects their fluidity. Furthermore, the FA environment likely affects the binding of many proteins to their receptor localized at the cell surface.

Raft lipid composition

Closely related to the cell membrane are microdomains called lipid rafts. These domains within the plasma membrane represent a plateform that compartmentalize and facilitate protein-protein interactions and it has been suggested that LCPUFA composition of the lipid rafts may modulate these interaction and/or affect protein co- and post-translational lipidation like N-myristylation, which subsequently may modify the protein targeting to lipid rafts.

Effects on eicosanoids and dosocanoids

The LCPUFA, particularly EPA (n-3) and AA (n-6), are converted into eicosanoids, which are lipids that modulate inflammatory and immune responses. However, AA is the major precursor for eicosanoids because AA if found in higher levels in cell membranes compared to EPA. One particularity is that LCPUFA of the two series compete as substrates, after being released from membrane phospholipids by various phospholipases, for cyclooxygenases to produce
prostaglandins and thromboxanes and lipoxygenases (high activity in neutrophils) to produce leukotrienes, hydroxy FA and lipoxins. The simple picture is that EPA-derived eicosanoids are lipid mediators with anti-inflammatory effects while AA-derived eicosanoids have more potent biologic functions with pro-inflammatory effects. However, some AA-derived eicosanoids like prostaglandine E2 (PGE2) may also show anti-inflammatory properties. The thromboxane synthetase synthesises the thromboxane A2 (TXA2), which is derived from AA and TXA3, which is derived from EPA. TXA2 is a vasoconstrictor and a potent aggregator while TXA3 is biologically less active than TXA2.

In addition to production of eicosanoids, EPA and DHA are precursors to potent bioactive mediators that possess both anti-inflammatory and protective properties. These mediators were coined resolvins, docosatrienes, and protectins as general classes, since each possesses unique chemical structures that are features of the new chemical classes and are biosynthesized by new pathways. Resolvins are specific lipid-derived mediators initiated by lipoxygenases that are involved in the resolution phase of acute inflammation. Docosatrienes contain conjugated triene structures generated from DHA as a defining feature. The protectins comprise docosatrienes and resolvins of the D serie that have both a neuroprotective and an anti-inflammatory function.

**Modification of transcription factor activity**

PUFA control gene transcription by two mechanisms. In the first one, LCPUFA and their metabolites interact with G protein-coupled receptor (GPCR). It has been reported that a deficient diet for (n-3) PUFA reduced the signalling efficiency in rat retinal rod outer segments. It has also been shown that PGE2 and leukotriene B4 (LTB4) interact with various GPCR implicated in physiological processes and inflammation in host defense.

In the other mechanism, PUFA control gene transcription by direct interaction of PUFA with transcription factors. Several experimental data showed in cell culture that (n-3) LCPUFA inhibit nuclear factor kB (NfkB) directly though decreased degradation of IkB, the inhibitory subunit of NfkB. LCPUFA modulates also gene transcription activity via peroxysome proliferator activated receptors (PPAR). PPAR activation controls several genes implicated in lipid metabolism.

It has been reported that EPA and DHA are natural ligands of PPAR and that eicosanoids are much stronger activator of PPAR than LCPUFA. It has also been shown that DHA can bind retinoid X receptors (RXR), which normally form homodimers or heterodimers with retinoic acid receptors (RAR). These receptors play multiple roles in the lipid metabolism and catabolism and binding of FA stimulates an exchange of co-activators for co-repressors on the chromatin-bound receptor.

**Anti-inflammatory properties**

(n-3) LCPUFA have anti-inflammatory properties via various mechanisms. EPA and DHA, overall suppress eicosanoids associated with systemic inflammatory response syndrome and shift to the less biologically active 3-series prostaglandins and 5-series leukotrienes. In addition to (n-3) LCPUFA modulation of eicosanoids, a novel group of mediator termed E-series resolvins formed from EPA by cyclooxygenase (COX)-2 have been shown in cell culture and animal models to be anti-inflammatory. Other mechanisms have been demonstrated including surface receptor modulation, binding to transcription factors (eg NfkB), gene interactions and generation of growth factors.
Effects of LCPUFA on the immune system

Today it is clear that LCPUFA play a key role in the modulation of the immune system in many diseases. In addition to pro-inflammatory effects, prostaglandin E\textsubscript{2} –produced from (n-6) PUFA– exerts effect on the Th1/Th2 balance. It decreases the production of the Th1-type cytokines interferon (IFNg) and interleukin 2 (IL-2), enhances the production of Th2-type cytokines IL-4 and IL-5, and promotes IgE synthesis by B-cells.

(n-6) PUFA are essential in relation to a thymus/thymocyte accretion of AA in early development, and the high requirement of lymphoid and other cells of the immune system for AA and LA for membrane phospholipids. Low (n-6) PUFA intakes enhance whereas high intakes decrease certain immune functions. AA metabolites can limit or regulate cellular immune reactions and can induce deviation toward a Th2-like immune response. By competition with AA for several enzymatic pathways (ie prostaglandin production), (n-3) LCPUFA influence the Th1/Th2 balance.

As mentioned above, (n-3) LCPUFA induce also direct alteration of gene expression through modification of transcription factor activity such as nuclear factor kappa B (NFkB). NFkB plays a role in inducing a range of inflammatory genes including cyclooxygenase (COX-2), intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, tumour necrozing factor (TNF-a), IL-1b, inducible nitric oxide synthase (iNOS), acute phase protein, in response to inflammatory stimuli. (n-3) LCPUFA decrease the activity of NFkB, via the inhibition of I\textk\textsubscript{B}, the inhibitory subunit of NFkB. (n-3) LCPUFA are natural ligands of nuclear receptors such as PPAR\textalpha and g PPAR are ligand-activated transcription factors present in a variety of cell types including inflammatory cells. (n-3) LCPUFA have also been shown to influence the expression of adhesion molecules (ICAM-1, VCAM-1 and E-selectin). Adhesion molecules direct the leucocyte-endothelium interactions, transendothelial migration of leucocytes and leucocyte trafficking in general.

LCPUFA and immune function in early life

A few studies have suggested that early intervention with (n-3) LCPUFA may influence immune functioning and may affect the cytokine phenotype during development. Some of these studies demonstrated that early exposure to (n-3) LCPUFA during foetal and neonatal period has a prolonged impact on Th1/Th2 immune responses and T cell cytokine profiles. Maternal fish oil supplementation during the first 4 months of lactation resulted in an increased production of lipopolysaccharide-induced IFNg upon stimulation in 2.5 y old children, whereas IL-10 production was similar than the olive oil group. The IFN-g/IL-10 ratio was two-fold higher in the fish oil group and was positively correlated with EPA/DHA in erythocytes at 4 months. Adding DHA + AA to a standard infant formula for healthy infants increased the proportion of antigen mature (CD45RO+) CD4+ cells, improved IL-10 production, and reduced IL-2 production to levels not different from those of human milk-fed infants. Healthy term infants receiving at age 2 weeks the same formula supplemented with ARA and DHA produced less TNF-a (unstimulated) and had a higher CD3+CD44+ cells before stimulation with phytohemagglutinin and higher CD11c+ cells post-stimulation. Compared with formula fed controls, the infants receiving LCPUFA had an immune cell distribution (higher percentage CD3+CD44+ and CD4+CD28+ cells) and cytokine profile (lower production of TNF-a post-stimulation) that did not differ from breast-fed infants.

All these results demonstrate that early diet influences both the presence of specific cell types and function of infant blood immune cells.
**Perspectives**

There are strong data from experimental studies showing that (n-3) LCPUFA alter immune cells function and could influence immune system. (n-3) LCPUFA may influence the number and/or activity of certain subpopulations of cells which, could affect subsequent maturation and polarization of the immune system. Application during infancy should be prevention of infection and allergy. However mechanisms involved are complex since several modes of action have been described (reduction of synthesis of some type of eicosanoids, modification of gene expression, and modification of signalling process). Effects on immune system may also vary according to age and polarization Th1/Th2 immune status, dose of (n-3) LCPUFA, and type of T cells. Effects of (n-3) LCPUFA on naturally or adaptative Treg cells is a promising but largely unexplored area of research. Supplementation of the maternal diet in pregnancy or early childhood with (n-3) PUFA may provide a non-invasive intervention with significant potential to prevent the development of allergic and possibly other immune-mediated diseases. Preventive effect deserves further studies in several inflammatory processes. One promising perspective could also be association (n-3) PUFA with other pharmacological or nutritional approach in preventing or limiting immune and inflammatory diseases.

**Reference List**

ESOPHAGEAL AND GASTRIC LESIONS IN NEONATES
NAHIDA RIFAI, MD

The occurrence of severe lesions in the upper gastrointestinal tract in the neonatal period is relatively frequent. Upper gastrointestinal bleeding from mucosal lesions has been seen in 6 – 12% of children in intensive care. The precise etiology of such lesions is poorly substantiated. Any stressful event during pregnancy or labor or soon after birth may be inducive of mucosal lesions. Bleeding from the upper gastrointestinal tract can occur in the setting of hypotension, respiratory insufficiency, renal failure, sepsis, and in the presence of fetal distress. Antacids and anti-ulcer medications taken during pregnancy may play a role. Perinatal indomethacin exposure constitutes another additional risk factor. The technical improvement in pediatric gastrointestinal endoscopy allowed the evaluation of esophageal and/or gastric lesions in neonates even in very low birth weight infants. The key of prevention and treatment of stress-induced gastric lesions is the optimal intensive care. Breast feeding may play a protective role against severe lesions in neonates. Some of them may benefit from ulcer prophylaxis.

CONGENITAL SHORT BOWEL SYNDROME: REPORT OF THREE CASES
*Raphah Borghol MD, ‡Dany Hamod MD, §Reva Matta MD,
†Pierre Mouawad MD, *Nabil Diab MD, ‡Elie Aramouni MD

Congenital short bowel syndrome (CSBS) is a rare entity compared to the acquired form. We present three cases of CSBS manifested in the neonatal period by complicated severe necrotizing enterocolitis (NEC), and pseudoobstruction. The diagnosis was suspected by barium intestinal series swallow, and confirmed by surgical laparotomy. The management consists of total parenteral nutrition (TPN), with one still living case and two fatal outcomes secondary to septicemia from the central catheter line, and multiorgan failure. In the literature, we note rare reported cases of such short congenital small bowel length. Normally the small bowel in neonates measures around 240 cm, in our cases the length were 30 cm, 58 cm, and 75 cm. The factors in the pathogenesis in these cases are mostly related to antenatal ischemic events, such as intrauterine volvulus, in utero infarction of bowel, defective neuroenteric system, and mechanical etiology such as delayed return of fetal gut into the abdomen due to gastroschisis. The management and prognosis depends mostly on the length of the small bowel and other factors related to the age of the patient, and their general status.

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SUCCESSFUL USE OF BIOFEEDBACK FOR THE TREATMENT OF DEFECATION DISORDERS AND VESICO-SPHINCTERIC DYSSYNERGIA IN CHILDREN

ADIB MOUKARZEL

To evaluate the effectiveness of biofeedback in children, we retrospectively reviewed clinical and manometric parameters of outpatients referred to our Pediatric GI private office in two locations. They were divided into 3 groups: Group 1 - functional constipation or encopresis (n = 42): biofeedback indicated when symptoms fail to respond to 12 months of conservative treatment or presence of high EMG activity in pelvic floor muscles with evidence of rectal or anal canal pain. A pelvic floor dyssynergy (obstructive defecation or anismus, failure to relax the pelvic floor muscles during attempts to defecate) was present in 75% of these children. Group 2 (n = 23) included children with fecal incontinence following surgery for imperforated anus, Hirschsprung’s disease or meningomyelocele. Biofeedback training was directed towards teaching sphincter contraction, improving sensory impairment and coordination of sensation with squeeze or defecation. Group 3 included 14 subjects with vesicosphincteric dysynergia. The principle of therapy and the technique used are the same as for the ano-rectal biofeedback. Using a computerized device that measures pelvic floor muscle strength and sphincter tone by pressure sensors and/or stick-on surface EMG electrodes, the child is showed how to propel kegel exercises and relax muscles tone by watching a color TV monitor and listening to the sound generated. We have developed for young children a special display based on commonly used video or computer games. The treatment continued at home included keeping toilet diaries, home exercises with the use of a Foley catheter, and a diet modification.

Results:
The mean age was 8.2 ±1.4 years (range 4-16). The mean number of biofeedback sessions was 7.3 ± 2.8. Group 2 needed significantly more sessions (9.4 ± 2.4, p< 0.05) than group 1 or 3. Overall, there was a significant improvement in 96%; 73% became completely asymptomatic. The improvement was maintained for 25 ± 6 months. There was a significant decrease in the sensation threshold (34.6 ±9.8 to 4.5 ± 2.5 ml). When present, there was a significant (p<0.005) decrease in the number of accidents/day (3.1 ± 0.4 to 0.2 ± 0.3). In group 1, the pelvic floor dysynergia and the high EMG activity was corrected in 96% of the cases. The functional rectal pain disappeared within 3 sessions. In group 2, there was a significant decrease in the sensation threshold and a significant increase in squeeze pressure (32 ± 2.3 to 85 ± 12 mmHg), and total duration of the squeeze (6.7 ± 0.9 to 32 ± 8 sec). In group 3, symptoms improved or disappeared in 89% of children.

Conclusions:
Biofeedback is useful for the treatment of defecation disorders and vesico-sphincteric dyssynergia in children. We report its success in very young children (4 year old) and its availability in Lebanon.

Keywords:
Biofeedback, constipation, incontinence, encopresis
UPDATES IN PEDIATRIC OBESITY: WHY SHOULD WE CARE?

Nadine H Yazbeck, MD

Obesity is currently the single most prevalent disease in childhood; obese children constitute a significant portion of every primary care and specialty practice in Pediatrics. It is of utmost importance to use the percentile BMI for age and gender as the most appropriate and easily available method to screen and diagnose overweight and obesity in the general pediatrician’s clinic.

In this talk I will quickly go over the different possible etiologies of this global epidemic and review the wide spectrum of complications including the respiratory, gastroenterology, endocrinology and psychological problems.

I will stress mainly on the treatment with its three primary components: the dietary modifications, the increase in physical activity and the behavioral modifications for both the patient and the family.

Superficially, it would seem that the treatment of overweight is straight forward: counsel children to eat less and be more physically active. In practice, treatment of childhood overweight is time consuming, frustrating, difficult and expensive. The considerable challenges of addressing and treating obesity throughout the life cycle have led to an increase in interest in preventing obesity altogether.

EOSINOPHILIC COLITIS

Sibylle Koletzko MD and Haunersches Kinderspital, MD

Eosinophilic colitis (EC) is a descriptive term for a condition characterized by eosinophilic infiltration of one or more layers of the total colon or some segments, but it is not a single entity. Primary EC is a manifestation within the eosinophilic gastrointestinal disease (EGID) spectrum and occurs in all age groups, particularly during infancy. Primary EC needs to be distinguished from secondary forms, due to different infectious diseases, particularly helminth or parasitic infections, inflammatory bowel disease, hyper-eosinophilic syndrome and drugs such as rifampicin, gold or non-steroidal anti-inflammatory drugs. More recently secondary EC has been recognized in a proportion of children after liver transplantation as a side effect of immunosuppression with tacrolimus.

The clinical spectrum varies from hardly any symptoms to rectal bleeding, dysmotility with constipation or diarrhoea, abdominal pain or even ascitis. A peripheral eosinophilia is common; however a normal differential blood count does not exclude EC. The diagnostic work up depends on age, but infections and drug-induced EC should be ruled out. In breastfed or formula fed infants with hematochezia endoscopy is rarely needed, because in most cases the condition is self-limiting or resolves after dietary intervention. Colonoscopy should be performed if symptoms persist, or in older children to differentiate from secondary forms, particularly inflammatory bowel disease. The macroscopic appearance may vary from normal to aphthous ulcerations with or without lymphatic hyperplasia. Eosinophilic infiltrations may be segmental or continuous.

Treatment includes nutritional exclusion and corticosteroids. In breast-fed infants the elimination of cow’s milk protein from the maternal diet or addition of supplementary feeding after 17 weeks
of age may be sufficient. Formula fed infants should be switched to a therapeutic formula based on extensively hydrolysed protein or amino acids only. Certain probiotics may be helpful to improve gut microbiota, however data are insufficient to give recommendations. In older children, extensive allergy testing for food allergy should be performed including a few food diet or elemental diet with food challenges. If no offending food can be identified systemic prednisolone or slow release budesonide are effective, but relapse may appear after weaning.

Literature

NON INVASIVE VENTILATION IN THE NEONATE

Laurent STORME MD

Nasal Continuous Positive Airway Pressure (NCPAP) is widely used in Neonatal Intensive Care Units, especially in premature infants. Clinical trials have shown that NCPAP may benefit preterm infants with respiratory distress. Little is known about the mechanisms involved in NCPAP-induced improvement of respiratory function. NCPAP may reduce apnea in preterm infants by splinting the pharyngeal airway, thereby relieving upper airway obstruction. Furthermore, NCPAP improves the synchrony of thoracic and abdominal motions and increases the end-expiratory lung volume. In addition, NCPAP alters the dynamic behavior of the respiratory system in premature neonates.

NCPAP requires a device for pressure generation and a nasal interface. Many NCPAP devices can be used to apply a constant pressure at the airway opening, including mechanical ventilator, underwater tube called “bubble CPAP”, or the Infant-Flow® Driver. Several nasal interfaces have also been developed such as nasal mask, nasal cannulae, nasal prongs of varying length and size. Compared to conventional constant-flow NCPAP devices, Infant-Flow® NCPAP uses a dedicated driver and generator to adjust the gas flow throughout the respiratory cycle. Infant-Flow® NCPAP is generated by converting kinetic energy from a jet of humidified gas. More recently, a positive distending pressure was observed when supplemental O_2 is delivered via nasal cannulae. As Infant-Flow® system, high flow through nasal cannulae generates a jet of fresh gas into the upper airways. Benefits of nasal cannulae gas flow on the respiratory function have been suggested in preterm infants. Thoracoabdominal asynchrony decreases when gas flow is delivered via nasal cannulae. Furthermore, nasal cannulae were found as effective as conventional constant-flow NCPAP in the prevention of apnoea of prematurity. However, the optimal NCPAP method is presently unknown.
LONG-TERM IMPACT OF PERINATAL ENVIRONMENT

Laurent Storme MD

The main causes of morbidity and mortality have perinatal environmental origins. Early intrauterine and postnatal development is a unique period of vulnerability during which adverse environmental stressors, disruptors and insults, may have lifelong impact on health. Perinatal programming may permanently modify disease susceptibility. We now know that such insults, even transient, program lifelong alterations in homeostatic regulations which lead to the commonest diseases encountered in adulthood, including diabetes, hypertension, infarcts, stroke, and cancer.

