Contribution of Cardiac Biomarkers to Emergency Department.

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INTRODUCTION

- **Clinical Focus**
  - Acute Heart Failure
  - Acute Coronary Syndromes
- **BNP and Troponin biomarkers**
- **Other biomarkers**

PRINCIPLES

- **First:** use clinical expertise
  - To detect emergencies with immediat risk of death
  - To produce hypothesis
- **Second:** use biomarkers
  - To *increase* the value of clinical process
  - To *stratify* a risk
  - To *guide* the therapy
- **Third:** use biomarkers
  - To *implement* Research

Problems

- **Systematic** use of biomarkers for clinical situation where they are not useful (dizziness, fall in elderly, stroke…)
- **Lack** of knowledge on test performances (Se, Sp, NPV, PPV, vraisemblance rate…)
- **Lack** of knowledge and use of Guidelines
- **Lack** of knowledge on economical costs

GUIDELINES

Recommendations for the use of cardiac troponin measurement in acute cardiac care.
Kristian Thygesen*, et al, the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care
European Heart Journal (2010) 31, 2197–2206

Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology.
European Heart Journal (2008) 29, 2909–2945.

Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes.The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology
European Heart Journal (2007) 28, 1598–1660

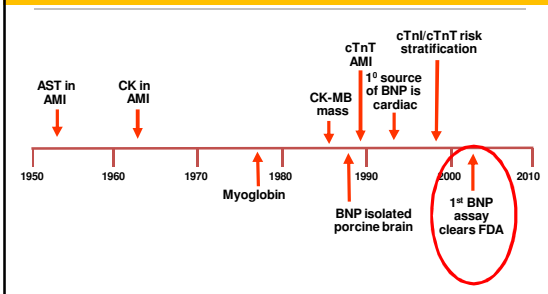
DEFINITION

- The release of cardiomyocyte components, i.e. biomarkers, into the bloodstream in higher than usual quantities indicates an **ongoing pathological process**.
- Thus, detection of elevated concentrations of cardiac biomarkers in blood is a **sign of cardiac injury** which could be due to supply–demand imbalance, toxic effects, or haemodynamic stress.
- It is up to the clinician to determine the **most probable aetiology**, the proper therapeutic measures, and the subsequent risk implied by the process.
- For this reason, the measurement of biomarkers always must be applied in relation to the **clinical context** and **never in isolation**.

THE BEST BIOMARKER

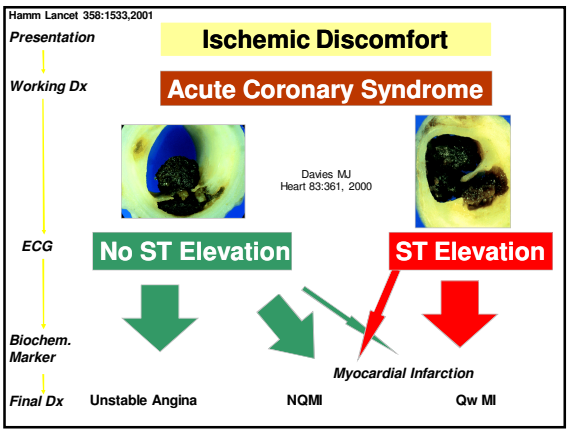
- Easy and reliable measurement.
- High PPV and NPV for diagnosis and prognosis assessment.
- **Incremental diagnosis / prognosis value**.
- Guide Clinical Decision Making.
- Cost effective.

