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IV Italian GREAT Network Congress
Abstracts of Speakers Presentations
What is ST2 telling you in patients with cardiovascular disease?

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ST2 is a marker of cardiomyocyte strain and is involved in the pathway leading to cardiomyocyte hypertrophy and fibrosis. Information gained from ST2 levels appears to be additive to natriuretic peptides, and is useful for prognosis in the settings of acute and chronic heart failure and acute coronary syndromes. In heart failure patients, measurement of ST2 now carries a class Ib recommendation in the recent American College of Cardiology/American Heart Association guidelines for the management of heart failure. In Emergency Department patients presenting with dyspnea higher ST2 levels predict 30-day and 1-year mortality. Patients with elevated levels of both ST2 and NT-proBNP are at even higher risk. In heart failure patients, higher ST2 levels are associated with greater left ventricular size, lower left ventricular ejection fraction, higher pulmonary artery pressures, and a more decompensated hemodynamic profile. Among inpatients with acute decompensated heart failure, ST2 levels are also associated with mortality, and “ST2 responders” (i.e. those whose ST2 levels fall at least 25% within 48 hours of treatment) have better outcomes than “non-responders”. In the setting of myocardial infarction, elevated ST2 levels are associated with an increased risk of incident heart failure and mortality. After large myocardial infarctions, an ST2 level $>35$ ng/mL may identify a subset of individuals more likely to benefit from therapy with a mineralocorticoid receptor antagonist. ST2 levels are also useful in the outpatient setting, in patients with either heart failure with reduced (HFrEF) or preserved (HFpEF) ejection fraction. Patients with chronic heart failure whose ST2 levels fail to drop by at least 25% within 2 weeks after a heart failure decompensation may identify a particularly high-risk subgroup who should be targeted for more aggressive medical titration and follow-up. ST2 levels may also be useful as part of a multimarker panel to identify individuals from the general population who are at increased risk of developing heart failure and cardiovascular disease. Future studies will continue to clarify the optimal way to utilize ST2 in inpatient and ambulatory settings, to maximize the clinical benefit for all those we treat.

Circulating thrombopoietin in patients with SIRS in the Emergency Department

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Thrombopoietin (TPO) is a humoral growth factor mainly characterized for its ability to stimulate the proliferation and differentiation of megakaryocytes. It is constitutively produced by the liver and kidneys, and acts by stimulating its receptor, c-Mpl. TPO also directly modulates the homeostatic potential of mature platelets. In particular, although unable to induce platelet aggregation per se, TPO enhances platelet activation and leukocyte-platelet adhesion in response to different agonists.

A deep dysregulation of the TPO/c-Mpl receptor system has been described in sepsis. Elevated TPO levels have been reported, indeed, in healthy volunteers after endotoxin infusion, as well as in septic children and neonates, and in septic adult patients. Moreover, Zakynthinos and coll. have shown that sepsis severity is the major determinant of elevated TPO levels in septic patients.

We have previously shown a correlation between TPO concentrations and platelet activation in septic burned patients, a phenomenon that may cause micro-thrombotic events leading to organ damage. In addition, we have shown that TPO cooperates with TNF-α and IL-1β in mediating the negative myocardial inotropic effect exerted in vitro by serum of septic shock patients. In another recent study, we have shown that the treatment with the chimeric fusion protein mTPOR-MBP, able to inhibit TPO biological activity in vivo, significantly reduced monocyte-platelet aggregation, and the severity of organ damage in two murine models of experimental sepsis.

On the basis of these experimental results, we aimed to study the utility of TPO concentrations as predictive biomarker of sepsis and of sepsis severity in patients admitted to the Emergency Department with Systemic Inflammatory Response Syndrome (SIRS). Ours is a sub-study of the “Need-speed trial” (Study on the applicability of a paNet of biomarkers in the early rule out sepsis in patients with “systEmic inflammatory response synDrome”), a multi-center observational study led by Prof. Carlo Giansante of the University of Trieste and involving 8 Italian centers affiliated to the GREAT Italian Network. We will present and discuss the preliminary results obtained in about 80 patients enrolled at the Emergency Department of the “Città della Salute e della Scienza” Hospital of Turin.

Experience with BIVA in AHF

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Acute heart failure (AHF) is the most common single cause of hospitalization for patients >65 years, accounting for about 2% of all hospitalizations as principal diagnosis and for 4% when listed with other conditions. The inhospital mortality of AHF varies from 4% to 8%. Follow-up after the hospitalization is characterized by a high incidence of death (8%-15% at 2-3 months) and rehospitalizations (30%-38% at 3 months). Although the rate of deaths and hospitalizations seems to have reached its peak in the last few years, there is still a continuous increase in the number of AHF episodes because of aging of the population and improvement in cardiovascular care.
As over 80% of HF admissions and readmissions originate in the ED, the emergency physician serves a very important role in management and right placement of patients with AHF. Recent literature shows much interest in identifying early clinical predictors of outcome in these subjects. In fact, earlier treatment in patients with a high severity of illness is associated with a decreased mortality.