The current hypothesis proposes that fetal adaptations to intrauterine and maternal conditions during development is able to impair structure and function of organs. Perinatal programming may cause permanent changes in vital organs, altered cell number, imbalance in distribution of different cell types, and altered blood supply or receptor numbers.

The mechanisms underlying the early programming of diseases later in life is presently uncertain. However, experimental data and clinical studies suggest that epigenetic changes in regulatory genes and growth-related genes play a significant role in the perinatal programming. Improvements in our understanding of the mechanisms would trigger the development of preventive and therapeutic strategies. There is an urgent need for a better understanding of what might well be a threat to the sustainable development of human individuals.

PERINATAL HEALTH IN MIDDLE EAST AND NORTH AFRICA AREA

Robert Sacy MD, R. Kamel, I. Dabaj

We will study main issues of perinatal health in MENA area which includes countries of Middle East and North Africa. Governments in region are trying their best to achieve equity among citizens and to respect human rights keeping the cultural values at primary importance. “Good Health is a basic human right” [12] and a must for a socioeconomic development. Women play a major role in raising children and family, thus, she has important role in society. In MENA area, despite all accomplishments in past years, there were lots of reproductive issues and major threats on women’s health which lead to threats on children’s health. There is a link between 3 important issues: health, social development and size of gaps between genders and different socioeconomic status. War was one of the major factors affecting all the 3 issues.

Maternal and neonatal death; war; consanguinity, early marriage; sexually transmitted diseases; violence will be reviewed. Data were collected from review studies. A large part of our information was taken from W.H.O, Ministry of Health in different Arabic countries and many reports from United Nations, USAID, UNDP, and UNICEF.

Mortality

Maternal mortality: Health of newborn is linked to safety of mother. Children before age 10 whom mothers died are 3 to 10 times more likely to die 2 years earlier than children with living parents. Maternal mortality in MENA region remains high with 18000 deaths. Mortality in Yemen is one of the highest in the world [10]. After Gulf war, mortality in Iraq increased rapidly. [11] Major causes of death are bleeding, infections and eclampsia [23]. (Fig.1)

Neonatal death and still birth: low birth weight is a debatable cause of death [13]. Stillbirths account
for over half of all perinatal deaths. Every year over 4 million babies die in the first four weeks of life of which 3 million occur in the early neonatal period. More than 3.3 million babies are stillborn every year; 33% of these deaths occurs during delivery and could largely be prevented [20].

Reproductive health
War and rape: In World-war II, 10000 women were raped in Japan, 200000 in Germany, 7000 in Italy, 200000 in Bangladesh, 5000 in Kuwait, 20 to 50000 in Bosnia, 250 to 500000 in Rwanda women raped resulting in around 5000 pregnancies [22]. In Congo, rape is a weapon against young girls and even grand-mothers. Aim of raping is destroying fundamentals of society. According to an NGO Olame more than 100000 women were raped in Congo in 2004-2005. Mac-Ginn and al in stated that rape survivors have an HIV seroprevalence of 17% compared to 11 % in the overall population [9]. Reproductive health is not affected by war. A study among Palestinian refugees in Lebanon in 1995, showed high, early fertility, and short birth intervals. Same results appear in 8 countries: Ethiopia, Cambodia, and Belize. There is short decline in annual number of births during war but only as a short response. Somali Refugees women are 9 times more likely to deliver post 42 weeks gestation, 4 times more likely to have oligohydramnios, and gestational diabetes. Among women aging 45 years 66% had 6 or more births, 33% had at least one miscarriage, 20% had at least one stillbirth, and 80% have experienced death of one child. Newborns in Somali are at increased risk of longer hospitalization, have lower Apgar score at birth, require more assisted ventilation, had more meconium aspiration.

Stress pregnancy and death of a relative: Khashan reported that extremely stressful events during first trimester of pregnancy such as death of a close relative can cause later schizophrenia.

Consanguineous Marriage and Hereditary Diseases: Commonly practiced, consanguinity occurs in 30 -60 %. Marriage with paternal first cousins gives stable marriages enhanced family ties and secured properties (fig2). However, there is increase in risk of hereditary diseases that are endemic in MENA area like: G6PD deficiency, Thalassemia, Sickle-cell anemia, and Hypothyroidism [3, 7, 8, 10, 14, 15, 16, 21].

Early marriage in: High teen-age fertility in MENA is a result of high incidence of early marriage because sexual relations outside marriage are culturally unacceptable. Legal age for marriage is younger than 18 and therefore marriage before 20 is frequent. 60% of married women in Yemen and Oman, 40% in Egypt and 20-30% in other MENA countries are under 24, and were married before age of 20. Almost 70-80% of women aged 45 were married before 20 (fig3) About 1.6 million girls in area are married before 20. About 900,000 babies are born of teen-age mothers. Young women hope to get pregnant as soon as possible because with a child, women’s status will be enhanced and stabilized. [3, 4, 14, 16, 21].

Recently in Saudi-Arabia a 70 year old man was obliged to divorce by religious authorities from a 9 year old girl to whom he was previously married. In Yemen, a girl aged 12, married by force at 11, died while delivering her baby a stillborn by a severe bleeding. Father was in renal dialysis and needed financial support (Siyaj) and another girl aged 13 died 5 days after wedding by bleeding during intercourse by vaginal laceration (Al-Chaqaeq). According to International Center for Research on Women there are 51 million child brides and almost all in Muslim countries. Polygamy: Less tolerated in recent generations due to increased awareness and worsening of socioeconomic status. In UAE and Oman, 10% of women 25-29 year old are engaged in polygamy. Proportion reaches 20 % in women aged 45- 49. A Muslim can marry 4 women but wives should be treated equally [3, 4, 14, 16, 21].
Teenagers’ pregnancy: range from 143 per 1000 in Sub-Saharan countries in conflicts to 2.9 per 1000 in South-Korea, higher rate of hypertension, anemia, and low birth-weight babies, mother perinatal and infant mortality. Post-abortion complications are higher. Physically immature girls compete with the fetus for essential nutrients. Cephalopelvic disproportion and prolonged labor may occur due to pelvic bone immaturity.

*Unintended pregnancy:* Defined as unwanted or mistimed. Frequency ranges between 14 -62% of recent births. Studies in MENA countries range from 18.5 to 29.6%. Conception intended by mother but not by father showed elevated risks of adverse events. Conception unintended by mother has higher risk of malnutrition, frequent illness and infections. Negative feelings toward pregnancy affect decision of breast-feeding. Child development and health behavior can be affected maternal depression, poverty, child neglect, maltreatment and domestic violence [5].

*Sexual behavior in adolescents:* In Lebanon sexual activity is delayed compared to developed countries. According to Adib et al only 50% of young males joining the army at 18 years are sexually active, and this proportion is very low in girls of this age. According to WHO figures proportion of HPV positive tested in Lebanon would be of 15.4 per 100 000. Considering this proportion of 7.5 in UAE or between 7 and 9 in surrounding Arab countries. subsequently, vaccination of young girls should be taken seriously because infection with HPV happens very quickly after first intercourse. In addition, there is high rate of mortality related to HPV ranging from 2 to 6 in surrounding Arab countries and 8 per 100 000 in Lebanon*(fig4) [2]

Concerning sexually transmitted diseases (STD), the estimated prevalence in MENA region is second lowest among 6 developing regions. Over 12 million people suffer from STD. Low prevalence is attributed to cultural value, intolerance of sexual relations outside marriage, and maybe to lack of reliable reporting systems. Among diseases encountered syphilis prevalence is 1.5% in Jordan and Morocco among blood donor and pregnant women, and around 1.2 to 15% in Yemen. In Jordan: 3-7% had sexual contacts outside marriage, 6% had homosexual contacts and only less than 50% use condoms. In 1997, 2278 related deaths took place in the region. Moreover, adult HIV prevalence is estimated between 0.005% and 0.18% among MENA countries. This prevalence is lower than developing countries in Africa, Latin America and Asia. [1, 17]

*Violence against women and children*

Special United Nation Officer for Women’s rights Nafi Pialey reported that violence against women increased in areas of war with total impunity to aggressors. In Congo where there is war for last 10 years, hundreds of thousands of women are being abused. Men can sexually harass wives and daughters without being prosecuted. WHO report that violence increases rate of abortions, medical complications in pregnancy and long term complications on reproductive organs and fertility. In Egypt, National Office of Statistics revealed that 47.4% of women between 15 and 49 years have been abused by their husband since age of 15 years.Almost 7% of Egyptian women have been sexually aggressed before marriage [6, 24] In Jordan, 600 cases of violence against women were reported in 2008 in Jordan with official medical reports according to Jordan National Office for Legal medicine [25]. In fact, the real figure would be of 5000 abused women. Recently a man killed his wife because she was chatting with an unknown man on Internet. Every year, in Jordan 15-20 women are killed for honor crimes. In Saudi Arabia, on March 2009, Arabian Business News stated that 84.7% of women would like to escape home because of violence against them, 44.3% would kill for revenge to be delivered from their husband. According to Saudi journal Al-Watan, violence against women result in: 77% of medical and psychological problems; 74, 3%
of educational delay; 74.2% of drug abuse; 73% of perturbation of sexual behavior. Moreover, divorce occurs in 68.6% of cases; rebellion of children in 65% of cases; permanent leaving with the husband in 64% of cases. Islamic religious authorities are trying to banish physical threats of husbands against wives and children but without real success [19].

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Figures

Fig 1: Maternal mortality ratios in MENA countries

Fig 2: Consanguinity in MENA region
SURVIVAL AND NEONATAL OUTCOME IN LEBANON

Khalid Yunis, MD

Worldwide, it is estimated that about 7.7 million children under five years of age died in 2009, where 40% were in the neonatal period (Rajaratnam et al, 2010, WHO, 2009). Although neonatal death rates are decreasing globally by 2.1% yearly from 1990 to 2010, they still represent the highest percentage of deaths under the age of 5 years (Rajaratnam et al, 2010; WHO, 2009). As such, in order to achieve the 4th Millennium Development goal (MDG-4) where the challenge is to reduce the under five mortality rate (U5MR) by two thirds in 2015, efforts are focused on reducing deaths in the neonatal period mostly in countries with the highest mortality rates (WHO, 2009).

In Lebanon, the U5MR decreased by 20% between 1990 and 2006 according to 2009 UNICEF report. At the current rate, Lebanon is not on track to meet MDG 4 goal which calls for 66% decline by 2015. According to the National Collaborative Perinatal Neonatal Network (NCPNN), a nationwide partnership and surveillance system in Lebanon, the rates of neonatal mortality didn’t show significant decline between 2001 and 2007 with an overall rate of 7.4 ‰. Prematurity and birth defects are the major causes of in hospital mortality accounting for 60% of the overall causes of deaths. Furthermore, there is a remarkable regional variation in neonatal mortality where rates in administrative Beirut were 8.0 ‰ as opposed to 17.4 ‰ in Akkar, an underserved area in Lebanon (NCPNN, 2001-2007 data). Therefore, developing adequate interventions are warranted to reduce neonatal mortality in Lebanon mostly through improving the quality of care in the perinatal, neonatal and immediate postnatal periods.
Je reprends ici les recommandations de la Haute Autorité de Sante en France. Le diagnostic repose sur :
1- Des critères anamnestiques classes en 2 catégories majeurs (fièvre maternelle, chorioamniotite, bactériurie asymptomatique etc.) ou mineurs (liquide amniotique teinte ou meconial, rupture de 18h etc...).
Il faut admettre que tout enfant qui va mal est suspect d’infection quelque soit la situation.
2- Les données du bilan biologique entre autres NFS et marqueurs de l’inflammation CRP, IL6, et Procalcitonine.
3- La bactériologie Entre autres l’hémoculture les frottis périphériques et la Ponction Lombaire L’ECBU n’est pas recommande.

Indication d’un traitement antibiotique chez un nouveau-né symptomatique
VIRAL HEPATITIS
Florence Lacaille MD

Hepatitis B

Chronic hepatitis B remains a public health problem in many countries, due to the very efficient neonatal and sexual transmission of the virus, the low rate (increased by alcohol drinking) of severe complications before late adulthood, and despite the extension of vaccination programs. Acute hepatitis B is rare in childhood, and may occur very rarely after neonatal transmission, or after sexual exposure in adolescents.

In children, chronic hepatitis B is mostly asymptomatic, and the children are often « tolerant » to the virus. However, hepatocarcinoma may develop even at a young age. Cirrhosis may be seen from adolescence.

The treatment in childhood is difficult. It is most often not the treatment of a disease, but the prevention of possible complications in adulthood. Therefore it is neither mandatory nor urgent. Screening for complications of hepatitis B should be done once or twice a year. Vaccination of people in close contact with the patient (family) is mandatory, in order to prevent horizontal transmission.

Interferon (preferentially long-acting = pegylated) is efficient only in children with elevated transaminases and a low viral load. It is not very well tolerated, should not be used before 3-4 years of age and avoided at adolescence, and should be strictly monitored. Nucleot(s)ide analogues are increasingly used in adults, but the duration of treatment is not well defined, and may be very long (life long ?). Lamivudine leads to the frequent emergence of resistant mutants and should not be used alone. Adefovir is not very efficient. Tenofovir, entecavir and telbivudine have not yet been studied in children. They should not be used outside of a protocol.

Hepatitis C

The virus is only parenterally transmitted, explaining the high rate of contamination in Egypt due to massive antischistomiasis treatment. Unsafe blood transfusion can also be a cause. The rate of mother-to-child transmission during pregnancy is low (5%), but it is nowadays nearly the only way of contamination for children in countries with a safe blood bank system.

The risk of complications in childhood is even lower than for hepatitis B. Cancer has not been seen, and cirrhosis is extremely rare. Alcohol use should be prevented, and vaccination against hepatitis A and B implemented.

The treatment, pegylated interferon and ribavirin, depends on the viral genotype. It is very efficient in genotypes 2 and 3 (over 80% success rate), and totally eliminates the virus. In genotype 1 (the more frequent), it is only 50% efficient. Like in hepatitis B, it does not cure a disease, but prevents complications later in life. It is therefore neither mandatory nor urgent. It should be discussed individually, according to the symptoms (usually none), the child’s age, the genotype, the viral load (to determine the duration, 6 or 12 months), the additional risk factors for the liver (hepatotoxic treatment, iron overload of a chronic anemia, co-infection with another virus...).
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EXPLORATION OF AN HEPATOMEGALY
Florence Lacaille MD

The liver is palpable beneath the costal rib only in infants. The span is measured clinically by palpation and percussion, and can be controlled by ultrasonography. The characteristics are defined: normal, firm, hard, soft; painful or not. Other symptoms of liver disease are looked for. The complete interview and examination is completed by the first line of tests:

- Ultrasonography
- AST and ALT
- Alphafoetoprotein

The cause can be a:

- tumour
  - cancer: especially hepatoblastoma in young children
  - benign: focal nodular hyperplasia in teenage girls
- acute or chronic liver disease
  - acute viral hepatitis
  - cirrhosis
  - congenital hepatic fibrosis
- metabolic liver disease
  - glycogen storage disease
- infection
  - hydatid cyst
- heart failure: in infants
- vascular disease: Budd-Chiari syndrome

The first tests allow for a specific orientation, and the diagnosis of emergencies (cancer, heart failure) and further specialized explorations.

PEDIATRIC GASTROENTEROLOGY HEPATOLOGY AND NUTRITION
Firas Semaan MD

How should *Helicobacter pylori* infected children be managed? It is now recognized that *Helicobacter pylori*, like most enteric infections, is mainly acquired in Childhood. The findings in a number studies suggest that infection is acquired before the age of five. The prevalence of infection is highest in children in the developing world where up to 75% of children may be infected by the age of 10. In the developed world the prevalence of infection is noticeably increased among socially deprived children.

The diagnosis of *H pylori* infection in childhood is most often made at endoscopy, for which there are many indications. Symptoms such as abdominal pain, vomiting, and haematemesis may be associated with duodenal ulcer and *H pylori* infection.
Currently, there are no consensus guidelines for the management of \textit{H pylori} infected children. Duodenal ulcer disease associated with \textit{H pylori} is the only definite indication to treat this infection in children.

Treatment studies on children are particularly difficult because of the small number of infected children in each individual center. As a first-line treatment, bismuth triple therapies (Bis, Clari, and Metro) were more efficacious than proton pump inhibitor triple therapies. Compliance is a very important factor in achieving high eradication rates in children.

Reinfection in adults and older children following successful treatment is rare. A treated child for \textit{H pylori} infection should be assessed to whether that treatment has been successful or not. This can be achieved noninvasively using the 13C-urea breath test.

\textbf{Conclusion:}
\begin{itemize}
  \item Should receive treatment: All children with a duodenal ulcer who have \textit{H pylori} infection
  \item Consider treatment: If infected children have a strong family history of duodenal ulcer disease or gastric cancer.
  \item May be of benefit treatment: Children with sideropaenic anaemia which is refractory to treatment with iron should be screened for \textit{H pylori} infection.
  \item No data/Benefit treatment: Children with recurrent abdominal pain.
\end{itemize}

\section*{NUTRITION IN PREVENTION OF FOOD ALLERGY}
\textit{Dominique Turck MD}

Both the frequency and severity of food allergy are increasing. The primary strategy in the prevention of food allergy relies first on the detection of at risk newborns, i.e. with allergic first degree relatives. In this targeted population, as well as for the general population, exclusive breastfeeding is recommended until the age of 6 months. In the absence of breastfeeding, prevention consists in feeding at risk newborns until the age of 4 to 6 months with a partially hydrolysed formula or “hypoallergenic” formula, provided that its efficiency has been demonstrated by well-designed clinical trials. Soy based formulae are not recommended for allergy prevention. Complementary feeding, i.e. solid foods and liquids other than breast milk or infant formula and follow-on formula, should not be introduced before 17 weeks and not later than 26 weeks. There is no convincing evidence that avoidance or delayed introduction of potentially allergenic foods, such as fish and eggs, reduces allergies, either in infants considered at risk for the development of allergy, or in the general population. It is prudent to avoid both early (<4 months) and late (≥7 months) introduction of gluten, and to introduce gluten gradually whilst the infant is still breast-fed, as this may reduce the risk of wheat allergy, celiac disease, and type 1 diabetes. This preventive policy seems partially efficacious on early manifestations of allergy but does not restrain the allergic march, especially in its respiratory manifestations. Probiotics, prebiotics as well as n-3 fatty polyunsaturated acids have not yet demonstrated any definitive protective effect.
NUTRITION IN INFLAMMATORY BOWEL DISEASE

Dominique Turck MD

Children represent 10-15% of cases of Crohn’s disease (CD), mainly arising after the age of 10, i.e. during puberty. Thus, it is not surprising that main nutrition, impaired growth and pubertal delay are major complications of pediatric CD. Decreased oral intake, malabsorption and increased needs and losses in energy and nutrients are major determinants modulating nutritional status and growth. A deleterious effect on growth of corticosteroids has also been shown. Impaired growth or altered growth velocity may precede the occurrence of clinical symptoms of CD. At diagnosis, weight loss and growth delay are present in 80-90% and 1/3 of cases, respectively. No diet has been shown as efficient in the maintenance of remission. Exclusive enteral nutrition (EN) for 6-8 weeks should be the first choice for the treatment of a flare-up. Prolonged nocturnal EN can be helpful for the treatment of growth retardation and in case of steroid-dependent or steroid-refractory CD. However, immunomodulating (azathioprine, 6-mercaptopurine, methotrexate) and biological agents (infliximab, adalimumab) are nowadays an efficient alternative to prolonged nocturnal EN in most patients with active disease. Efficacy of polymeric solutions is identical to that of semi-elemental or elemental solutions. Parenteral nutrition is limited to a flare-up with resistance to medical treatment and/or EN, and contraindications to surgery; occlusion or fistula; short bowel syndrome. At diagnosis of ulcerative colitis (UC), weight loss and growth delay are present in 50% and 5-10% of cases, respectively. As opposed to CD, nutritional therapy can not be used per se to treat a flare-up of UC.