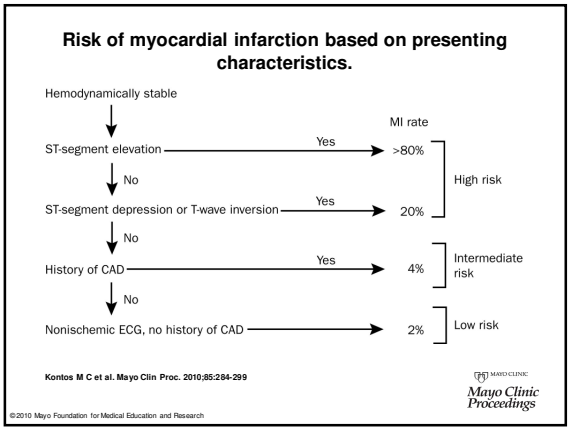
Evolution of BioMarkers



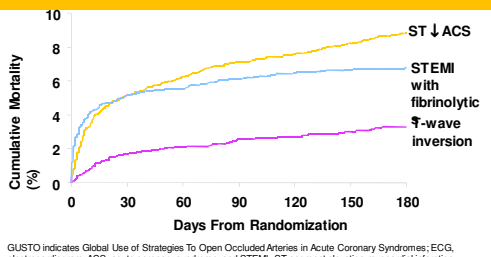
BIOMARKERS

- **Necrosis**: TNT, TNI, Myo, CKMB, FABP, Co Peptin
- **Ischemia**: IMA, uFFA, Co Peptin
- **Plaque rupture**: MMPs, PAPP, SCD40L, PIGF
- **Thrombosis**: PAI-1, SCD40L, vWF, D dimer
- **Neurohormones activation**: BNP, NE
- **Inflammation**: hsCRP, OxLDL, MCP-1, MPO, IL18
- **Endothelial activation**: sICAM, pSelectine





GUSTO IIb: Correlation of 6-Month Mortality With Baseline ECG Findings in Patients With ACS



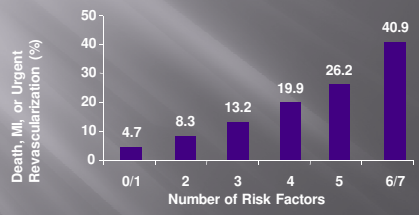
GUSTO indicates Global Use of Strategies To Open Occluded Arteries in Acute Coronary Syndromes; ECG, electrocardiogram; ACS, acute coronary syndrome; and STEMI, ST-segment elevation myocardial infarction. Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. *JAMA*. 1999;281:707-713.

TIMI Risk Score for NSTE ACS (Mortality, MI)

Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*. 2000;284:835-842.

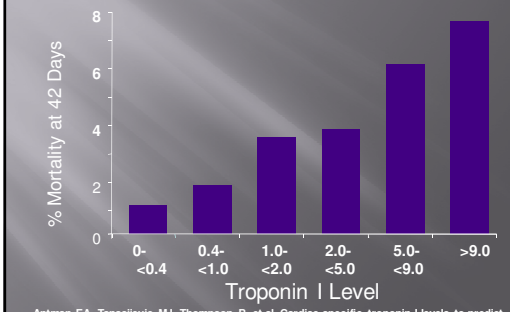
- Age ≥65 years (**1 point**)
- ≥3 CAD Risk Factors (**1 point**)
- Prior Coronary Stenosis >50 % (**1 point**)
- ST deviation (**1 point**)
- ≥2 Anginal events ≤24 hours (**1 point**)
- ASA in last 7 days (**1 point**)
- Elevated Cardiac Markers (CK-MB or troponin) (**1 point**)
- (Since 2007=ESC= CRF, diabetes, arrythmias, hemodynamic troubles, recurrent ACP)

The TIMI Risk Score and Incidence of Adverse Ischemic Events in Patients with NSTE ACS



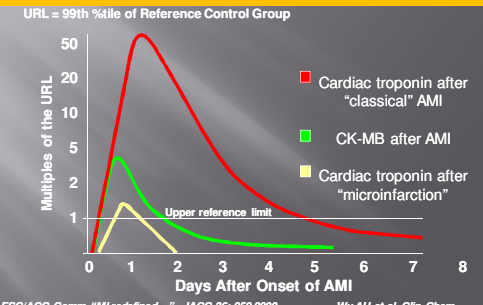
Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*.. 2000;284:835-842.