More recently bio-impedance vector analysis (BIVA) has been suggested as a tool to highlighting congestion in AHF patients with altered body fluid mass due to neurohormonal abnormalities. Indeed BIVA is able to differentiate cardiac and non cardiac dyspnea in emergency department, to quantify peripheral congestion and to detect peripheral congestion, even when it is not clinically remarkable yet.

In the last years, our experience with BIVA and biomarkers in evaluating acute heart failure patients progressively increased and led to interesting results.

In a previous study published in 2010, we evaluated hydration status at the admission, 24, 72 hours after admission and at the discharge in AHF patients, with a multidimensional approach, using BIVA, BNP, Caval Index and vascular pedicle width obtained through chest X-ray.

Our results confirmed the strong correlation between hyperhydration demonstrated by BIVA and central venous congestion and between hyperhydration and oliguria. From our data it is possible to conclude that the BIVA measurements are strictly related with the other three methods.

Hydration Index obtained by BIVA and Caval Index showed a significant and indirectly proportional correlation at the time of ED presentation and 24 and 72 hours after hospital admission, and moreover the BIVA values’ shift from an hydrated state to a normal hydrated state related with the improvement due to diuretic treatment in AHF patients. Furthermore, the efficacy of diuretic therapy and the validity of BIVA measurements were bedside confirmed by normalization of BNP, vascular pedicle width and caval index values at discharge.

Recently we assessed BIVA measurement in AHF patients at the moment of their admission in ED to evaluate its diagnostic and 30-days prognostic role. It seems that Hydration Index (HI) obtained by BIVA, added to BNP measurements, provide an improvement in patients’ reassessment for the diagnosis and risk stratification, especially for those patients with a BNP values between 100-400 pg/ml (“grey zone”) (Net reclassification improvement, NRI 77% for diagnosis and NRI 65% for prognosis).

Furthermore we found a significant vector migration, from admission to discharge, in hospitalized AHF patients. This suggests a greater reduction of congestion during hospitalization and it is probably linked to cardiac function improvement and diuretic therapy.

Conclusions: A quantitative evaluation of body fluid congestive status performed in AHF patients by HI through BIVA, obtained at admission in ED, provides significant additive diagnostic and 30-day prognostic information to BNP, particularly in the “grey zone”.

Moreover, BIVA serial assessment could provide important information on treatment efficacy and patients effective response to therapy in patients with shortness of breath due to AHF.

References

Evaluation of drug abuse for polytrauma prevention

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The aim of this presentation is to illustrate the effective correlation between driving under the influence of drugs and severe traumatism caused by traffic accidents.

The first part of the study try to shows the effects of use of drugs on brain and in sensitive perception, not only during the drive time, but also during the normal life activities as results from several studies done by scientist and psychologists, with the aim to confirm that drugs effects modify the normal perception of real and can compromise responses to danger and also to other not normal situations. Also is considered how the drivers using drugs or psychotropic substances think that this misbehavior is not a real problem and for them is possible to drive with not consequences on the road.

After this light overview, the presentation passes to illustrated the percentage of traffic accidents involving drivers under the influence of drugs, using the results from the National Traffic Police Service database, also discovering different situation in correlation to the daily period (night and day) and to the different hours during the same night. The approach of this part of study is more objective as possible, using only confirmed data an results from official files from Polizia di Stato and Carabinieri. No data are available from other Local Police Forces (Polizia Municipale) working in the major cities and municipalities, as well statistic is not complete but only cover the 65% of the total.

In the following segment is considered how traffic accidents produces injuries and especially polytraumatic injuries, especially because the misuse or the complete not use of seat belts, and how this results is more present, with more severe results, in drivers under influence. Is clear that there is a correlation, with different point of views, between use of drugs and traffic accidents, as result of minor capability to approach several situations on the road.
Hypertensive crisis in the emergency department

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Hypertensive emergencies can be defined as severe elevations of blood pressure (BP) in the presence of acute target organ damage. Among hypertensive emergencies the most common clinical conditions are acute coronary syndromes, dissecting aortic aneurisms, acute pulmonary edema, hypertensive encephalopathy, acute cerebral infarction, intracerebral haemorrhage or acute arterial bleeding or eclampsia. In these circumstances an immediate blood pressure reduction is needed to prevent the progression of target-organ damage. On the opposite hypertensive urgencies are characterised by severe elevations in BP (>180/120 mm Hg) without evidence of acute TOD and BP can be reduced in the emergency department (ED) by orally administered drugs with strict outpatients follow-up, avoiding hospital admission. Both hypertensive emergencies and urgencies are characterized by a poor cardiovascular prognosis.