NUTRITION IN INFLAMMATORY BOWEL DISEASE

Dominique Turck MD

Life expectancy for patients with cystic fibrosis (CF) has steadily improved during the last 3 decades, and death in childhood is now uncommon. Nutrition is a critical component of the management of CF, and nutritional status is directly associated with both pulmonary status and survival. Expert dietetic care is necessary, and attention must be given to ensuring an adequate energy intake in the face of demands which may be increased by inadequately controlled malabsorption, chronic broncho-pulmonary colonisation by bacteria and fungi, exacerbations of acute lung infection, impaired lung function, and the need for rehabilitation, repair and growth. Pancreatic enzyme replacement therapy (PERT) is needed by up to 90% of CF patients in Northern Europe, but a smaller proportion in Mediterranean countries and elsewhere. Complications of CF including liver disease and CF-related diabetes pose further challenges. In addition, deficiency of specific nutrients including fat soluble vitamins (particularly A, E and perhaps K) essential fatty acids and occasionally minerals occur for a variety of reasons. Osteopenia is common and poorly understood. Liver disease increases the likelihood of vitamin D deficiency.

Glucose intolerance and diabetes affect at least 25% of CF adults, and the diabetes differs from both types 1 and 2 diabetes mellitus, but it inversely correlates with prognosis. Management consists of anticipating problems and addressing them vigorously as soon as they appear. Supplements of vitamins are routinely given. Energy supplements can be oral, enteral or, rarely, parenteral. All supplements, including PERT, are adjusted to individual needs.
Sickle cell disease is an inherited hemoglobinopathy affecting over 80,000 people in the US and many more worldwide including the Arab world. The myriad clinical complications of sickle cell disease have their starting point in a single amino acid substitution in the \( b \) chain of human hemoglobin. This substitution results in sickle hemoglobin (Hb S) that polymerizes under conditions such as hypoxemia and acidosis. The polymerization causes perturbations in the erythrocyte integrity which lead to hemolysis and vaso-occlusion. Recently, two clinical phenotypes of sickle cell disease have been described. The hemolysis associated phenotype is characterized by severe anemia, leg ulcers and pulmonary hypertension. When vaso-occlusion predominates the clinical picture is defined by severe painful episodes, acute chest syndrome, splenic infarction, stroke and avascular necrosis of target joints. The disease is also characterized by endothelial dysfunction and a vasculopathy. The course of the disease is very unpredictable but for many patients is associated with significant morbidity, decreased life expectancy and poor quality of life. The risk of early mortality is highest in older patients with a history of severe complication such a recurrent acute chest syndrome, renal failure and pulmonary hypertension.

Chronic transfusions are effective in preventing many complications of sickle cell disease but this modality of therapy has significant complications such as iron overload and alloimmunization. Hydroxyurea has been show to be very effective in ameliorating certain manifestations of the disease, such as painful crises and acute chest syndrome. This modality of therapy also and leads to a longer life expectancy. Many patients however will have poor response to hydroxyurea and still require other forms of therapy. Like for thalassemia the only curative modality is correction of the genetic defect by allogeneic hematopoietic cell transplantation. This presentation will focus on recent findings in the pathophysiology and therapy of sickle cell disease.

ITP is frequent in young children, characterised by severe isolated thrombocytopenia and presence of auto antibodies to platelets. The risk of severe bleeding is often over estimated and seriously impacts the way of life of the child and his family, more than the disease itself would do. Most of ITP are post infectious (viral or post vaccination). Since a few years, ITP management has been modified. Bone marrow examination is usually not necessary for diagnosis if clinical examination and blood count exclude leukemia. Treatment is based on Buchanan score and platelets count. In case of mild bleeding and platelets >10 000/mm3 one can just clinically survey, hospitalization is not necessary.

On the other hand, in case of severe hemorrhage or life threatening bleeding, treatment will associate IV Ig to steroids (4mg/kg, during 4 days), sometimes platelets transfusions are necessary. In case of refractory ITP, one can have to use Vincristine and sometimes Rituximab. Chronic ITP is lasting for more than 12 months. The diagnosis of primary chronic ITP remains one of exclusion. There are a lot of secondary ITP. It’s necessary to establish diagnosis with accuracy to adapt
treatment. Specific treatment of these diseases can improve thrombocytopenia, for example hydroxychloroquine in lupus or Rituximab in lupus or Evans syndrome.

In case of primary chronic ITP, there is no more place for prolonged corticotherapy. A treatment will be initiated only if there are mucosis bleedings or headach in case of intracranial bleeding. Splenectomy is still indicated in chronic refractory ITP. It can cure ITP in 60-70% cases. A prevention of infections by encapsulated agents is necessary: vaccination and antibiotics prophylaxy.

Some studies with Thrombopoietin analogs are going to be initiated in children.

**INDICATIONS OF BONE MARROW TRANSPLANT (BMT) IN CHILDREN**

Françoise Mazingue MD

Since 30 years progress in understanding and treatment of hematological diseases have been important. A lot of children can be cured. BMT has a full place in the treatment of malignant hemopathies but it also takes an important place in the treatment of non malignant hemopathies, solid tumors and in the treatment of some rare diseases such as metabolic diseases, congenital BM dysfunctions and severe Immunodeficiencies.

- **BMT and malignant hemopathies:**
  - Auto BMT keeps a few indications in the treatment of Hodgkin disease and in non Hodgkin lymphomas. In these diseases, BM is usually normal and BMT just allows an intensification of chemotherapy, shortening aplasia, with less infectious complications.

Treatment of the disease doesn’t consist in BMT but in conditioning chemotherapy.

- Allo BMT is the most frequent situation

**Its interest is double:**
- First normal BM of the donor takes the place of leukemic BM,
- Secondly, alloreactivity and GVL act against leukemia and can evitate relapse.

**Indications of allo BMT are essentially:**
- leukaemia in first remission with bad prognosis factors
- leukaemia in second remission after a relapse
- preleukemic syndromes, myelodysplasia before leukemic transformation

**BMT and non malignant diseases:**

In that case, geno identical donors are preferred, because GVH and GVL are not usefull.

Severe idiopathic aplasia: BMT must be done as soon as possible if there is a good donor (geno identical)

Congenital bone marrow dysfunctions such as Fanconi anemia, pure red cell aplasia refractory to steroids, congenital amegacaryocytosis, severe congenital neutropenia, refractory to GCSF....
Hemoglobinopathies:
- sickle cell anemia, refractory to other treatments
- thalassemia
  Usually with geno identical donors in that case

Metabolic diseases:
Mucopolysaccharidosis, Gaucher’s disease as soon as possible if there is a good geno identical donor

Some rare diseases such as osteopetrosis

Severe Congenital Immunodeficiencies (SCID)
In that situation, BMT is an emergency
Best situation is geno identical BMT, but if it’s not possible, if there is no pheno identical donor,
neither geno identical blood cord, haplo identical BMT is sometimes realized with father or
mother’s marrow

Since 30 years, there were a lot of progress in BMT:
- better understanding of haematological diseases
- easier access to pheno identical registers
- better prevention and control of GVH disease
Though BMT is still a heavy treatment
Indications have to be discussed by hematologists, transplanters, taking in account the
hematologic disease, the type of donor (geno or pheno identical), the type of graft: BM,
PSC (peripheric stem cells), Blood Cord
Parents, geno identical brothers or sisters, patient need a lot of explanations and have to be
supported by medical team before, during and after BMT

Iron deficiency anemia is the most common hematologic disease of infancy and childhood. It is
estimated that 30% of the global population suffer from IDA, most of which are from developing
countries.
We measured the prevalence of transferrin saturation (TS) <12%, and iron-deficiency anemia
(IDA) in Lebanese children, and tried to determine their association with dietary habits, socio-
demographic characteristics, and blood lead levels.
A cross-sectional study was performed over a period of 2 years. Of 268 children studied, 142
(53%) were boys and 126 (47%) were girls with an age range of 11 to 75 months. Information
collected included nutritional status, blood counts, TS, and blood lead levels.
The total prevalence of Transferrin saturation <12% and iron deficiency anemia were 33.6% and
20.5%, respectively, and were associated with not having received iron supplements. IDA
was more prevalent among males (P=0.04). TS<12% and IDA were significantly associated with
elevated blood lead levels in the first age group (11 to 23 months) (P=0.04, odds ratio=3.19) and
IDA is common in Lebanese children and is associated with increased blood lead levels, lack of iron supplementation, and cultural dietary habits. Remedial measures such as iron fortification of commonly consumed food are needed on the national level. Lead exposure must be controlled and awareness must be raised about the potentially devastating consequences of combined iron deficiency and lead poisoning on young children.

NON-INVASIVE VENTILATION IN CHILDREN: INDICATIONS AND PREDICTIVE FACTORS FOR THE OUTCOME

Francis Leclerc MD-PhD

Non-invasive ventilation (NIV) provides respiratory support without endotracheal tube or tracheostomy. It usually refers to continuous positive airway (CPAP) or bilevel positive airway pressure (BiPAP) delivered through nasal prongs, facemasks or head boxes. Many evidence is accumulating that it may be beneficial for children with acute respiratory failure (ARF). In a 5-year retrospective study, 83 of 114 children (77%) were treated successfully with NIV; the success rate was 100% for acute chest syndrome, 92% for immuno-compromised children, 87% for community acquired pneumonia, while only 22% for acute respiratory distress syndrome (ARDS) (1). In a 3-year prospective study, 32 episodes of ARF in 26 children (pneumonia: 46%) were treated with NIV by a volumetric ventilator; there was a clinical (at 2-4 hours) and radiological (at 24 hours) improvement and only 4 children required intubation (2). The mechanism by which NIV acts was recently studied by Essouri et al. in 12 children with hypercapnic ARF by the mean of an eso-gastric catheter: the authors observed that NIV was associated with a significant improvement of breathing pattern, gas exchange and respiratory muscle output (3). Also, NIV limits alveolar collapse (1). NIV includes simpler technology and equipment allowing use in settings other than critical care units; this means that patients may benefit from additional respiratory support earlier in the progression of their illness. Furthermore, NIV is associated with less need for sedation and a decrease in nosocomial ventilator associated infections. This is, at least partly, due to the diminished need for intubation, as reported by Yanez et al in their prospective randomised controlled study (intubation rate: 60 % in controls, 28% in NIV group) (4).

When use NIV for acute respiratory failure?

Whilst for some problems, such as upper airway obstruction, stenting of the upper airway with CPAP is often adequate to improve overall ventilation, there are other conditions where additional BiPAP to enhance minute ventilation is used. For ARF, a combination of factors determines whether assisted ventilation is needed, most commonly the degree of respiratory distress and whether the child is tiring, exhausted, unable to vocalise, looking frightened, has altered conscious level or deteriorating vital signs. The child’s clinical condition usually guides the need for intubation and critical care, but continuous measurement of pulse oxygen saturation (SpO₂) and PtcCO₂ (5) (as NIV is generally used for hypercapnic ARF) may help identify the progression of respiratory failure and allow for earlier intervention with NIV. Several papers have summarized the published evidence on NIV for ARF in adult patients: the results are presented in table 1 (6-8). The authors of these meta-analyses concluded that NIV for ARF was supported by strong evidence from patients with chronic obstructive pulmonary disease, acute cardiogenic pulmonary edema.
and weaning off invasive ventilation, but there was only weak support for NIV in others, such as immunocompromised patients. For other groups, such as patients with asthma, pneumonia, or acute lung injury, RCT-level evidence was lacking or did not suggest benefit (6-8). More recently, 53 adult patients with severe acute asthma (FEV1 < 30% of predicted) were randomized to NIV (n=28) or standard medical therapy (n=25). ICU and hospital stay was significantly shorter and the mean dose of inhaled bronchodilator was significantly less in the NIV group. The four patients with standard-medical-therapy failure improved with NIV. Two patients in the NIV arm required invasive ventilation. There was no mortality in either of the arms. The authors concluded that a larger study is required (9).

For children, there is little evidence from randomised controlled trials that early intervention with NIV reduces mortality; however, a number of reports suggest that NIV is useful in ARF by avoiding the need for intubation (10). In the prospective series by Yanez et al, comparing 25 children NIV plus standard therapy (n=25) with standard therapy (n=25), diagnoses were moderate asthma (n=5), viral bronchiolitis-pneumonia (n=42), bacterial pneumonia (n=3). Tracheal intubation was lower in the NIV group (28%/60%; p=0.045) (4). In another series, 20 children (mean age 48 months) with lower airway obstruction were randomized to receive alternatively 2 hours of nasal NIV, followed by crossover to 2 hours of standard medical treatment. Compared to the baseline values, NIV was associated with lower respiratory rate, total Clinical Asthma Score, and delivered oxygen concentration needed to maintain oxygen saturation ≥ 90% (all p < .01) (11). Viral bronchiolitis-pneumonia, mainly due to RSV, represents the largest cohort of children treated with NIV (2, 4, 12-16). In all reported series (none of them was randomized and prospective), a decrease in respiratory rate and pCO₂ level was usually observed within 1 or 2 hours, and 75-80% of infants did not need intubation (15). Clinical conditions with ARF where NIV is used are summarized in table 2 (10). Finally, NIV may also be palliative.

Do we have predictive factors of NIV failure in children with acute respiratory failure?

In children with severe exhaustion from respiratory failure or reduced conscious level, there are risks from treatment with NIV without an adequately secured airway, including gastric distension and aspiration. NIV does not protect the airway or allow as effective clearance of lower airway secretions as does intubation, particularly in the child with a reduced conscious level. However, effective airway clearance is helped by any ventilation that allows maintenance of good lung volumes from which a more effective cough may be generated.

The best predictive factors for the success of NIV in acute respiratory failure appear to be the respiratory rate and the level of inspired oxygen 1 or 2 hours after starting NIV. Lack of effectiveness arises mainly from agitation, poor airway protection or abdominal distension. Several authors have identified different predictive factors of NIV failure in the PICU: the results of studies, which regard children with ARF of different causes, are given in table 3. Other studies have focused on only one disease such as bronchiolitis in infants (12-15). In conclusion, NIV is a treatment option available for children experiencing acute respiratory failure. NIV needs an experienced staff and is not appropriate for children who are unable to protect their own airway, severely exhausted or have a reduced level of consciousness. The selection of the NIV interface is essential in order to achieve the most successful outcome (17). Clinical assessment with continuous monitoring of SpO₂ and if possible PtcCO₂ must be rigorous in order to identify patients not responding to NIV and needing intubation.
Table 1: Randomized controlled trials of noninvasive ventilation for acute respiratory failure in adults.