Troponin I Levels and Mortality in Patients with NSTE-ACS



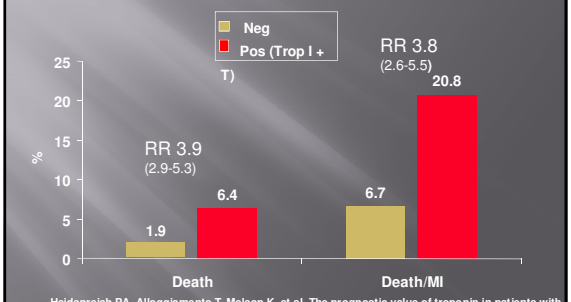
Antman EA, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med*. 1996;335:1342-1349.

Use of Cardiac Markers in ACS



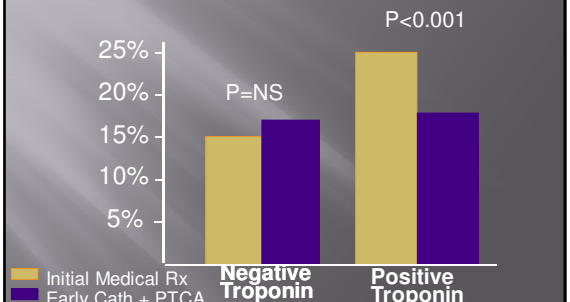
ESC/ACC Comm "MI redefined..." JACC 36: 959,2000 *Wu AH et al. Clin Chem 1999;45:1104.*

Prognostic Value of Troponin T or I in ACS: A Meta-Analysis



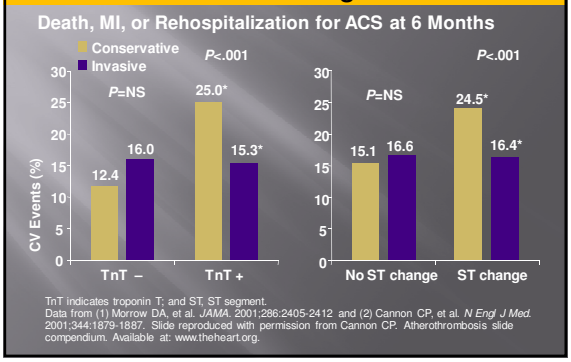
Heidenreich PA, Alloggiamento T, Melsop K, et al. The prognostic value of troponin in patients with non-ST elevation acute coronary syndrome: a meta-analysis. *J Am Coll Cardiol*. 2001;38:478-485. Slide modified with permission from Cannon CP. Atherothrombosis slide compendium. Available at: www.theheart.org.

TACTICS Trial Results Based on Troponin



Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001;344:1879-1887.

Benefit of Invasive Strategy by Troponin and ST Changes



TnT indicates troponin T; and ST, ST segment.
Data from (1) Morrow DA, et al. *JAMA*. 2001;286:2405-2412 and (2) Cannon CP, et al. *N Engl J Med*. 2001;344:1879-1887. Slide reproduced with permission from Cannon CP. Atherothrombosis slide compendium. Available at: www.theheart.org.

Personnal Troponin Study

- **5931 patients** were included.
- Excluding incomplete files, 5694 patients were kept for the study. 3136 patients (55%) had reported acute chest pain, 2243 (39.3%), abdominal pain, 239 (4.4%) dizziness and 76 (1.3%) dyspnea.

Personnal Troponin Study

- After retrospective records review, Troponin I measurement was in fact not indicated in **65.6% of cases**.
- Also, Troponin I had been measured simultaneously with Myoglobin.
- The total cost of these two cardiac markers over two year time period is **183,047 euros**.