<table>
<thead>
<tr>
<th>Condition</th>
<th>RCTs (n)</th>
<th>Benefit</th>
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<tbody>
<tr>
<td><strong>Hypoxemic Acute Respiratory Failure</strong></td>
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<tr>
<td>Cardiopulmonary edema</td>
<td>4 NIV</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>6 CPAP</td>
<td></td>
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<tr>
<td>ALI/ARDS</td>
<td>3 NIV</td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td>1 CPAP</td>
<td>No</td>
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<tr>
<td>Severe community-acquired or hospital-acquired pneumonia</td>
<td>2 NIV</td>
<td>Unclear</td>
</tr>
<tr>
<td>Chest trauma</td>
<td>1 NIV</td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td>1 CPAP</td>
<td>Unclear</td>
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<tr>
<td>Atelectasis</td>
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<tr>
<td>Acute on chronic respiratory disease (eg. Interstitial lung disease)</td>
<td>0</td>
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<tr>
<td><strong>Hypercapnic Acute Respiratory Failure</strong></td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>17 NIV</td>
<td>Yes</td>
</tr>
<tr>
<td>Asthma</td>
<td>2 NIV</td>
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<tr>
<td>Neuromuscular</td>
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<tr>
<td>Primary central nervous system</td>
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<tr>
<td><strong>Weaning from invasive ventilation</strong></td>
<td>12 NIV</td>
<td>Yes</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial; ALI = acute lung injury; ARDS = acute respiratory distress syndrome; NIV = noninvasive ventilation; CPAP = continuous positive airway pressure
Table 2:
Clinical conditions with acute respiratory failure where non-invasive ventilation is used.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ref.</th>
<th>n/% of success</th>
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<td>ARF post extubation</td>
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<td></td>
<td>(18)</td>
<td>114/66</td>
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<td>P</td>
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<td>20/50</td>
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<td>(21)</td>
<td>21/82</td>
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<td></td>
<td>(20)</td>
<td>7/100</td>
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<td>7/100</td>
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<tr>
<td>Community acquired pneumonia</td>
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<td></td>
<td>(18)</td>
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<td>(21)</td>
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<td>Immunocompromised</td>
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<td></td>
<td>(18)</td>
<td>30/286</td>
<td>(22)</td>
<td>23/46</td>
<td>(23)</td>
<td>120/74</td>
<td>(24)</td>
<td>16/75</td>
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<tr>
<td>Acute chest syndrome</td>
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<td>(18)</td>
<td>9/100</td>
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<tr>
<td>Bilateral diaphragm paralysis</td>
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<td>2/100</td>
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<tr>
<td>Viral bronchiolitis-pneumonia</td>
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<td>(4)</td>
<td>19/68</td>
<td>(12)</td>
<td>69/83</td>
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<td>53/75</td>
<td>(13)</td>
<td>64/77</td>
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<tr>
<td>Asthma</td>
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<td>(4)</td>
<td>4/100</td>
<td>(11)</td>
<td>20/80</td>
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<tr>
<td>Upper aiway obstruction</td>
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<td>Weaning from tracheotomy</td>
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<td>Different conditions</td>
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<td>(21)</td>
<td>28/89</td>
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<td>34/91</td>
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<td>63/90</td>
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<td></td>
<td>(31)</td>
<td>42/57</td>
<td>(32)</td>
<td>45/73</td>
<td>(16)</td>
<td>116/84</td>
<td>(2)</td>
<td>47/81</td>
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<tr>
<td></td>
<td>(33)</td>
<td>40/72</td>
<td>(34)</td>
<td>278/79</td>
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</tbody>
</table>

ARF: acute respiratory failure; Ref.: reference; P: prospective (other studies were retrospective)
Table 3.
Predictive factors for the outcome of non-invasive ventilation in children with acute respiratory failure.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year (P or R*)</th>
<th>Number of patients or episodes</th>
<th>Median age (years)</th>
<th>Overall success rate (%)</th>
<th>Predictors of failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>(31)</td>
<td>2005 (P)</td>
<td>42 patients</td>
<td>2.45</td>
<td>57</td>
<td>FiO₂ &gt; 0.8 at 1 hour</td>
</tr>
<tr>
<td>(18)</td>
<td>2006 (R)</td>
<td>114 patients</td>
<td>5.3 (mean)</td>
<td>77</td>
<td>ARDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High PELOD</td>
</tr>
<tr>
<td>(32)</td>
<td>2007 (R)</td>
<td>45 patients</td>
<td>1.5-22</td>
<td>73</td>
<td>Age ≤ 6 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FiO₂ &gt; 60% within first 24 h</td>
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<td></td>
<td></td>
<td></td>
<td>PCO₂ ≥ 55 mmHg</td>
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<tr>
<td>(16)</td>
<td>2009 (P)</td>
<td>116 episodes</td>
<td>0.85</td>
<td>84</td>
<td>Type 1**</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(type 1 : 68%**)</td>
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<td></td>
<td></td>
<td>Higher PRISM</td>
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<td></td>
<td>(type 2 : 92%**)</td>
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<td></td>
<td>Lower RR***</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>decrease at 1 and 6 h</td>
</tr>
<tr>
<td>(35)</td>
<td>2010 (P)</td>
<td>47 patients</td>
<td>7.1 (mean)</td>
<td>81</td>
<td>Mean airway pressure &gt; 11.5 cmH₂O</td>
</tr>
<tr>
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<td></td>
<td>FiO₂ &gt; 0.6</td>
</tr>
<tr>
<td>(34)</td>
<td>2010 (P)</td>
<td>278 patients</td>
<td>0.72</td>
<td>76</td>
<td>High PRISM</td>
</tr>
<tr>
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<td></td>
<td>Sepsis</td>
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<td></td>
<td></td>
<td></td>
<td>High RR***</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Higher FiO₂</td>
</tr>
</tbody>
</table>

* P: prospective; R: retrospective;
** type 1: hypoxemia with normal to low PaCO₂; type 2: elevated PaCO₂ with or without hypoxemia;
*** RR: respiratory rate.
References.


18. Essouri S, Chevret L, Durand P, et al. Noninvasive positive pressure ventilation: five years of


SEPTIC SHOCK IN CHILDREN: NINE YEARS AFTER THE CONCEPT OF EARLY GOAL DIRECTED THERAPY
Francis Leclerc, MD-PhD

Severe sepsis is a major cause of mortality and morbidity with around 1000 children admitted in United Kingdom PICUs annually (death rate: up to 20%) (1). Since the surviving sepsis campaign was launched in 2002, numerous studies in adults have demonstrated the salutary effects on mortality of the application of the sepsis bundles (http://ssc.sccm.org/6hr_bundles) based on early goal directed therapy (EGDT) (2) and depicted in table 1 (3, 4). In fact, in their survey of centers that had instituted sepsis programs totalizing 1,298 patients, the mean mortality rate was reduced from 44.8 ± 7.8% prior to implementation to 24.5 ± 5.5% after implementation (5).

1. What do we know on the benefits of guidelines application in children?

In children, several studies have provided important information: 1) in their retrospective study including 91 children with septic shock, Han et al observed that resuscitation practice was consistent to American College of Critical Care Medicine – Pediatric Advanced Life Support (ACCM/PALS) guidelines (early resuscitation with fluids and inotropes (6)) in only 30%; when practice was in agreement with guidelines, a lower mortality was observed (8% vs. 38%; p<0.001) (7). In the retrospective chart review of 90 children with severe sepsis (n=15) or septic shock (n=75), Oliveira et al reported that patients with septic shock who received less than 20 ml/kg of fluid in the first hour of treatment had a mortality rate of 73%, compared to 33% in those who received more than 40 ml/kg (p <0.05). Patients treated less than 30 min after diagnosis of severe sepsis and septic shock had a lower mortality rate (40%) than those treated more than 60 min after diagnosis (73%) p<0.05 (8). Thus, early aggressive therapy has beneficial effects. 2) The 2002 ACCM-PALS guidelines were not followed in 62% of 107 shocked children in the recent UK paediatric intensive care society sepsis audit including the data collected from 17 PICUs and 2 PICU retrieval services (1). Similarly, a French study reported that among 21 children who died from severe bacterial infection, management was considered suboptimal in 76%; identified errors included delay in administering antibiotics in the case of purpura (38%) and insufficient doses or failure to repeat fluid resuscitation (24%) (9). These studies illustrate that there is much to do to obtain widespread application of ACCM/PALS recommendations. 3) De Oliveira et al have recently compared treatment according to ACCM/PALS guidelines, performed with and without ScvO₂ goal-directed therapy; 102 children were prospectively included. ScvO₂ goal-directed therapy received by 51 children resulted in less mortality (28-day mortality 11.8% vs. 39.2%, p=0.002), and fewer new organ dysfunctions (p=0.03).

ScvO₂ goal-directed therapy resulted in more crystalloid (28 (20-40) vs. 5 (0-20 ml/kg, p<0.0001), blood transfusion (45.1% vs. 15.7%, p=0.002) and inotropic (29.4% vs. 7.8%, p=0.01) support in the first 6 h (10). This study confirms that goal-directed therapy using the endpoint of a ScvO₂ ≥70% has, like in adults, a significant impact on the outcome of children with septic shock.

2. What are the barriers to the implementation of the “surviving sepsis campaign” guidelines?

Barriers to implementing protocol-based sepsis resuscitation have been identified by physicians
and nurses in a telephone survey (response rate: 53% of 100 emergency departments – ED - for adults); lack of available nursing staff, inability to monitor central venous pressure in the ED and challenges in identifying septic patients were the most frequent; 16% of physicians also endorse lack of agreement with the EGDT protocol (11). A questionnaire survey conducted in France in 2008 has given the following results: 83% of pediatric intensivists and 91% of the pediatricians of the pediatric retrieval systems used a written sepsis protocol; the main barriers to implementing the surviving sepsis guidelines were monitoring of ScvO\textsubscript{2} (76%), collaboration between ED and PICU (27%) and access to a sepsis protocol (24%) for the pediatric intensivists, and monitoring of ScvO\textsubscript{2} (89%), central catheter insertion and monitoring central venous pressure (CVP) (33%) for the pediatricians of the pediatric retrieval systems (12). In the study by Oliveira et al, the most important barriers in implementing the ACCM/PALS guidelines were lack of adequate vascular access, lack of recognition of early shock, shortage of health care providers and non-use of goals and treatment protocol (8). In brief, these studies have identified numerous and important barriers to the optimal resuscitation of patients with severe sepsis.

3. Is early goal therapy largely adopted or criticized 9 years after the publication by Rivers et al? The EGDT has been frequently criticized (5, 13, 14). In fact, if early initiation of effective antibiotic treatment and rapid fluid resuscitation is a scientifically sound concept, other elements of the “EGDT bundles” are not supported by scientific evidence, particularly the choice of CVP as a guide for fluid administration and the use of ScvO\textsubscript{2} as the end point of resuscitation and the steps to normalize this parameter (blood transfusion and inotropes) (13). Questions about the EGDT algorithm are summarized in figure 1 (14). It is noteworthy that the incidence of low ScvO\textsubscript{2} values in adults with sepsis or septic shock has been reported as low as 16% (15) (this incidence was 41% in the control group and 31% in the intervention group in the pediatric study by de Oliveira (10)); also, abnormally high ScvO\textsubscript{2} (90% to 100%) was associated with increased mortality (16). At the present time, no study has demonstrated if the reduction in mortality of patients with severe sepsis observed in many studies (5) is due to some or all bundle elements, or to other factors (17). As a consequence, some parts of the EGDT protocol are anecdotally adopted. Indeed, a recent multicentre prospective study (324 adults with severe sepsis or septic shock), in which management did not include a ScvO\textsubscript{2} catheter, reported a in-hospital mortality of 23% that compared favorably with that of recent EGDT trials (18). Furthermore, Jones et al recently compared lactate clearance and ScvO\textsubscript{2} as goals of early sepsis resuscitation in 300 adults admitted with severe sepsis and septic shock and randomly assigned. These two protocols did not result in significant different in-hospital mortality (23% in the ScvO\textsubscript{2} group vs. 17% in the lactate group) (19).

Conclusion:

There is no doubt that early recognition and application of recommendations for the acute management are the first step toward improved outcomes of sepsis and septic shock. Early fluid resuscitation and antibiotics administration represent uncontroversial key points (20). However, other elements of the EGDT, particularly CVP and ScvO\textsubscript{2}, are seriously criticized. Norepinephrine in case of ineffective fluid resuscitation, early and repeated echocardiography-Doppler and dynamic indices to guide fluid resuscitation and inotropic therapy, and lactate as a marker of severity and therapy responsiveness are probably supported by more scientific evidence than some EGDT elements (21). They are included in our protocol, beside CVP and ScvO\textsubscript{2}, according to the French guidelines (22). This, however, needs further evaluation.
References:


Table 1. **Resuscitation bundle that must be completed within 6 hours (adapted to children).**

<table>
<thead>
<tr>
<th>Resuscitation bundle elements</th>
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<tbody>
<tr>
<td>1. Measure serum lactate.</td>
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<tr>
<td>2. Obtain blood cultures prior to antibiotic administration.</td>
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<tr>
<td>3. Administer broad-spectrum antibiotic within 1 hour of ED or non-ED admission.</td>
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<tr>
<td>4. In the event of hypotension [&lt;45 mm Hg (&lt;1 month); &lt;50 mm Hg (&lt;2 years); &lt;60 mm Hg (&lt;10 ans)] and/or serum lactate &gt; 4 mmol/L: minimum of 20 mL/kg of crystalloid or an equivalent hypotension not responding to initial fluid resuscitation</td>
<td></td>
</tr>
<tr>
<td>a. Deliver an initial minimum of 20 mL/kg of crystalloid or an equivalent hypotension not responding to initial fluid resuscitation</td>
<td></td>
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<tr>
<td>b. Apply vasopressors for to maintain mean arterial pressure (MAP): &gt; 45 mm Hg (&lt;1 month);</td>
<td></td>
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<tr>
<td>&gt; 50 mm Hg; (&lt;2 years); 60 mm Hg (&lt;10 ans)</td>
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<tr>
<td>5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate &gt; 4 mmol/L: a. Achieve a central venous pressure (CVP) of ≥8 mm Hg oxygen saturation (ScvO₂) ≥ 70% or mixed venous oxygen saturation (SvO₂) ≥ 65%</td>
<td></td>
</tr>
<tr>
<td>b. Achieve a central venous oxygen saturation (ScvO₂) ≥ 70% or mixed venous oxygen saturation (SvO₂) ≥ 65%</td>
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</table>
ARDS is a devastating disorder leading to hypoxemia and respiratory failure. It remains an important challenge for the pediatric intensive care physician.

In this review, I will discuss the definition of ARDS and the available intensive care treatment modalities including newer lung-protective mechanical ventilation strategies, fluid management and nutritional needs.
EARLY CHILDHOOD DEVELOPMENT WORKSHOP

Durriyah Sinno, MD AND Lama Charaffeddine, MD

More than 200 million children worldwide fail to reach their potential in cognitive development due to poverty, poor health and nutrition, and deficient care. Early experiences during development form the basis for enhancing the physical, mental, and psychological well-being of children through an entire life time. This workshop is an introduction to the Care for Child Development. The goal is to provide pediatricians with additional skills to allow them to better **screen** for developmental delays and **intervene** to enhance early childhood development. It is intended to help physicians recognize the importance of Early Childhood Development (ECD), describe the scientific basis and implications of ECD, identify available developmental screening tools and discuss their culture specificity. The workshop will be interactive where the audience will practice using the WHO/UNICEF Care for Child Development tool kit, in addition to recognizing the four domains of child development and analyzing mother-child interaction.

PERINATAL MANAGEMENT OF DISORDERS OF SEXUAL DEVELOPMENT (DSD)

Alaa EL GHONEIMI, MD, PhD, FEBPS, FEAPU

Fetal sex determination is now a current and accurate ultrasound finding during the routine prenatal ultrasound. Any discrepancy of the typical aspect of the fetal external genitalia should alert the gynecologist and a multidisciplinary prenatal counseling be arranged. Th Prenatal thérapeutique measures are now available for the congénital adrenal hyperplasia, otherwise for the oser anomalies; the main advantage of the prénatal diagnosis is to expand the work up and to prépare an optimal néonatal management in a specialized center witlof an extensive delay in sex détermination or in worse cases a mistake in the sex determination.

The aim of neonatal management is mainly to identify the anomaly and to determine the optimal choice for sex determination. The urgent medical management of congenital adrenal hyperplasia (CAH) cases should start immediately.

The initial workup (hormonal, karyotype, imaging, molecular biology) and the clinical assessment by experienced pediatric endocrinologist and surgeon, can clarify in most of the cases the exact diagnosis and the determination of sex breading. This decision should be made in a multidisciplinary way including all the participants in the future management of the child, and the parent’s opinion should be taken seriously in consideration. The role of a specialized psychologist is mandatory in the process of evaluation of the family environment and in establishing a strong trusting relationship with the parents for the future management of the child. The decision is a major step and will depend on many factors: external genitalia, internal genitalia, hormonal synthesis, fertility, social environment (especially in delayed diagnosis).

The reconstruction surgery will be planned according to the final diagnosis and the choice of sex breading. The feminizing genitoplasty is usually done when the child is 3 to 6 months of age. Currently there is still a controversy regarding the age and the type of surgery to be done. The virilizing genitoplasty is planned around the age of one, hormonal stimulation of external genitalia is sometimes needed, but again there is still controversy on its benefits and indications.

In conclusion, the DSD should be considered as a major anomaly and that even with the most sophisticated techniques of investigations or reconstruction, it is still a challenging anomaly to manage. For one more this entity needs an optimal multidisciplinary management to be able to give children and their families the optimal therapy.
POSTERIOR URETHRAL VALVES, CURRENT PERINATAL AND LONG TERM MANAGEMENT

Alaa EL GHONEIMI, MD, PhD, FEBPS, FEAPU

“Thrombosis, both venous and arterial, is a major cause of morbidity and mortality worldwide. Consequently, there is an ongoing search for new antithrombotic drugs, particularly novel anticoagulants. Recently, this armamentarium undergoes a major change with the introduction of new specific and oral anticoagulants that are likely to fulfil many of the unmet needs of current warfarin and heparin therapies. A direct thrombin inhibitor, dabigatran etexilate, and a direct factor Xa inhibitor, rivaroxaban are actually marketed for an easier and safer venous thromboembolism prevention following orthopaedic surgery. Large ongoing trials try to demonstrate that these drugs would also simplify and optimize stroke prevention in atrial fibrillation, treatment of venous thromboembolism and prevention of ischemic events in acute coronary syndrome. This presentation reviews the latest developments of new anticoagulants and focuses on those which have been approved or are in advanced development.”

NEPHROPROTECTION IN PEDIATRICS

Georges Deschênes M.D, Ph.D

Nephroprotection is an advanced form of the conservative treatment of chronic renal failure that aims at preventing the progression of chronic renal disease to end stage renal failure, whatever the level of the glomerular filtration rate. All patients with a history of congenital or acquired renal disease that is known to decrease the nephron mass are concerned: congenital abnormalities of the kidney and urinary tract, polycystic diseases, chronic glomerular disease (Berger-Hinglais disease, Alport syndrome, membranous and membranoproliferative glomerulonephritis, lupus nephritis and autoimmune vasculitis), acute and chronic haemolytic and uremic syndromes. In addition, nephroprotection also concerns patients with a systemic disease potentially affecting the kidney: diabetes mellitus, sickle cell disease, metabolic syndrome, essential hypertension, obesity and also history of low birth weight for term.

Chronic renal disease is now classified according to the level of glomerular filtration rate: Stage 1: > 90 ml/min/1.73 m²; Stage 2: 60-90 ml/min/1.73 m²; Stage 3: 30-60 ml/min/1.73 m²; Stage 4: 15-30 ml/min/1.73 m²; Stage 5 < 15 ml/min/1.73 m² representing end stage renal failure. The most determinant factors of progression of renal disease are proteinuria/microalbuminuria and hypertension that have to be both carefully controlled using drugs modifying the renin-angiotensin-aldosterone axis. Inhibitors of angioconvertase (ACEi) and antagonists of the angiotensin-2 receptor (ARA-2) have definitely proven their efficiency to prevent the progression or chronic renal disease. The targets of these therapies are to maintain the blood pressure at the 50th percentile and the level of microalbuminuria below 3 mg/mmol of urine creatinine. Other factors able to aggravate the status of chronic renal disease include anemia, carbohydrate intolerance, hyperuricemia and dyslipidemia. Anemia has to be controlled by supplements in iron, vitamine B6 and B12, and erythropoietic stimulating agents, carbohydrate intolerance by a specific diet and insulin id needed, hyperuricemia by administration of allopurinol and dyslipidemia by the administration of statins. Of note, 1/ chronic renal disease and most of the associated factors of progression to renal failure are also factors at risk of cardiovascular disease in the adult age; 2/

Drugs used to control the progression of chronic renal disease are also efficient to prevent the cardiovascular risk at adult age.
PREVENTION OF HUMAN PAPILLOMA VIRUS INFECTIONS: CHALLENGES AND PROMISES
Ghassan Dbaibo M.D

Human papilloma virus (HPV) infections are exceedingly common in women and men. The oncogenic types are responsible for all cervical cancers and a large proportion of other anogenital cancers in women as well as in men. Non-oncogenic types cause skin and genital warts and represent a significant burden on affected individuals. Prevention of four of the most common HPV’s is now possible with vaccination. Studies have shown that vaccination is effective in preventing infection with HPV, preventing persistent infection with HPV, and preventing development of pre-cancerous lesions of the cervix as well as the vulva and the vagina. Although vaccination is highly effective, uptake of the vaccine has been slow due to several barriers. These barriers and possibilities to overcome them will be discussed.

ANTI-CD20 MONOCLONAL ANTIBODIES FOR THE TREATMENT OF LYMPHOID MALIGNANCIES AND AUTOIMMUNE CYTOPENIAS
Tadeusz Robak, MD

Over the last few years several monoclonal antibodies (mAbs) have been investigated in clinical trials in patients with lymphoid malignancies and autoimmune disorders [1]. The most important clinical value have at present rituximab (IDEC C2B8, Rituxan, Mabthera) that targets CD20 antigen and alemtuzumab (Campath-1H), a humanized form of a rat antibody active against CD52. The CD20 antigen is expressed on almost all B-cells but the intensity of expression appears to be lower on chronic lymphocytic leukemia (CLL) cells than in patients with non-Hodgkin lymphoma (NHL). The intensity of antigen expression or the number of receptor sites on the cell surface appears to be correlated with the clinical response. Rituximab is an IgG1 kappa immunoglobulin containing murine light – and heavy chain variable region sequences and human constant region sequences. The Fab domain of rituximab binds specifically to the CD20 antigen expressed on normal and malignant B-cells. The Fc domain recruits immune effect or functions to mediate B-cell lysis in vitro and in vivo. Mechanism by which rituximab may be cytotoxic include complement dependent cytotoxicity (CDC), antibody-dependent cell mediated cytotoxicity (ADCC) and induction of apoptosis. Furthermore, rituximab sensitizes malignant B-cells to the cytotoxic effects of chemotherapy. Rituximab was the first mAb approved in 1997 by the Food and Drug Administration (FDA) for the treatment of cancer. The drug is usually administered as an intravenous infusion with a recommended dosage 375 mg/m² given once weekly for 4 weeks. Treatment with this agent is well tolerated. However, infusion-related reactions occur in the majority of patients, although the incidence of these side effects decrease with subsequent rituximab infusion. Rituximab is currently validated as first-line treatment for aggressive and indolent subtypes of B-cell non-Hodgkin lymphoma (NHL). In diffuse large B-cell lymphoma (DLBCL) R-CHOP (Rituximab + CHOP) has became the new standard of care, which led to improve outcomes for this lymphoma [2]. The addition of rituximab to chemotherapeutic combinations (CHOP or CVP (cyclophosphamide, vincristine, prednisone) has also resulted in a significant increase in overall response rate (ORR), complete response rate (CR) and time to progression (TTP) in patients with follicular lymphoma [FL] [3]. In relapsed/resistant FL rituximab maintenance considerably improves progression free survival (PFS) not only after CHOP but also...
after R-CHOP induction [4]. Rituximab is an active drug in CLL when used as a single agent. However, the combination of rituximab with fludarabine and cyclophosphamide (R-FC regimen) demonstrate particularly high rates of OR, complete response (CR) and duration of PFS in previously untreated and relapsed/refractory CLL [5,6]. In randomized trials R-FC demonstrated higher OR rate, CR rate and PFS than FC in previously untreated and relapsed/refractory CLL. The U.S. Food and Drug Administration and European Commission approved rituximab in combination with fludarabine and cyclophosphamide for use in patients with previously-treated and untreated CLL. The approval was based on clinically meaningful and statistically significant increases in PFS [5,6]. Rituximab seems to be also an effective and safe agent for the treatment of immune thrombocytopenias (ITP), autoimmune haemolytic anaemia (AIHA), cold agglutinin disease (CAD) and pure red cell aplasia (PRCA)[7].

A new generation of mAbs has been developed to have augmented antitumor activity by increasing CDC or ADCC activity and these mAbs are now in clinical trials [8-10]. Ofatumumab is a second-generation, fully human, anti-CD20, IgG1 mAb in phase I, II and III trials for hematological malignancies, autoimmune diseases such as rheumatoid arthritis and multiple sclerosis [8]. Ofatumumab recognizes a different CD20 epitope to rituximab and has demonstrated a higher CDC potential than rituximab. In April 2010, the European Medicines Agency granted a conditional marketing authorization for ofatumumab, for the treatment of Fludarabine-refractory CLL patients. Veltuzumab, as a second-generation, humanized, anti-CD20, IgG1 mAb in phase II trials for NHL, CLL and autoimmune diseases including immune thrombocytopenic purpura. Veltuzumab has enhanced binding avidities and a stronger effect on CDC compared with rituximab. GA-101 is a third-generation, humanized and glycoengineered anti-CD20 IgG1 mAb, for a potential treatment of B-cell malignancies [10]. Compared with classical type I CD20 antibodies (eg, rituximab) GA-101 binds with high affinity to the CD20 type II epitope, which results in induction of ADCC that is 5- to 100-fold greater than by rituximab. GA-101 also exhibits superior caspase–independent apoptosis induction compared with rituximab while CDC activity is low. In a phase I/II trial GA-101 has demonstrated a similar safety profile to rituximab and promising efficacy in patients with relapsed/refractory CD20+ lymphoid malignancies. GA-101 is a promising therapeutic agent for CD20+ B-cell lymphoid malignancies, including NHL and CLL.

References
NEW ORAL ANTICOAGULANTS

Ismaïl Elalamy MD

“Thrombosis, both venous and arterial, is a major cause of morbidity and mortality worldwide. Consequently, there is an ongoing search for new antithrombotic drugs, particularly novel anticoagulants. Recently, this armamentarium undergoes a major change with the introduction of new specific and oral anticoagulants that are likely to fulfil many of the unmet needs of current warfarin and heparin therapies. A direct thrombin inhibitor, dabigatran etexilate, and a direct factor Xa inhibitor, rivaroxaban are actually marketed for an easier and safer venous thromboembolism prevention following orthopaedic surgery. Large ongoing trials try to demonstrate that these drugs would also simplify and optimize stroke prevention in atrial fibrillation, treatment of venous thromboembolism and prevention of ischemic events in acute coronary syndrome. This presentation reviews the latest developments of new anticoagulants and focuses on those which have been approved or are in advanced development”.

ADVANCES AND CHALLENGES IN PEDIATRICS ONCOLOGY

Rima Fuad Jubran MD, MPH

Cancer is the leading cause of disease related mortality in children in the United States and approximately 12, 4000 children are diagnosed in the U.S. every year. During this talk we will discuss the history of major advances in pediatric oncology therapy and approach to patients. We will discuss the future challenges for the field as well as overall strategies for developing more effective therapies for high risk pediatric cancers. Finally we will talk about cancer survivorship and issues faced by survivors.

BREAST SCREENING WITH MRI FOR HIGH RISK WOMEN IN ADJUNCT TO MAMMOGRAPHY

Nagi Atallah, MD

The demand for breast MRI is increasing. Image quality is improving. The sensibility is high and with high resolution. Image specificity is higher, based on enhancement or DWI or spectroscopy. Screening high risk women represent 70% of the indications in the USA in response to the recommendations of the ACS.

What is high risk women?
- Women with genetic mutation (BRCA), with strong family history or personal history of breast or ovarian cancer

Life time risk >20-25% is considered as high risk depending on the risk models (Gail or Tyrer-Cuzick). Used for risk estimation (NCI, IBIS).

Breast MRI is done in adjunct to mammography because there are some DCIS or ILC that do not enhance.

In that group of women MRI alone detects twice more cancers than mammography alone. But there are some radiologists or other specialists that believe we are living the impending decline of screening mammography.
ADVANCES IN MANAGEMENT OF CONGENITAL CARDIAC DISEASES AND CHANGING OUTCOMES
Zohair Al Halees, MD

Congenital heart surgery is special. It is a profession that combines art and science, skill and decisiveness. Though it is considered a young specialty, great advances have been made over the last 50 years. Almost all congenital cardiac defects are now manageable one way or another. Fetal diagnosis helped in better planning intervention.

In the presentation, we go through the milestones of cardiac surgery and talk about the advances that have occurred over the years through the pioneering efforts of many innovative and visionary surgeons. Advances were also related to critical reviews of outcomes and adopting changes that prove beneficial. Pediatric Cardiology became a subspecialty of its own which helped in better defining management pathways of patients with congenital cardiac defects. Cardiac morphology improved the understanding of the structural changes associated with congenital cardiac defects and allowed both cardiologists and surgeons to better plan repairs and avoid complications. A good example of this is the delineation of the conduction system within the heart and avoidance of heart block postoperatively. Improved technology particularly imaging technology [echocardiography, CT scanning, MRI] together with advances in anesthesia, critical care, and surgical techniques all made an impact in improving outcomes of these patients. This also led towards operating on patient at an earlier age with a strong trend towards early corrective surgery. Palliation became less and mostly have become a part of planned strategy towards full repair.

HEART FAILURE UNIT: IS IT ESSENTIAL TO ESTABLISH?
Hadi Skouri MD

Heart failure is a leading cause of hospitalization and death and its prevalence continues to increase. The clinical care of patients with HF encompasses a continuum from acute settings to chronic management. Chronic management in the outpatient setting provides an opportunity to improve patient care and health outcomes through early identification of symptom progression, utilization of evidence-based medication, quality-of-life evaluation, and patient education to increase adherence. HF is a leading cause of ambulatory visits and outpatient care accounts for a significant proportion of total heart failure expenditures. Observational studies have shown improved outcome if patients are being treated and followed up by specially trained providers. So “HF clinic” has become a vital element in comprehensive care of the patients with HF. It reached the level of national and international HF Guidelines.

BEDSIDE ASSESSMENT AND MANAGEMENT IN ACUTE HEART FAILURE SYNDROME
Hadi Skouri MD

Acute Heart Failure Syndrome (AHFS) includes patient with reduced and preserved LV function. In acute settings they have similar clinical presentation. Immediate therapy to optimize hemodynamics and improve symptoms is similar or overlapping. There are some clinical and
hemodynamic features that are considered key features in determining the appropriate management for faster recovery with the least complications and hospital stay. These key elements can be obtained from clinical history, adequate physical examination, electrocardiogram and blood studies. In addition, with technology advancement, HF biomarkers, fluid assessment by bioimpedance and other technologies as well as bedside echocardiographic hemodynamic assessment will improve diagnostic accuracy and offer a better optimization of individualized therapy without any invasive procedures. In this presentation clinical and hemodynamic features pertinent to HF assessment will be discussed with mentioning some of the new technologies and the future perspective in this field.

**ATRIAL FIBRILLATION IN HEART FAILURE**

*Samer Nasr, MD*

There is little doubt that atrial fibrillation increases mortality rates in the heart failure population. Therapy for atrial fibrillation, in the absence of heart failure, is tailored mainly for symptomatic relief and quality of life improvement.

In the heart failure population, therapy should target specifically the mortality increase by:

1. Either rhythm control with direct current cardioversion, amiodarone, and serious consideration for atrial fibrillation ablation

2. Or aggressive rate control with a target heart rate allowing biventricular pacing above 90 percent during 24 hour period.

This is achieved with AV nodal ablation, if betablocker/digoxin combination is not effective.

Anticoagulation is indicated in the heart failure population with atrial fibrillation in either rhythm or rate control strategies.

An additional challenge we have face frequently is the programming of intracardiac defibrillators to prevent inappropriate delivery or therapy. Multiple SVT discriminators are available with advancing technologies but tailoring of the programming to specific patient remains the cornerstone of therapy.

**ANEMIA AND HYponATREMIA IN PATIENTS WITH HEART FAILURE**

*Samer Kabbani MD, FACC, FSCAI*

- Understanding the pathophysiology of anemia and hyponatremia in Heart Failure.

- Treatment of hyponatremia and management of anemia in Heart failure.

- Outcome of patients with hyponatremia and untreated anemia in Heart failure.
ROLE OF ECHOCARDIOGRAPHY IN CARDIAC RESYNCHRONIZATION THERAPY

Elie Chammas MD, FESC

Cardiac resynchronization therapy (CRT) with biventricular pacing, is now recommended for patients with heart failure (Ejection fraction < 35%), under maximal therapy with wide QRS (> 130 ms). After implantation of a CRT device, one third of the patients remain symptomatic without any improvement. The presence of mechanical dysynchrony is one of the possible causes. Cardiac echography is a powerful tool to detect mechanical dysynchrony by analyzing the interventricular, the intra ventricular and the auriculo ventricular delays. With the new technologies (Tissue synchronization imaging, 2D and 3D strain...), the echocardiography diagnosis of mechanical dysynchrony became more accurate. Despite these techniques, the clinical data still disappointed. One of the explanations is the complexity of cardiac mechanics which can not be explored by one technique, another is the position of the pace maker leads.

During this presentation, all the echo techniques to detect dysynchrony will be presented with the clinical data recently published.

SHOULD WE EXPAND CRT TO MILD HEART FAILURE?

Samer Nasr, MD

Cardiac resynchronization therapy has become an established therapy for ischemic and non ischemic cardiomyopathies, with QRS widening. The effects of biventricular pacing were shown to have hemodynamic and non hemodynamic positive influence on myocardial function and increase in effectiveness of LV contraction with decrease in mitral regurgitation. Pathology studies have also shown Changes in myocytes and surrounding fibrotic changes similar to the changes seen with ACE inhibitions.

The initial target of cardiac resynchronization therapy was to alleviate symptoms. This is confirmed by the design of the main trials that included improvement in NYHA class, and six minute walk test and measurement of quality of life using the Minesota quality of life score.

With the success of the positive main initial came the AHA/ACC and ESC guidelines that we know recommended cardiac resynchronization trials in NYHA class two, three, and ambulatory four. The group of paucisymtomatic patients with severe left ventricular dysfunction and NYHA class one were left to be candidates for defibrillator implantation and not for biventricular pacing. The sole purpose of the therapy in this group of patients, was the prevention of sudden cardiac arrhythmic death. The common thinking was to implant a defibrillator and upgrade to biventricular pacing only if the patients worsen clinically and start showing signs and symptoms of salt and water retention.

With growing experience it was left that many symptomatic patients with severe left ventricular dysfunction and QRS widening worsened rapidly with time. Recent large clinical trials have addressed this specific issue.

Not surprisingly the benefits of CRT proved to be as good as in the symptomatic patients. We will go over the latest evidence covering the topic with emphasis on survival benefits and pathophysiologic data available to us at this time.
ELECTROPHYSIOLOGY IN HEART FAILURE
Oussama Musbah Wazni, MD

As more patients with heart failure are being diagnosed and treated it is becoming more evident that these patients invariably need to be treated by electrophysiologists.

In addition for the need of device therapy such as ICDs and CRTDs these patients frequently develop VT or recurrent ICD shocks. This is usually first treated with antiarrhythmics medications but also not infrequently these patients need EPS and ablation. Also patients with heart failure increasingly develop atrial fibrillation with worsening functional status and also worsening left ventricular function again in this group of patients AF ablation has been shown to be effective.

In this session we will discuss in more depth the role of electrophysiological studies and ablative therapy in patients with heart failure.

SURGICAL VENTRICULAR RESTORATION (SVR)
THE EARLY EXPERIENCE IN SAUDI ARABIA
Walid Abukhudair; E. Ahmed; A. Ajam; W. Ahmed;
K. Shaibi; M. El-Hamami; A. Ashmeg

Objectives: To evaluate our early experience with SVR as therapy for a subset of patients with ischemic cardiomyopathy.

Background: Ischemic cardiomyopathy poses a challenging problem to the cardiologist and cardiac surgeons. Following myocardial infraction, 20% of patients develop ventricular dilation and congestive heart failure (CHF) even with early reperfusion therapy. This is due to “ventricular remodeling” process that results in the loss of the normal elliptical shape of the ventricle and CHF. Ventricular volume reduction, and shape restoration surgery has recently become an available option for this subset of patients. We prospectively examined the early outcome of SVR in our institution.

Methods: Eight prospective post anterior myocardial infraction patients underwent SVR with concomitant CABG /or mitral valve repair are presented. We also reviewed the stich trial result in a critical EBM method.

Results: 110 SVR patient were done between March 2006 to March 2010. The mean age was 50.6 (+ 5.1) years. All patients were males. The mean left ventricular fraction was 20 % ± 3.16. One hundred patient had SVR with concomitant CABG. Thirty five patients had mitral valve repair as well. The average number of grafts was 2 + 0.63. The NYHA class has improved from 3.3 (+ 0.8) to 1.8 + 0.4. The mean left ventricular ejection fraction improved from 20 + 3.16 to 30.8 + 5.8. The post-op ventilation period was 40 hours (+ 1.9) and the mean length of stay was 12.8 (+ 4.7) days. Intra aortic balloon pump (IABP) and Levosimendan were used in 40 patients. There is one intra operative mortality and mortality rate was 5 %. STICH did not select same patient population and did not treat them the write way in terms of technique and LV reduction.
Conclusion: In our preliminary group, SVR may afford significant improvement of symptoms and ejection fraction, and that the procedure can be performed safely. Further studies are needed to define the patients best served with the procedure. Stich trial is not the final answer to SVR.

EVOLUTION OF INTERVENTIONAL CARDIOLOGY

Spencer B. King, III, M.D., M.A.C.C.

Interventional cardiology evolved from concepts created in the disciplines of surgery, radiology and cardiology. The pivotal developments of radiographic imaging enabled the development of coronary arteriography which facilitated coronary bypass surgery and the dilatation of vessels was a peripheral procedure developed to improve claudication.

All of these elements were integrated by the father of interventional cardiology, Andreas Gruentzig. From the earliest experiments of vascular dilatation to the clinical application of coronary angioplasty, the development of steerable guidewire techniques, the introduction of coronary stents, and the control of restenosis, interventional cardiology has been at the forefront of modern medical evolution. No other specialty has created so many areas of research interests or performed as many clinical trials to establish the effectiveness of those interventions.

The technologic developments have been dramatic and now have their greatest potential in managing structural heart disease. As we pass 33 years of interventional cardiology, the disciplines that were necessary for its foundation are reuniting to move developments forward.

The recently published guidelines of the European Society of Cardiology were developed by cardiologists and cardiac surgeons working in tandem. The evolution has been dramatic but the future looks even more promising.