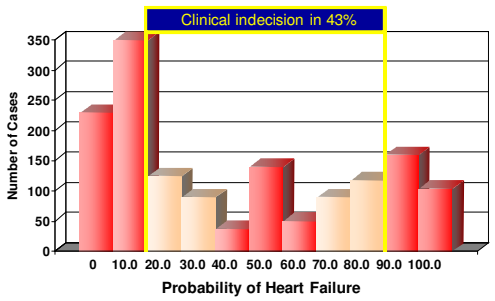
Causes of Troponin elevation

- Trauma (including contusion, ablation, pacing, Apical ballooning syndrome
- implantable cardioverterdefibrillator firings Coronary vasospasm
- including atrial defibrillators, cardioversion, Inflammatory diseases, e.g., myocarditis, e.g.,
- endomyocardial biopsy, cardiac surgery, Parvovirus B19, Kawasakidisease, sarcoid,
- after interventional closure of atrial septal defects) smallpox vaccination, or myocardial extension
- Congestive heart failure—acute and chronic of bacterial endocarditis
- Aortic valve disease and hypertrophic obstructive Post-percutaneous coronary intervention patients
- cardiomyopathy with significant left ventricular who seem to have no complications, hypertrophy Pulmonary embolism, severe pulmonary
- Hypertension hypertension, Hypotension, often with arrhythmias Sepsis
- Postoperative noncardiac surgery patients who Burns, especially if total body surface area is >30%, seem to do well Infiltrative diseases including amyloidosis,
- Renal failure hemachromatosis, sarcoidosis, and scleroderma, Critically ill patients, especially with diabetes, Acute neurological disease, including

HEART FAILURE

- Heart Failure (HF): major health problem
  - 2 to 3% of the general population, 10 to 20% after 70 years
  - High mortality rate (25% at 1 year after acute episode)
  - USA:
    - Underlying cause of 40.000 deaths/year
    - Associated cause in 250.000 deaths/year
  - Clinical presentation is often complex, e.g. Dyspnea

Clinical probability of heart failure at ED presentation with dyspnea

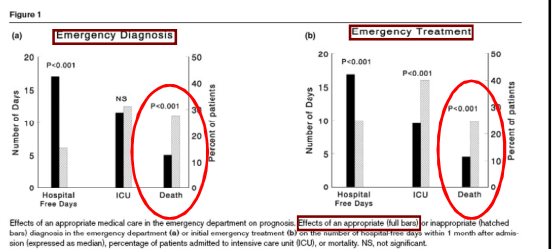


N=1586 patients

Maisel et al. NEJM 2002

Effect of Appropriate Diagnosis on Outcome of patients with dyspnea in ED

N=514 patients



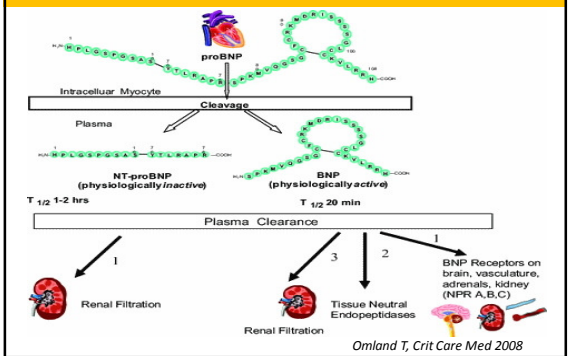
Effects of an appropriate medical care in the emergency department on prognosis. Effects of an appropriate (full bars) or inappropriate (hatched bars) diagnosis in the emergency department (a) or initial emergency treatment (b) on the number of hospital-free days within 1 month after admission (expressed as median), percentage of patients admitted to intensive care unit (ICU), or mortality. NS, not significant.

Ray et al. Crit. Care 2006

Diagnostic Performance Tests in Acute Heart failure

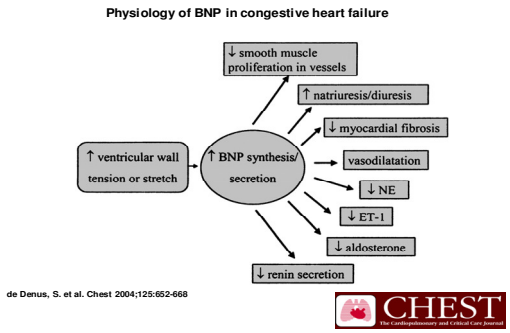
	Diagnostic value
➢ Clinical datas	+
➢ Chest X ray	+
➢ EKG	+
➢ Echocardiography	+++ gold standard