TREATMENT OF STABLE ISCHEMIC HEART DISEASE

Spencer B. King, III, M.D., M.A.C.C.

Ischemic heart disease comes in various forms and is most feared when it is acute and abrupt. The occurrence of myocardial infarction is often life-threatening and its’ treatment has been the most important success story for interventional cardiology.

Cardiac surgery demonstrated the ability to manage highly symptomatic ischemic heart disease, albeit through significantly invasive methods. Now interventional cardiology’s role in the management of stable ischemic heart disease is being questioned. Whereas a mortality benefit is clearly demonstrated in the patients presenting with acute coronary events, studies to date have not demonstrated a comparable result for patients with stable conditions. Because of that many advocate the use of revascularization primarily for symptomatic relief, and indeed, revascularization is the most effective method for alleviating symptoms due to ischemic heart disease. The two questions being asked are whether revascularization should be performed at all in patients with stable ischemic heart disease, and, if revascularization is to be performed, which method, i.e. percutaneous coronary intervention or coronary bypass surgery, should be employed.
Recent trials examining the need for revascularization have concentrated on patients who could be managed medically or with revascularization after a complete work-up including angiography. The COURAGE trial and the BARI 2D trial both showed equivalence for medical therapy or interventions. The question of percutaneous intervention or surgery as the revascularization choice for patients who are judged to require it has been investigated in a number of trials ranging from the EAST and BARI to SYNTAX. All of these trials, starting with balloon angioplasty and moving to drug eluting stents, have shown relative equivalence of the two techniques for the patients selected. Of most current interest is the longer-term follow-up of the SYNTAX trial which investigated patients with extensive three-vessel disease and left main disease and which to date shows no major difference in survival but an advantage for surgery in the avoidance of repeat interventions. Most importantly, this trial demonstrated angiographic and clinical predictors of a gradient of outcomes based on the extent of disease. This is helpful in selecting patients; however, significant gaps still exist. Pertinent to the first question (should revascularization be done?), the currently proposed trial, ISCHEMIA, will investigate patients who have significantly more ischemia than those in the BARI 2D and COURAGE trials and will randomize them prior to coronary arteriography to either continued medical therapy or angiography with planned intervention. Pertinent to the second question, the group with greatest survival differential favoring surgery, i.e. patients with diabetes, has been investigated in the FREEDOM trial. This study of 1,900 patients completed enrollment in 2009 and will be the most definitive comparison of diabetic patients undergoing drug eluting stenting or bypass surgery. The advances in medical therapy, coronary intervention, and surgery have all made the outlook for patients with stable ischemic heart disease much brighter than it was at the dawn of the interventional cardiology era. Better understanding of the comparative effectiveness of these approaches will help guide therapy in the future.

**TAVI WHERE DO WE STAND IN 2010?**
Samir R. Kapadia, MD
E. Murat Tuzcu, MD

**Mitral Regurgitation**

1. Mitral regurgitation (MR) is a significant problem, and the number of patients with MR is growing with increase in patients with congestive heart failure. Surgical correction of MR with repair techniques yields better results than valve replacement, however, a significant number of patients undergo valve replacement even in the current era.

2. Various percutaneous approaches to mitral valve repair are under preclinical and clinical investigation and show great promise for the future. These approaches are predominantly based on established surgical strategies.

3. Different percutaneous techniques provide specific advantages depending on the anatomical and functional characteristics of mitral regurgitation. Selection of the appropriate technique/s for each individual patient will ultimately determine the success of these emerging technologies.

4. Integration of established imaging modalities both in and out of the catheterization laboratory is critical for safety and efficacy of percutaneous repair technologies. The development of emerging imaging modalities will likely play a role in the future of percutaneous technologies.

5. Evaluation of new percutaneous devices poses a significant challenge because these devices have to be compared to surgical options that may have different expectations in the overall management of the patient. It is likely that percutaneous techniques will have a complimentary role to surgery.
Transcatheter Aortic Valve Implantation

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Opinion statement
Aortic stenosis is the most important valvular heart disease affecting the elderly population. Surgical aortic valve replacement is the mainstay of treatment, although a substantial number of patients are considered high risk for surgery. Many of these patients do not undergo surgery and have poor outcomes from medically treated asymptomatic, severe aortic stenosis. Transcatheter aortic valve implantation (TAVI) provides a promising treatment option for some of these patients. Several devices are under investigation. The Edwards Sapien valve (Edwards Lifesciences, Irvine, CA) and the CoreValve (Medtronic, Minneapolis, MN) have the largest human experience to date. Initial data suggest that these devices have an acceptable safety profile and provide excellent hemodynamic relief of aortic stenosis. The Edwards Sapien valve is currently under investigation in the United States in the PARTNER (Placement of Aortic Transcatheter Valve) trial in high-risk surgical or inoperable patients; TAVI is available for clinical use in both Canada and Europe. TAVI is not used in low- or intermediate-risk surgical patients; however, future studies may prove its applicability in these subsets. The major complications of TAVI include access site–related problems and device malpositioning/migration. There are several new-generation prosthetic valves and delivery systems designed to be low profile and repositionable. Technical advances and refinement of the implantation methods may make TAVI even safer and ultimately a better treatment option, not only for patients with high surgical risk but also for those with moderate or low risk.

Introduction
Valvular heart disease has a significant impact on cardiovascular mortality and morbidity [1–3]. Aortic stenosis (AS) is the most common valvular lesion in the aging population, with a prevalence of 4.6% in adults ≥ 75 years of age [2–4]. The advancing age of the population, combined with the lack of pharmacologic therapies to prevent, halt, or effectively slow the progression of AS, has led to an even greater burden of this disease in developed countries [1–3].

Surgical aortic valve replacement (SAVR) is the recommended treatment for patients with symptoms [5]. After the onset of symptoms, average survival may be as brief as 1 to 3 years without SAVR [5–9]. Within the United States, more than 30,000 aortic valve replacements (AVRs) are performed annually for severe AS. Many patients with severe symptomatic AS do not undergo surgery for various reasons. Some are not referred for surgery because of comorbidities or patient preference; others are deemed inoperable by the surgeon because of the presence of coexisting illnesses. This issue is particularly the case with the elderly. In the Euro Heart Survey on valvular heart disease, 33% of patients with severe symptomatic AS did not undergo surgery [10]. Other studies similarly have shown that 27% to 41% of patients with severe symptomatic AS do not undergo SAVR [9,11–13]. The advent of transcatheter aortic valve implantation (TAVI) provides a unique treatment option for some of these patients [14–19,20●,21].

SAVR remains the gold standard of treatment for patients with low and intermediate surgical risk. However, the surgical risk is difficult to judge at times because several subjective variables may play critical roles in
Valvular, Myocardial, Pericardial, and Cardiopulmonary Disease

Treatment

Devices

• Percutaneous AVR was first performed in a closed-chested pig model by Andersen in 1992 [22]. Since then, several different prostheses have been developed and implanted using different transcatheter approaches. Currently, the most data are available from studies involving the two valves approved for clinical use in Europe under the CE (European Conformity) mark: the Edwards Sapien valve (Edwards Lifesciences, Irvine, CA) and the CoreValve (Medtronic, Minneapolis, MN). Several other second-generation valves have been tested in humans in initial feasibility studies. These valves are repositionable and are potentially deployable via smaller delivery systems. Some examples of these newer valves are the Direct Flow (Direct Flow Medical, Santa Rosa, CA), AORTex, and Lotus (Sadra Medical, Los Gatos, CA) valves. The details of these valves are beyond the scope of this review.

• The Edwards Sapien valve is a trileaflet bovine valve attached to a stainless steel frame, constituting a balloon-expandable stent. The proximal portion of the stent is covered by a fabric skirt on its outer perimeter to minimize paravalvular leak. The valve is available in two sizes. The 23-mm valve is mounted inside a 14.5 mm–long stent, whereas the 26-mm valve requires a 16-mm stent. About 4 or 5 mm of the distal part of the stent is not covered by the skirt. The newer-generation Edwards valve, the Sapien XT, has a lower crimped profile because it is a cobalt-chromium stent with thinner struts and a more open design, without compromise of its radial strength. Bovine pericardial leaflets are matched for thickness and elasticity and incorporate treatment with ThermaFix anticalcification (Edwards Lifesciences) [23]. The scalloped geometry and attachment method of the leaflets have been modified to achieve a naturally closed design. The 23-mm Sapien valve can be introduced via a 22F sheath, whereas the 26-mm valve needs a 22F to 24F sheath, depending on the type of catheter on which the stent is mounted. The Sapien XT valve has a significantly lower profile.

• The CoreValve ReValving system consists of a self-expandable nitinol stent with a trileaflet porcine pericardial valve. The stent is carefully designed with three contiguous leaves of structure and function. The upper third of the frame has low radial force and sits within the ascending aorta to orient the prosthesis in the aortic root. The middle third of the frame has high hoop force; the valve leaflets are attached to this portion of the stent. The lower third of the frame exerts high radial force and sits within the left ventricular outflow tract. A skirt of pericardium borders the lower portion of the valve to create a seal and prevent paravalvular aortic regurgitation. This valve design is such that although the prosthesis is anchored within the annulus, its function is supra-annular. This valve also is available in two sizes: 26 and 29 mm. The 26-mm valve sits within a 55-mm stent; the 23-mm valve is deployed within a 53-mm stent. The skirt height is 12 mm for both valve sizes.
Implantation approaches

- The prosthetic valves can be delivered in retrograde or antegrade fashion (Fig. 1). Currently, the CoreValve can be deployed only retrogradely, whereas the Sapien valve can be deployed antegradely or retrogradely. The retrograde delivery is commonly performed from the femoral artery, but subclavian access has been used in some patients with significant iliofemoral disease receiving the CoreValve device. In the initial experience with the first-generation Cribier-Edwards valve (an equine valve; Edwards Lifesciences), transseptal access allowing an antegrade approach was used. An antegrade approach from the apex of the heart (transapical) has been used in some patients with severe iliofemoral disease receiving the Edwards Sapien valve.

- The transfemoral approach (Fig. 1A) is the simplest and quickest way to access the aortic valve. Access is obtained by percutaneous puncture or by surgical cutdown of the femoral artery. Perclose devices (Perclose, Menlo Park, CA) typically are used to close the arteriotomy if the percutaneous approach is used. The aortic valve is then crossed in the usual manner, commonly using an AL1 catheter and a straight wire. A stiff wire is placed in the left ventricle with a big loop. A temporary pacing wire is placed in the right ventricle for rapid pacing. Rapid pacing is critical for the balloon-expandable valve to avoid unintentional motion of the valve during deployment. Initially, the aortic valve is dilated using a 20- to 23-mm balloon with rapid pacing. Following this procedure, the prosthetic valve is advanced into position and the native aortic valve is crossed. Positioning of the valve at the correct height is a crucial step during transcatheter valve replacement because currently available valves are not repositionable. Transesophageal echocardiographic and fluoroscopic guidance is necessary for accurate positioning. The valve is deployed under rapid pacing once the satisfactory position is achieved for the Edwards Sapien valve. The CoreValve is deployed without pacing by unsheathing the valve. Proper valve deployment is confirmed by online imaging.

- With the transapical approach (Fig. 1B), access is obtained by mini-thoracotomy. The apex of the heart is punctured using a needle after two layers of pursestring sutures are placed around the intended site. The aortic valve
is crossed antegradely, dilated, and then stented under rapid pacing as in the transfemoral route, except that the Edwards Sapien valve is mounted appropriately with its sleeve on the ventricular side of the valve.

- The transseptal approach (Fig. 1C) is somewhat more challenging for an interventionalist who may not be accustomed to working in the left atrium. There is some danger of damaging the mitral valve with the stiff wire if adequate slack is not maintained during the procedure. Femoral venous access is obtained and a balloon-tipped catheter advanced into the left ventricle after transeptal puncture. The aortic valve is then crossed with a wire or the catheter itself. The wire is then snared via femoral arterial access, and a catheter is passed to the aortic valve for adequate control of the wire. Valvuloplasty and valve replacement steps are similar to those of other approaches.

## Outcomes

- Percutaneous AVR was first performed via transseptal access by Dr. Allan Cribier in Rouen, France in April 2002. The initial experience from compassionate use of the balloon-expandable 23-mm valve from the antegrade approach was reported in the I-REVIVE (Initial Registry of Endovascular Implantation of Valves in Europe) and RECAST (Registry of Endovascular Critical Aortic Stenosis Treatment). The procedural success rate was 75%, with a 30-day mortality rate of 23%. Moderate to severe aortic regurgitation was reported in 63% of patients, partly as a result of the valve size. Concerns also were raised about the procedural challenges posed by the transeptal puncture and the potential for damage to the mitral valve apparatus by the stiff wire and aortic prosthesis.

- Significant advances were made by Dr. John Webb in Vancouver in implanting this valve retrogradely via the transfemoral route. His team successfully implanted the Cribier-Edwards valve in 14 of 18 patients who had previously been deemed unsuitable for SAVR [16]. The measured aortic valve area increased from 0.6 ± 0.2 to 1.6 ± 0.4 cm² and remained stable at 1-month follow-up [16]. The early mortality rate was 11% (2 of 18), and short-term survival was 89% (16 of 18) at a mean follow-up of 75 days [16]. The same group reported both short- and long-term outcomes in an extended cohort of 50 patients [24••]. Procedural success increased from 76% in the first 25 patients to 96% in the second [25], and 30-day mortality fell from 16% to 8%. Further, this series demonstrated that paravalvular leak is not a major issue if the valve size is larger than the annulus (ie, a 23-mm valve for a 17- to 21-mm annulus and a 26-mm valve for a 21- to 24-mm annulus). It also was apparent that the success rate was very dependent on proper patient selection, with the main focus on vascular access to prevent procedural vascular complications.

- Lichtenstein et al. [25] successfully implanted the Cribier-Edwards valve using the apical approach and fluoroscopic guidance in all seven patients in whom they attempted the procedure. All patients were deemed by an experienced operator to be unsuitable for SAVR and also for percutaneous transfemoral percutaneous heart valve implantation because of severe aortoiliac disease [25]. Four of the seven patients were alive at 6 months [26]. Subsequently, Walther et al. [27] published their data describing implantation of the Cribier-Edwards valve in 30 elderly patients. At a mean follow-up of 108 days, 86% of the patients reportedly were doing well [27].
• These initial experiences led to the development of multicenter registries from the United States (REVIVAL II [Transcatheter Endovascular Implantation of Valves II trial], the European Union (REVIVE II [Registry of Endovascular Implantation of Valves in Europe II]), and Canada (Canadian Special Access), which included patients with a valve area $\leq 0.8$ cm$^2$ and high predicted operative mortality. REVIVAL II included patients treated with both the transfemoral and transapical approaches. Of the 55 transfemoral patients, the procedure was successful in 87%; the 26-mm valve was used in 62% of the patients. The 30-day observed mortality rate was 7.8%. The transapical cohort had survival rates of $81.8\% \pm 6.2\%$ at 1 month and $71.7\% \pm 7.7\%$ at 3 months [28].

• The first human recipient of the CoreValve aortic prosthesis was reported in 2005 by Grube et al. [29]. The CoreValve system has progressed in a manner similar to that of the Edwards valve system in the several stepwise advances made to the device, deployment techniques, and patient selection. The initial study, in 25 patients, used general anesthesia with extracorporeal support and femoral access via a surgical arterial cutdown. With the change from a bovine to porcine valve, the system decreased in size from 24F to 21F, and the third-generation device is 18F. In the second intention-to-treat series, the CoreValve was implanted in 50 and 36 patients using second-generation (21F) and third-generation (18F) devices, respectively [30]. A vascular closure device was used in all patients following percutaneous access (18F system) [30]. The composite periprocedural rate of death, stroke, and myocardial infarction was 14% [30]. The overall 30-day mortality rate was 12%, whereas the combined rate of death, stroke, and myocardial infarction at 30 days was 22% [30].

• Based on these initial data, the CoreValve and Edwards Sapien valve were approved in Europe under the CE mark in 2007 and in several other non-US countries thereafter. Approval led to a rapid increase in the number of percutaneous heart valve implants. By mid-2009, approximately 4000 each of the CoreValve and Edwards Sapien valves were implanted worldwide. The PARTNER EU (Placement of Aortic Transcatheter Valve) trial was a feasibility study conducted in the European Union before the Edwards Sapien valve was granted the CE mark in Europe. European experience after the CE mark approval has been collected in the SOURCE registry (Edwards Sapien Aortic Bioprosthesis European Outcome Registry). Data from these two registries have been presented at various national and international meetings. The aggregate procedural and outcome data are presented in Table 1.

**Complications**

• Both valves are reported to have several procedural complications, some of which can be prevented by proper patient selection and careful procedural monitoring. Complications can be classified into access site–related complications, malpositioning of the valve (valve embolization, paravalvular regurgitation), compromise of surrounding structures (coronary ostia, conduction system, mitral valve), and systemic complications (eg, stroke, infection, bleeding).

• The rate of access site–related complications was as high as 30% in earlier experiences, and these usually were associated with significant mortality. With proper patient selection based on preprocedural CT angiography and, at times, intravascular ultrasound, the complication rate has decreased to as low as 5% to 6%. Femoral access complications include arterial rupture, dissection, and, occasionally, limb ischemia. Apical bleeding and pseudoaneurysm have been reported with the apical approach.
Positioning of the valve in an accurate location is critical to procedural success because it cannot be repositioned once deployed. Location for deployment as well as appropriate sizing are crucial for proper functioning. If the Edwards Sapien valve is placed too deep within the ventricle, it may embolize into the ventricle or the overhang of native leaflet may prevent proper functioning of the prosthetic valve leaflets, leading to central aortic regurgitation. If the valve is placed too high within the aorta, it may embolize into the aorta, cause coronary compromise, or lead to significant paravalvular regurgitation. It is proposed that the inherent ventricular positioning of the CoreValve may lead to a higher incidence of heart block. Heart block is more common with self-expanding valve implants and can manifest hours or even a few days after the procedure. Although mild to moderate paravalvular regurgitation is not uncommon, severe regurgitation is infrequent. The size of the prosthesis, size and shape of the annulus, extent of calcification of the aortic valve and annulus, and height of implantation and deployment pressure are some of the factors that determine the severity of postimplant regurgitation. Although there is some indication that the paravalvular leak improves somewhat with fibrosis over time, more data are needed to confirm this observation.

Occlusion of the coronary ostia may be catastrophic and has been reported in about 1% of cases [31•]. Left coronary occlusion is most commonly seen when the coronary ostium lies low in the sinus (< 7 mm from the bottom of the leaflet), the native leaflet is long and has bulky calcification of the tips, and the prosthetic valve is slightly oversized. Percutaneous restoration of flow is possible and may be life saving. Mitral valve compromise is a concern with CoreValve implantation, although data to support or refute this concern are lacking.

### Table 1. Procedural success with transcatheter aortic valve implantation

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Mean age, y</th>
<th>Procedural success, %</th>
<th>ES/STS score, %</th>
<th>30-Day mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Edwards Sapien valve</strong>: transfemoral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REVIVE/REVIVAL [32]</td>
<td>161</td>
<td>83.7</td>
<td>88.2</td>
<td>34.3/13.1</td>
<td>11.2</td>
</tr>
<tr>
<td>Vancouver [33]</td>
<td>114</td>
<td>83.9</td>
<td>92.1</td>
<td>30.3/--</td>
<td>7.9</td>
</tr>
<tr>
<td>PARTNER EU [34]</td>
<td>59</td>
<td>82.5</td>
<td>96.3</td>
<td>24.7/10.9</td>
<td>5.0</td>
</tr>
<tr>
<td>SOURCE [34]</td>
<td>295</td>
<td>81.8</td>
<td>94.0</td>
<td>26.4/--</td>
<td>6.4</td>
</tr>
<tr>
<td><strong>CoreValve</strong>: transfemoral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grube et al. [35•]</td>
<td>136</td>
<td>81.5</td>
<td>70/70.8/91.2*</td>
<td>23.1</td>
<td>40/8.3/10.8*</td>
</tr>
<tr>
<td>Bleiziffer et al. [36]</td>
<td>137</td>
<td>81.4</td>
<td>98.5</td>
<td>24.3</td>
<td>12.4</td>
</tr>
<tr>
<td>Tamburino et al. [37]</td>
<td>30</td>
<td>82</td>
<td>97</td>
<td>25.3</td>
<td>6.7</td>
</tr>
<tr>
<td>Laborde [38]</td>
<td>1265</td>
<td>82</td>
<td>98</td>
<td>22.7</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>Edwards-Sapien valve</strong>: transapical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REVIVE/REVIVAL [32]</td>
<td>40</td>
<td>83.7</td>
<td>83.8</td>
<td>35.5/13.1</td>
<td>17.5</td>
</tr>
<tr>
<td>Vancouver [33]</td>
<td>58</td>
<td>80.0</td>
<td>96</td>
<td>37.1/--</td>
<td>18</td>
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<tr>
<td>PARTNER EU [34]</td>
<td>172</td>
<td>82</td>
<td>92.9</td>
<td>26.7/--</td>
<td>15.1</td>
</tr>
<tr>
<td>SOURCE [34]</td>
<td>70</td>
<td>82</td>
<td>94</td>
<td>33.8/12.2</td>
<td>18.8</td>
</tr>
</tbody>
</table>

*Edwards Lifesciences, Irvine, CA.
†Medtronic, Minneapolis, MN.
‡For 25F, 21F, and 18F systems, respectively.
ES—European System for Cardiac Operative Risk Evaluation (EuroSCORE); PARTNER EU—Placement of Aortic Transcatheter Valve; REVIVAL—Transcatheter Endovascular Implantation of Valves; REVIVE—Registry of Endovascular Implantation of Valves in Europe; SOURCE—Edwards Sapien Aortic Bioprosthesis European Outcome Registry; STS—Society of Thoracic Surgeons.
Stroke is an important complication of transcatheter as well as surgical aortic valve implantation. This complication is embolic in origin and thought to be a result of manipulation of the devices in the ascending aorta and arch. It was thought that embolic stroke would be more frequent with the retrograde approach, but data suggest that stroke is equally common with the transapical approach (Table 2). This outcome may be a result of the fact that intracardiac introduction of devices through the apical sheath may lead to cerebral embolization. It also has been observed that strokes commonly occur in cortical watershed zones with the transapical approach, raising the possibility that hemodynamic instability or preexisting cerebrovascular disease may contribute to some strokes with this technique. Careful imaging of the aorta and screening for carotid disease may help identify patients at higher risk for stroke.

### PARTNER trial

The PARTNER trial is a randomized prospective study designed to assess the safety and efficacy of the Edwards Sapien percutaneous valve in high-risk patients with symptomatic severe AS. The primary end point is 1-year mortality. This study has two independently powered arms. One, powered to prove superiority, will compare outcomes of patients who are deemed inoperable and then randomly assigned to receive best available therapy (medical with or without balloon valvuloplasty) or transcatheter AVR. Enrollment has been completed in this arm of the study, with 350 patients. The 1-year outcome data will be available by the end of 2009. The second cohort, powered to prove noninferiority, will compare outcomes of patients who are at high surgical risk (> 15% operative mortality). These patients then will be randomly assigned to TAVI or SAVR. The transapical approach...
can be used for patients in this cohort who do not have adequate transfemoral access. Enrollment in this arm also was completed recently.

- This study is unique in several ways. All patients were carefully selected after review by the investigators during twice-weekly conference calls. During each stage of the study, surgeons and cardiologists work very closely to select patients and to determine the approach, the actual procedure, and postprocedural care. This study will provide critical information on treatment options for this expanding patient population.

### The future

- The rapid application of this procedure in Europe and Canada suggests that it is a very valuable treatment option for a subset of symptomatic patients with AS at high risk for surgery. Objective proof will come from the PARTNER trial. New questions will arise as fundamental questions are answered. The next step will be to expand this procedure to lower-risk patients while making it safer with device and procedural modifications. The new devices will potentially provide the option to reposition the valve, making the procedure more dependable and safer. Decreasing the size of the delivery system will be critical for a more widespread application of this technique. Availability of multiple valve sizes also will be crucial for improved success. As more devices become available, it will be important to determine which device is better for any specific patient or anatomy. Further, the training of cardiovascular physicians, development of appropriate interventional suites for performing the procedure, and continued refinements in the devices and delivery systems will be critical for the overall success of this exciting new era of transcatheter treatment for valvular heart disease.

### Disclosure

No potential conflicts of interest relevant to this article were reported.

### References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance
  •• Of major importance


This is a concise review of the current status of TAVI. Zajarias A, Cribier AG: Outcomes and safety of percutaneous approaches to transcatheter heart valve implantation: impact on clinical and valve-related outcomes. Circulation 2009, 119:3009–3016.


This interesting case report sheds light on coronary ostial compromise after percutaneous AVR.


The authors report on the safety and efficacy of the self-expanding CoreValve system.


EMERGENT CORONARY ANGIOGRAM FOR GRAFT FAILURE SUSPICION AFTER CORONARY ARTERY BYPASS GRAFTING: THE MONTREAL HEART INSTITUTE EXPERIENCE

Gilbert Gosselin, MD

Between September 2000 and August 2008, we identified 58 consecutive patients who underwent a coronary angiogram following CABG during the same hospital admission for suspected myocardial ischemia. Patients were divided in 2 groups: conservative treatment (group 1) and revascularization (group 2). We reviewed the medical records of all 58 patients as well as the pre-operative and post-CABG angiographies.

Results
Among a total of 158 inserted grafts, 50 (32%) were identified as failing ones. The most common cause of graft failure was graft occlusion or subtotal (> 70%) anastomotic stenosis (n=35), followed by graft kinking (n=11). Diffuse post-operative graft vasospasm was found in 4 patients. Conservative treatment was decided for 23 patients (39.7%) and percutaneous revascularization was the treatment in 35 patients (60.3%). When conservative treatment was decided, the left internal mammary artery (LIMA) graft was functional in all cases. Revascularizations were performed on the native coronary arteries in 26 cases (74.3%). In 31.4% (31 pts), the revascularization was realized in or through the graft.
One intervention was complicated by anastomosis rupture during stent implantation. The 30-day mortality was 19% (11 pts) in the whole cohort and reached 29% in the revascularization group (10 pts).

Conclusions
Overtime rescue PCI following failed CABG was increasingly used in our institution. Anastomotic lesions should be considered with caution considering the risk of rupture.

OPTIMAL ANTIPLATELETS THERAPY IN ACUTE CORONARY SYNDROME BEFORE INTERVENTION

Gilbert Gosselin, MD

ASA has been used as a standard therapy for ACS along with heparin following the paper of Dr Théroux in the New England Journal of Medicine in 1992.
With the use of PCI and stents in ACS patients, the use of thiopyridines was established, first with ticlopidine and more recently with clopidogrel. In spite of many in vitro trials, the optimal dose of clopidogrel as well as ASA is not established in ACS patients undergoing intervention. The results of the CURRENT trial will give us an answer to these questions. More recent drugs (prazugrel…) will soon be widely available and be part of our optimal medical treatment.
ROLE OF CCT AND CMR IN CURRENT CARDIOLOGY PRACTICE

Mouaz H. Al-Mallah MD MSc FACC FAHA FESC

Cardiac CT and MRI are increasingly being used in the clinical evaluation and management of patients with suspected or known cardiac pathology. In this lecture, we will review the top ten indications for Cardiac CT and Cardiac MRI:

Cardiac CT:
1. Evaluation of patients with chest pain and intermediate pretest likelihood of CAD, negative markers and ECG
2. Evaluation of patients after equivocal stress testing
3. Evaluation of patients with suspected coronary anomalies
4. Evaluation of patients with new onset heart failure
5. Evaluation of patients with

Cardiac MRI:
1. Assessment of Viability
2. Assessment of cardiomyopathy
3. Assessment of patients with pericardial disease
4. Patients with elevated troponin and normal coronaries on angiogram
5. Patients with congenital heart disease

LESSONS FROM FFR IN THE CATHETERIZATION LAB

Samir Alam MD FACC

Coronary Heart disease (CHD) is a leading cause of death worldwide. The predictors of outcome of CHD remain elusive. Clinical and pathologic studies have underscored marked dissociation between severity of coronary lesion stenosis and clinical outcome specifically events related to plaque disruption and ACS (Acute Coronary Syndrome). Despite vast advances in imaging particularly MSCT and IVUS/VH, there are no parameters which help identify candidates likely to benefit from revascularization added to, or in comparison to, optimal medical therapy (OMT). Whereas revascularization of ischemic territories exert significant impact on prognosis, revascularization of non-ischemia producing lesions is associated with increase morbidity and worsened clinical outcome compared to OMT alone. Clinical non invasive Ischemic indices are emerging as highly important determinants of prognosis. In the cath Lab FFR measurement seem superior to QCA/IVUS in predicting lesions prone to future adverse events. Although the link between stenosis hemodynamics and clinical event is poorly understood, defining ischemia producing lesion seems to reliably define appropriateness of revascularization as shown in major recent clinical trials.

FFR guided revascularization beyond Angiography is emerging as most cost effective method of intervention both for reducing mortality as well as cost saving by averting unnecessary procedures.
INTRA VASCULAR ULTRASOUND A NICHE VERSUS ROUTINE APPLICATION IN
THE EAR OF DRUG ELUTING STENTING

Samih Lawand MD, FRCPC, FACC

For many years Intra Vascular Ultrasound (IVUS) remained a tool of interest to those who primarily engaged in research. IVUS since then became a resource for true luminal and vessel wall histopathological definitions that provided invaluable details. However since the era of good old balloon angioplasty the role of IVUS remained limited to certain applications that included among others angiographic borderline lesions, limited dissections, ambiguous angiographic findings, calcifications and to a lesser extent thrombi.

The era of Drug Eluting Stenting (DES) brought additional challenges to modern Per-cutaneous Coronary Interventions (PCI) including issues of Stent sizes and deployment pressures, issues of Stent mal-apposition acute or acquired and Geographic miss. Many of these concerns remained under estimated until we were shocked with the scare of stent thrombosis early late or very late. The role of IVUS hence became much more contributing and set additional standards of Stent deployment techniques; Of particular importance the various niche applications like Left Main, Bifurcational and Osteal Stenting and increasing Off-label applications of long overlapping stents.

IVUS as well enhanced our ability to define causes of Stent failures including Stent fractures, other Stent deformities and mal-appositions. More recently IVUS introduced a forward imaging catheters that is likely to enhance the safety and success of Chronic Total Occlusion Interventions. In addition to grey scale IVUS the introduction of Histo-Pathological simulations using Virtual Histology (VH) and more recently i-map technology is increasingly becoming a niche application for detecting vulnerable plaque providing better definition of Thin Cap Fibro Atheroma (TICFA) that emerged as potential cause of vessel or Stent failure if associated with geographic miss. Thus VH is likely to provide An emerging strategy of potential remedial approaches for Vulnerable plaque including lesion pacification whether by intensive medical therapy or possibly Stenting.

IVUS IN DES FAILURES

Lisette Okkels Jensen, MD DMSci Ph.D

In percutaneous coronary interventions (PCI), drug-eluting stent (DES) implantation is used increasingly for revascularization in patients with coronary artery disease. Compared with bare metal stents, DESs have shown improved results with reduced need for repeat revascularization. DES failures include in-stent restenosis and stent thrombosis. Stent thrombosis is a rare, but devastating adverse event after PCI associated with high mortality and morbidity.

It has a multifactorial occurrence that has been attributed to a range of patient and lesion related factors as well as the quality of implantation of the stent. The only routinely available tool for assessing many features of stent implantation, intravascular ultrasound (IVUS) has become indispensable in trials of DESs and is currently the best way to identify or exclude causes of DES failure. IVUS enables optimization of DES implantation and DES underexpansion. Although IVUS resolution is not sufficient for determining reendothelialization, serial (postprocedure and follow-up) IVUS can measure intimal hyperplasia, assess acute and late incomplete stent apposition,
detect the presence and persistence of edge dissections, assess vascular responses such as remodeling, study edge effects, compare overlapping with nonoverlapping segments, and look for causes of restenosis and thrombosis.

In conclusion, IVUS provides unique insights during DES implantation, allows DES optimization and should always be used during the management of DES failures: in-stent restenosis and DES thrombosis.

**MANAGEMENT OF HAEMOPERICARDIUM DURING PERCUTANEOUS MITRAL COMMISSUROTOMY**

Georges Ghanem MD, FESC, FACC

Background: Haemopericardium is a severe complication of percutaneous mitral commissurotomy (PMC) due to transseptal catheterization. There are no particular recommendations in the literature on the management of this complication during PMC. Our objective is to review and analyze the cases of haemopericardium in a series of 245 patients, and provide certain recommendations for its management during PMC.

Patients and Methods: Between January 1993 and December 2008, 60 males and 218 females with severe mitral stenosis were enrolled. The mean age was 44 years old. 89% were class III NYHA. The mean echo score was 8.5.

Results and Haemopericardium Management: The Inoue technique was used for all the procedures. Overall, the procedure was performed successfully in 98%. Death occurred in 0.4%, severe mitral regurgitation occurred in 0.8% and haemopericardium in 2.1% (all female patients). The management of haemopericardium in these patients was as follows: The 1st patient, a 45 year-old female, was sent immediately to surgery for open pericardiocentesis and mitral valve replacement. The 2nd patient, a 28 year-old female, had a pericardiocentesis in the cath lab, and then surgery was performed on an elective basis. The 3rd patient, a 50 year-old female, had a pericardiocentesis in the cath lab, and then 24 hours later a PMC was done with successful results. The 4th patient, a 35 year-old 7-months pregnant female, was managed as follows: Heparin was immediately reversed with Protamin. Then, a pericardiocentesis was performed after 6F sheath installation into the pericardium under echo-guidance.

We Re injected the drained blood from the pericardium into systemic circulation via the femoral vein. Due to pregnancy, the patient was at high risk for surgery, therefore, the procedure was continued with one balloon inflation immediately at the appropriate diameter corresponding to the patient’s height (height/10 + 10) with successful result. The follow-up and the delivery were totally normal. The 5th and 6th patients, 53 and 64 year-old females, were managed exactly the same way as the 4th patient with successful results. To note that the 5th patient was operated for open pericardiocentesis on the cath lab table for a large posterior right atrium tear, immediately after a successful dilation of the valve and balloon retrieval.

Conclusion: Although haemopericardium is a complication of PMC, our clinical experience demonstrates that it could be successfully managed in the cath lab through continuing PMC after pericardiocentesis and heparin reversing. Such management regime could be particularly beneficial for patients at high risk for surgery (ex. pregnancy).
“STATUS ON T-EVAR” (THORACIC ENDOVASCULAR ANEURYSM REPAIR)
Fady Haddad MD

Thoracic Aortic pathologies (Aneurysms, Dissections, Traumatic ruptures) remain challenging despite substantial improvements in surgical and critical care techniques.

Over the past few years, endovascular approach (T-EVAR: Thoracic Endovascular Aneurysm Repair) rapidly became the first option in most centers, when anatomically feasible, specially with short and mid-term data showing reduced aneurysm related mortality and peri-procedural morbidity and reduced incidence of spinal cord ischemia (SCI). With the encouraging results, endovascular management is being extended to more difficult anatomy beyond the original IFU, with the combination of “hybrid procedures” or endovascular branched devices. Today there are already three devices in the US that are FDA approved for T-EVAR, and others are under clinical trials.

Indications, procedure and outcome of T-EVAR will be discussed and a summarized algorithm for approach to a patient with TAA will be presented.

THE RADIA APPROACH IN PCI
Mohammad Zgheib M.D

The trans-radial procedure is often associated with improved patient’s safety and comfort and typically results in overall fewer bleeding complications. Over the past 30 years, trans-radial vascular access for coronary angiography and intervention has flourished in many countries while still accounting for less than 2% of all cases performed in the United States. The benefits of trans-radial access include decreased bleeding risk, increased patient comfort, lessened post-procedure nursing workload, and decreased hospital costs. The reasons why the trans-radial approach has not caught on in the US and worldwide are unclear, but are probably related to physician and ancillary staff’s comfort with femoral access, apprehension toward change, and higher operator radiation exposure. However, once the procedure is mastered, the operator and staff become extremely comfortable with the technique and radiation exposure can be substantially reduced. Although the femoral approach is more common, cardiac catheterization via femoral access demands greater post-procedural nursing care, is limited by prolonged bed rest (usually about 4 hours), and delays discharge. Femoral access is also more frequently associated with increased back pain, urinary retention, delayed ambulation, and neuropathy. To overcome some of these limitations, many operators have adopted the use of vascular closure devices, but published data have consistently shown that these devices are associated with the same or increased hemorrhagic risks in comparison with manual compression. In addition, rare complications such as infections, femoral artery stenosis, arterial laceration, uncontrolled bleeding, pseudo-aneurysm, arterio-venous fistula, and device embolism and limb ischemia have all been reported with the use of vascular closure devices. An increased awareness of the advantages of trans-radial catheterization is therefore necessary in order for interventionalists to adopt this safe and effective technique.
Peripheral Vascular Disease (PVD) is highly prevalent and underdiagnosed. More than 50% of physicians are unaware of PAD at screening. Thus, patients with PAD have an increased risk of morbidity and mortality. Risk factors for PAD includes DM, smoking, hyperlipidemia, hypertension and hyperhomocysteinemia. PAD often occurs with other manifestations of atherosclerosis, including cerebrovascular and cardiovascular disease. Among men with PAD, 29.4% had cardiovascular disease. Among women with PAD, 21.2% had CVD. In comparison, 11.5% of men and 9.3% of women without PAD had a history of CVD. Thus, in this study, other CVD occurred two to three times more frequently among persons with PAD.