BNP / NTproBNP

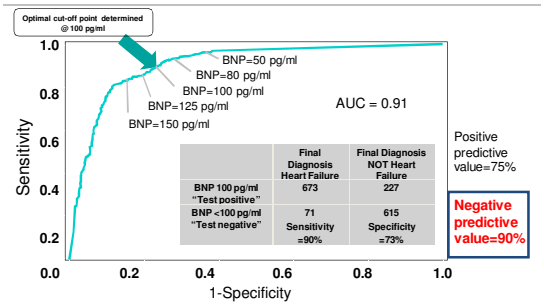


Omland T, Crit Care Med 2008

Biological Effects



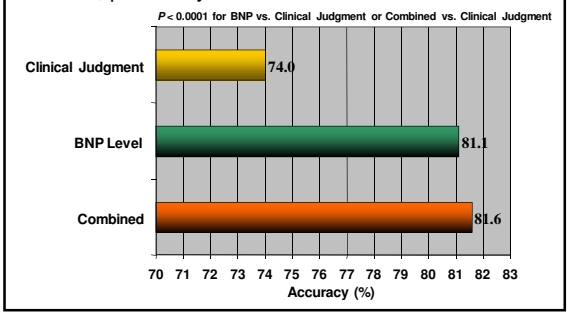
Diagnostic Accuracy of BNP in ER



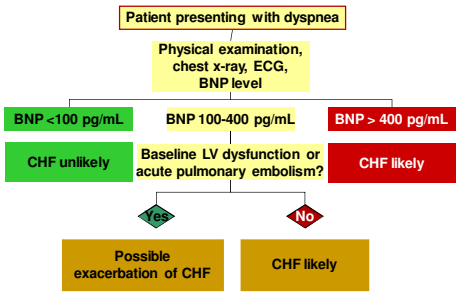
Maisel A., McCullough, P., N Engl J Med 2002; 347 (3): 161-7

Added value of BNP for AHF diagnosis

N = 1538, probability of AHF in ED



AHF Diagnostic Algorithm



Maisel A Eur J Heart Failure 2008, 10:824

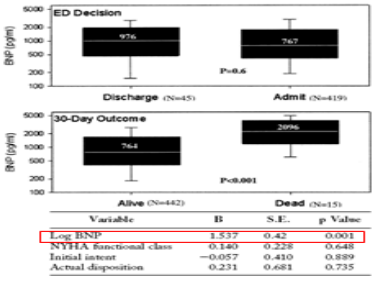
Factors increasing Natriuretic Neptides

- Age (> 75 years), women
- Renal failure (< 60 ml/min)
- Cardiac disease without heart failure
- Atrial fibrillation
- Pulmonary embolism
- Acute coronary syndrome
- Sepsis

Mc Cord, Arch Intern Med 2004
Ray, Int Care Med 2004

Risk Stratification at ED admission

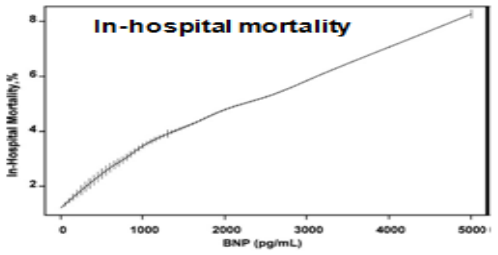
REDHOT study and early outcome: admission BNP > clinical judgement



Variable	B	S.E.	p Value
Log BNP	1.537	0.42	0.001
NYHA functional class	0.140	0.228	0.648
Initial intent	−0.057	0.410	0.889
Actual disposition	0.231	0.681	0.735

Maisel et al. JACC 2004; 44:1328-33

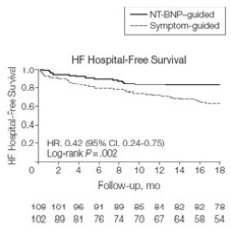
ADHERE registry 48,629 admissions for acute HF with BNP measurement on admission