Intermittent claudication is the most common manifestation of PAD. A small percentage of patients with intermittent claudication (1.5–5%) develop critical leg ischemia, which causes pain at rest and may result in gangrene and amputation of the affected limb.

Beside physical exam several non-invasive testing play an important position in the testing of patients for PAD that may include ABI, segmental pressure, PVR, duplex ultrasound CT angiography and/or MRA.

Managing PAD is essentially by risk factors modification. In patients with PAD, morbidity and mortality can be significantly decreased by stopping smoking, taking regular exercise (three times a day), and reducing dietary fat intake. Importantly, pharmacological treatment should include secondary prevention of ischemic events of atherothrombotic origin by an antiplatelet agent. Pharmacological treatment to reduce cholesterol, and to control diabetes and hypertension, where present, is also important. These risk-factor modification strategies also apply to reduction of ischemic risk in patients with symptomatic atherosclerosis affecting the coronary and cerebral arterial beds.

Intervention, either by direct reconstruction of diseased leg arteries by angioplasty (with or without subsequent stent placement), endarterectomy or by replacement by peripheral bypass grafting, can relieve symptoms caused by inadequate blood flow. The decision to operate should be based on symptom severity, degree of disability and perceived surgical risk.

The number of percutaneous revascularization procedures performed for symptomatic peripheral arterial disease (PAD) has significantly increased over the past several years. Traditionally, the use of percutaneous techniques were limited to certain anatomic subsets, such as stenosis or focal occlusions, with surgical treatment preferred for more extensive disease. More recently, endovascular specialists are facing the challenges of treating commonly-encountered peripheral chronic total occlusions (CTOs). Peripheral CTOs remain one of the most challenging lesions for the endovascular specialist. Unlike the coronary circulation, these occlusions are often long and associated with other features of complexity.

There are several techniques for crossing CTOs. The most recent one is the use of the CROSSER catheter that mechanically vibrates against a CTO. It allows central lumen navigation and avoid subintimal dissection that may benefit long term outcomes and optimize adjunctive treatments like atherectomy, PTA and/or stenting. Innovative technology is essential if long, calcified, and chronic occlusions are to be successfully recanalized without acute complications and with satisfactory short- and long-term outcomes. Although treatment of CTOs remains challenging and requires patience and knowledge of many devices, clinical success leads to significant improvement in the quality of life and, for some, limb salvage, and is therefore rewarding.
The main goal of a cancer screening programs is early detection allowing more effective therapeutic interventions and improved survival. With advances in medical technology and a better understanding of tumor biology, guidelines for cancer screening have evolved over the years for many malignancies.

Ovarian cancer is the sixth leading cause of cancer death in women in the United States. Carcinomas arising from the surface ovarian epithelium represent the most common type of ovarian cancer, are usually diagnosed in their advanced stages and carry a poor prognosis. When detected at an early stage, the 5-year survival rate is 90%. The signs and symptoms caused by ovarian cancer are frequently nonspecific. As a result, the majority of patients have advanced stage disease at diagnosis. Efforts have focused on identifying screening modalities for this disease. Ultrasound and blood Ca125 testing have been investigated in this setting either as isolated or as combined screening modalities. The major concerns have been their limited positive predictive value when used in screening women who have low to average risk. Therefore there is an ongoing need to identify new screening tests and strategies which should be readily available, well accepted by the population, cost effective and achieve high sensitivity, specificity, positive and negative predictive values. Recently a US based company, Laboratory Corporation of America, released OvaSure, a screening test that consists of a six-biomarker panel including leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibiting factor and Ca-125. The company claims that this new test discriminates between disease-free women and ovarian cancer patients and has 95.3% sensitivity and 99.4% specificity. There have been a number of statements by professional societies and recently a warning by the US Food and Drug Administration raising concerns about the limited available data on this test and the inadequacy in its validation.

An optimal screening test with high level of sensitivity and specificity is indispensable for early detection of ovarian cancer. Serological screening with serum biomarkers (serum proteins and autoantibodies) is being tested as a first-line screening test and this in combination with TVS or color-flow Doppler imaging may prove very effective in early detection of ovarian cancer.

Cervical cancer is a major cause of cancer mortality around the world. Deaths related to this disease account for 9% of all female cancer deaths claiming over 270,000 lives each year worldwide (2). In addition, cervical cancer contributes over 2.7 million years of life lost among women between the ages of 25 and 65; around 90% of these occur in developing countries (3). The risk factors associated with cervical cancer were identified decades ago. However, a breakthrough happened when the Human Papilloma Virus (HPV) was discovered and its association with cervix cancer was confirmed in a number of studies. Currently, it is widely accepted that HPV infection is the most important cause of cervix cancer.

In developed countries with an excellent public health infrastructure and a high compliance of women, early cytological detection of cervical cancer (PAP smear) has led to an impressive reduction of mortality while in other world regions, including Central America, South East Africa and India, incidence and mortality rates are still very high. Today, more than 80 per cent of all cervical cancer deaths occur in developing countries. This emphasizes the need to establish national cervical cancer screening program in developing countries comparable to those in
developed countries.

Over the past decade, we have witnessed significant advances in screening techniques for cervical cancer. The introduction of liquid based cytology has helped overcome the limitations of the conventional PAP smear by optimizing transfer of cells to slide, allowing the evaluation of a random and representative sample and minimizing the obscuring material. The development of hybrid capture technology has allowed easy and universal access to diagnosing HPV infection. The ALTS trial revealed that HPV testing improved the sensitivity for detection of high-grade cervical precancerous lesions in patients with ASCUS Pap. It improved patient management by directing at-risk patients to colposcopy.

Medical providers of gynecologic care should be well educated as to the correct interpretation of pap smears and HPV tests and should know the appropriate medical management of abnormal test results. In fact, early diagnosis and adequate treatment of precancerous cervical lesions are paramount to reduce cervical cancer associated mortality.

References

OVARIAN GERM CELL TUMORS
Adnan R Munkarah, MD

Ovarian germ cell tumors represent around 25% of all ovarian neoplasms. They usually affect women in the first three decades of life. The first step in the management is surgical and involves removal of the affected ovary and staging. Preservation of one ovary and the uterus is frequently possible especially that most patients have localized disease and are young with a desire to preserve their reproductive function. In most cases, postoperative chemotherapy is necessary.

The evolution of chemotherapy regimens in these neoplasms has paralleled those applied in testicular tumors. Currently, the combination of bleomycin, etoposide and platinum is the standard regimen achieving excellent cure rates. Fortunately, over 80% of patients regain their menstrual function after therapy. In addition case series have reported successful pregnancies following treatment. In patients with recurrent disease, cure is still a possibility. While combination
Chemotherapy is the standard in this setting, surgery to resect recurrence has a role especially in patients with recurrent immature teratomas.

Ovarian sex-cord tumors represent less than 10% of all ovarian malignancies. Granulosa cell tumors, the more common histologic type, usually present as a pelvic mass and can be hormonally active. The majority of cases present in early stage disease and the therapy is surgical. Because of the high incidence of synchronous endometrial pathology (hyperplasia and cancer), it is essential to evaluate the endometrium by biopsy especially if preservation of the uterus is being considered.

**SURGICAL STAGING IN ENDOMETRIAL CANCER**

Adnan R Munkarah, MD

Data from World Health Organization places cancer of the uterus as the seventh most common cancer affecting women with an estimated 189,000 new cases and 45,000 deaths occurring worldwide each year. The highest incidence rates are in the USA and Canada followed by Europe, Australia and New Zealand. Lower rates occur in Africa and Asia.

The 1980’s witnessed some important discoveries that improved our understanding of the biology of this disease. First, Bokhman proposed the hypothesis of two distinctly different forms of endometrial carcinoma and their associated differences in risk factors and prognosis. Type 1, or endometrioid carcinoma, was thought to represent an estrogen-stimulated progression, often arising in the setting of endometrial hyperplasia. Features of the type 1 carcinomas include increased exposure to estrogen (nulliparity, early menarche, chronic anovulation, and unopposed exogenous estrogen), obesity, and responsiveness to progesterone therapy. In contrast, type 2, or non-endometrioid carcinoma, often arises in those who are multiparous, and not obese. These tumors do not respond to progesterone therapy, and their prognosis is worse. The most common forms of type 2 endometrial cancers include uterine papillary serous carcinoma and clear cell carcinoma.

The second important milestone was a large prospective study by the Gynecologic Oncology Group that identified the risk factors and patterns of metastasis of endometrial cancer. The study showed that lymphatic spread represented the most common route of metastasis for endometrial cancer. Risk factors associated with increased incidence of lymphatic spread include histologic type and grade of the tumor, depth of myometrial invasion, lymph-vascular space invasion, ovarian metastasis and extension to the lower uterine segment and/or cervix. These findings prompted the International Federation of Gynecology and Obstetrics (FIGO) to implement a surgical staging system for endometrial cancer that incorporated surgical assessment of the retroperitoneal lymph nodes. Subsequent to these changes, a number of prospective studies have been conducted trying to better define the role of lymphadenectomy and adjuvant radiation therapy in the context of early stage endometrial cancer. Many of these studies have shown that adjuvant pelvic radiation therapy results in an improvement in progression-free survival but not overall survival. In the United States of America, most gynecologic oncologists perform surgical staging with lymph node dissection and use the information of the surgical staging to direct the use of adjuvant therapy postoperatively. Some cost-benefit studies have shown that such approach will be less costly than the liberal use of pelvic radiation that was used in the early 1980’s.
Another important change in the management of endometrial cancer is the increasing use of chemotherapy. The efficacy of chemotherapy in this disease was supported by a large prospective study that showed that systemic chemotherapy was superior to abdominal radiation therapy in patients with advanced stage disease. In addition, over half of the recurrences in early stage disease include sites outside the pelvis, a fact that supports the need for a systemic treatment.

References

THE ROLE OF AGGRESSIVE SURGERY IN THE MANAGEMENT OF EPITHELIAL OVARIAN CANCER (EOC)
Muhieddine Seoud, MD FACOG, FACS

Nearly every retrospective and prospective study has confirmed that the extent of cytoreductive surgery and the amount of residual disease are among the most important factors impacting the survival of women with advanced ovarian cancer.

Role of primary surgery: Large metanalyses have clearly demonstrated that the PFS and OS are proportional to the extent of the surgical surgical effort, and so with each 10% increase in the
proportion of patients in each cohort undergoing maximal interval cytoreductive surgery was associated with a 1.9 month increase in median survival time (95%CI=0.23 months–3.50 months, p=0.027). However, few centers around the world have adopted a more aggressive surgical approach to patients with extensive ovarian carcinomatosis, which include extensive upper abdominal surgeries. Until recently, however, no prospective RCT confirming the widely held belief that aggressive cytoreductive surgery should be the 1st step in the treatment.

Role of interval debulking: In an effort to increase the proportion of patients with advanced ovarian cancer that are ultimately left with an optimal volume of residual disease, the concept of interval cytoreduction has evolved into the treatment approach now referred to as neoadjuvant chemotherapy in which the initial attempt at cytoreduction is abandoned in favor of chemotherapy in order to reduce the extent of disease or improve patient performance. A recent prospective European trial has confirmed that surgery performed following neoadjuvant chemotherapy is routinely shorter in time, associated with a better nutritional state preoperatively, less blood loss, shorter intensive care unit stays, shorter hospitalizations, reduced risk of peri-operative morbidity, and a higher rate of optimal resection. More importantly survival was not compromised.

The role of surgery in recurrent disease: In properly selected patients, secondary aggressive debulking has a major impact on PFS similar, but to a lesser extent than in the primary setting. During this presentation, we will present convincing data on the role of aggressive surgery, including upper abdominal surgery, in the management of primary and recurrent ovarian cancer.

TWIN PREGNANCIES FRENCH 2009 GUIDELINES
Philippe Deruelle, MD

Development of new technologies and dissemination of new scientific information and incorporation of research findings into practice are major challenges to health professionals. Twin pregnancies are a high risk group which needs more intensive care than singleton. However, in France, the management may be widely different between centers and countries leading to inappropriate or usefulness practices.

Therefore in December 2009, the “College National des Gynécologues Obstétriciens Français” coordinated a National Consensus Conference in order to define, based upon the best evidence available, the standard care of twin gestation. The purpose of this guideline is to describe and, if possible, quantify the problems associated with twin management and to identify the best evidence to guide clinical care.

Methods: fourteen questions were identified including epidemiology of twins, ultrasound diagnosis of chorionicity, screening for aneuploidies, management of monoamniotic, monochorionic diamniotic and dichorionic twin pregnancies, prevention of spontaneous preterm birth, delivery and social and economic aspects of twin gestation. The MEDLINE database, the EMBASE database, the Cochrane Library, and the Guidelines published by foreign organizations or institutions such as Royal College of obstetrics and Gynaecology, American College of Obstetricians and Gynecologists, were used to conduct a literature search to locate relevant articles published. Additional studies were located by reviewing bibliographies of identified articles. The quality of evidence was evaluated and recommendations were made according to guidelines for assessing medical literature published by “Haute Autorité de la Santé”.

The short text of the guidelines is available on the CNGOF website at http://www.cngof.asso.fr/D_TELE/RPC%20GEMELLAIRE_2009.pdf (in French) and http://www.cngof.asso.fr/D_TELE/RPC_Gemel_en.pdf (in English). The full guidelines have been published in the December 2009 issue of the “Journal de Gynécologie Obstétrique et Biologie de la Reproduction”. Because many areas of practice have not been well studied, the level of evidence and strength of the recommendations are low. Indeed, many of the recommendations are made on best opinion of the experts group but not on best evidence. However, we hope that these guidelines will improve twin gestation management and prognosis. In addition, these guidelines highlighted several questions that will lead to conduct further multicenter clinical studies.

**DE DELAYED INTERVAL DELIVERY: OUR CASE SERIES AT MGH**

Mohamad Khaled Ramadan MD

It has been a frequent encounter to receive pregnant ladies in the emergency room presenting with full cervical dilatation or premature rupture of membranes rendering these unsalvageable in most cases of previability or severe prematurity in spite of efforts to rescue such pregnancies that are sometimes very precious and difficult to attain.

This disparate situation has increased several folds owing to the surge in the number of multiple pregnancies in recent two decades. However, though the risk of preterm labor and preterm premature rupture of membranes is increased in multiple pregnancies, yet having more than one fetus especially with independent sacs and placenta s provide a second or more chances of rescuing this pregnancy. A concept named delayed interval-delivery.

We describe the outcome of six attempts at (Delayed Interval-Delivery) at our service with varying degrees of success. Four twins, one triplet and one quadruplet gestations were managed with this intention during the past thirteen years. Five of these six pregnancies presented with advanced cervical dilation due to PTL with the leading member of multiple gestation within its bulging membranes while one was due to PPROM. Four were previable and two were at the limits of viability.

Two cases developed chorioamnionitis/septicemia and were delivered of the remaining members within 8 days after initial presentation. In all cases delivery of the latter sibling/s could be delayed and the range was 6-141 days. In all cases, except one twin gestation, the first member died immediately after delivery due to severe prematurity, while in 2 twin pregnancies the latter survived. In one case (25 weeks +1 day) the delivery of the second twin could be delayed 9 days with a 200g weight gain and 30 days less stay in the NICU together with better growth and neurodevelopment during the first year of life. The only case with impressive outcome was a delay of 141 days of the second twin following delivery of the first member at 19 weeks gestation. The salvage rate was 16% (1/6). There is no consensus as to the optimal management protocol of delayed interval-delivery and many components are still the grounds of debate.

In spite of the complications inherent in such management plan, and in the absence of any specific well-detailed action plan for such hopeless cases, we recommend a minimally invasive management plan to postpone delivery of the second/more member of multiple gestation, and cannot but agree to the principle that multiple gestations might represent multiple chances for survival in pregnancies doomed to perish if it were a single gestation.
Preterm birth is the leading cause of perinatal morbidity and mortality, accounting for 85% of neonatal deaths; one in eight babies was born preterm in 2005. This accounts for 530,000 newborns per year in the United States alone. Moreover, the complications of preterm birth can be devastating, as prematurity is the leading identifiable cause of neurologic handicap.

The uterine cervix plays a central role in the maintenance of normal pregnancy and in parturition. Thus, cervical disorders have been implicated in common obstetrical complications, such as “cervical insufficiency”, preterm labor, and abnormal term parturition. Yet, there is an incomplete understanding of the physiology and pathology of untimely cervical effacement and dilatation during pregnancy. Midtrimester cervical dilation is a major diagnostic and therapeutic challenge and a subject of intense debate among clinicians and researchers.

It is well established that a sonographic short cervix is the most powerful predictor of spontaneous preterm birth. Cervical sonography has been used most widely to assess the risk for spontaneous preterm birth in three circumstances: 1) asymptomatic patients; 2) patients at high risk for preterm delivery and/or mid-trimester loss; and 3) patients presenting with preterm labor. The cause of a sonographic short cervix is unknown; but it is proposed to be syndromic in nature.

Sonographic imaging of the cervix is a less invasive, more precise and objective method of assessing the cervical status when compared to digital examination. Effacement (or cervical shortening), changes in the anatomy of the internal os (funneling), endocervical canal dilatation, and spontaneous modifications, or induced (transfundal pressure) can be determined by ultrasound examination.

Therefore, several potential pitfalls should be avoided. These will be discussed at length and include: 1) excessive probe pressure (falsely long) 2) failure to observe cervical shortening for enough time (falsely long); 3) failure to recognize a poorly developed lower uterine segment; 4) unequal size and density of the anterior and posterior lips; 5) full bladder; 6) endocervical canal not visualized; and 7) lack of amniotic fluid sludge recognition.

Sonographic cervical length has also been utilized to identify the patients who may benefit from cerclage placement or progesterone treatment. Yet, despite numerous trials conducted to determine a treatment for a sonographic short cervix, no standard, effective intervention is available. We will discuss past and ongoing clinical trials of the use of progesterone for the prevention of preterm birth.