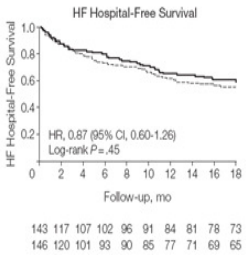
Fonarow et al. JACC 2007; 49:1943-50

BNP Therapy-Guided

< 75 years

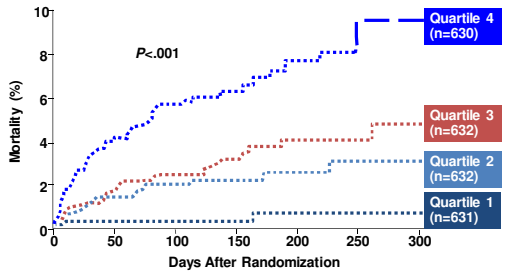


≥ 75 years



Pfisterer et al JAMA 2009, 301:383

B-type Natriuretic Peptide and Mortality in ACS Patients



Lemos JA, Morrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndrome. *N Engl J Med.* 2001;345:1014-1021. Atherothrombosis slide compendium. Available at: www.theheart.org.

CONCLUSION

- Most reported markers will not be clinically useful
- Troponins and BNPs come closest to meeting criteria as ideal biomarker
- Inflammatory markers show promise, but not completely clear yet
- Multimarkers panels will likely emerge as important clinical tools (troponin + CRP + BNP)

THE BIOLOGICAL HARD DRIVE

- **Potential roles in :**
  - Diagnosis and differential
  - Risk stratification
  - Therapeutic decision making
  - Disease monitoring
  - Identification of drug targets
  - Better understanding pathophysiology
- **With Education of doctors**
- **Costly effective**

BEDSIDE SYSTEM (POC)

Some commercial POC assays for cardiac markers

- Abbott i-STAT
- Response Biomedical RAMP system
- Biosite Inc. Triage® Cardiac Panel
- Roche Diagnostics
- Spectral Diagnostics Inc.
- Dade Behring Stratus®

- Rapid, Whole Blood Testing
- 15 Minute Time to Result
- Hand Held, Portable System
- Cardiac Panel
  - Troponin I
  - Myoglobin
  - CK-MB
  - BNP
  - D-Dimer
- Stored memory, printed results, Hospital Information System Interface

Point-of-care testing of cardiac markers: results from an experience in an Emergency Department
S. Altinier et al. Clinica Chimica Acta 311 (2001) 67–72

***Conclusions*:**
The point-of-care option evaluated also in relation to personnel issues for staff working in the ED, brought some interesting questions about the

- characteristics of POCT devices (easy to use 100%, safety for operator 91%) and the obtained results (quantitative and correlated to STAT lab, 91%)
- as well as the need of other options such as the implementation of rapid tube sample delivery.

The actual total turnaround time STAT in the management of samples sent to STAT lab was estimated to be equal to **82.5 min**.
In the same organizational setting, the use of a point-of-care device produced a turnaround time equal to **17 min**.

A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study.
Than M, Cullen L, et al. Lancet. 2011 Mar 26;377(9771):1077-84.

- **2-h accelerated diagnostic protocol (ADP)** to assess patients presenting to the emergency department with chest pain symptoms suggestive of acute coronary syndrome.
- The ADP included use of a structured pre-test probability scoring method (Thrombolysis in Myocardial Infarction [TIMI] score), electrocardiograph, and **point-of-care biomarker panel of troponin, creatine kinase MB, and myoglobin**. The primary endpoint was major adverse cardiac events within 30 days after initial presentation (including initial hospital attendance).
- 3582 consecutive patients
- ADP classified 352 (9.8%) patients as low risk and potentially suitable for early discharge. A major adverse cardiac event occurred in three (0.9%) of these patients, giving the ADP a **sensitivity of 99.3%** (95% CI 97.9-99.8), a **negative predictive value of 99.1%** (97.3-99.8), and a specificity of 11.0% (10.0-12.2).
- **Conclusion:** The ADP has the potential to affect health-service delivery worldwide.

FUTURE OF POC IN EUROPEAN EDs

- Cardiac Emergencies
- Diabetes
- Sepsis
- Metabolic and Electrolyte disorders
- Anaphylaxis


MEMC 6
KOS-GREECE
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www.eusem2012.org