Repeated blood pressure measurements should be obtained, both in sitting and standing positions, in both arms and, if indicated, in upper and lower extremities. A significant difference in BP between the two arms should raise the suspicion of aortic dissection. Blood pressure should then be strictly monitored in the ED.

The initial evaluation includes a complete history (with particular attention to pre-existing hypertension and TOD) and an accurate physical examination. A fundoscopic examination and laboratory studies such as urinanalysis, creatinine, urea, electrolytes and a full blood count should be performed. A sample for plasma renin activity and aldosterone should be drawn and urine collection for catecholamines should also be obtained, when a secondary form of hypertension is suspected. In each patient an electrocardiogram and a chest radiogram should be obtained in each patient, while further investigations including echocardiography, brain CT scan, abdominal ultrasonography, thoracic and abdominal CT scan and vascular ultrasound should be performed according to the clinical presentation.

Patients with hypertensive emergencies should be admitted to an intensive care unit for clinical surveillance and continuous BP monitoring during rapid and aggressive treatment with parenteral drugs. In the majority of cases the initial goal should be a partial reduction (around 20-25% during the first minutes up to 1-2 hours) of BP and possible cautious and further decrease. It should, however, kept in mind that an excessive reduction of BP values is potentially dangerous, possibly leading to ischaemic complications such as acute myocardial infarction and stroke.

Several parenteral agents are available for the treatment of hypertensive emergencies and the choice of first-line antihypertensive agents should be tailored to the patient’s clinical status.

In patients with hypertensive urgencies severe hypertension is not usually associated with signs of acute TOD. In these patients BP should be lowered gradually and this can often be achieved by orally administered drugs with a clinical surveillance during the first few hours after drug administration. A complete normalization can be obtained over a period of 24–48 hours and a follow-up is recommended in a Hypertension Specialist Clinic. In hypertensive urgencies also a gradual and progressive BP lowering should be reached, using a variety of antihypertensive classes of drugs and an initial approach with a combination of antihypertensive drugs will increase the likelihood of effective BP reduction. The use of sublingual nifedipine is not recommended because the induced degree of BP reduction cannot be predicted.

In the presence of severe elevations of BP a prompt and accurate initial work-up is crucial for the identification of acute TOD. Treatment should be started promptly in the ED with parenteral or oral drugs according to the findings of the initial evaluation. Blood pressure should be rapidly reduced but a precipitous fall in BP should be avoided and, in the majority of cases, reduction rather than normalization of blood pressure should be the initial goal of treatment.

In conclusion also an overview of the European Union vision of the problem and different legislations in Member States, with the different methodologies to operate checks on the road and consequences of positivity at the control in medical and judiciary terms.

Literature, studies et references
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Point of care ultrasound and telemedicine in pre-hospital care

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The World Health Organization defined Telemedicine (TM) as “the use in consultation of medical knowledge via communication networks when distance is a determining factor. TM has great potential in the field of emergency medicine. Emergency healthcare is complex but its most important requirement is rapid and correct decision-making on diagnosis and treatment. In addition, this occasionally must be performed in situations other than in a hospital emergency department. Thus in the case of accidents, emergencies, natural disasters, healthcare is necessary in poor conditions and, most importantly, away from the reference health center, so that the distance factor and the time factor acquire great relevance for the successful diagnosis and treatment of affected patients. Nowadays, light and mobile systems are available to everybody, making ultrasound the only imaging method usable in a prehospital environment. Mobile systems can improve physical examination, they may provide guidance for difficult procedures. Today’s emergency medicine also covers surgery and trauma management as well as the wide area of internal medicine (cardiology, oncology, hepatology, nephrology), obstetrics, pediatrics and others: in all these fields ultrasound remains a standard method of diagnostics. Ultrasound is the only imaging modality and a useful diagnostic tool in prehospital emergency medicine, examination time is short and it will not significantly delay medical care. Acute trauma is a leading cause of morbidity and mortality. The first hour of trauma, often termed the ‘golden hour’, is the most crucial predictor of mortality in patients with acute trauma. Especially notable is the inefficiency in the use of the ‘downtime’ during which patients are transported from the prehospital setting to the ED. This ‘downtime’ provides an opportunity to reduce the time-to-diagnosis during transportation from the prehospital setting by paramedics to the ED. Recent technological advances in broadband and satellite communications systems, the increasing role of telemedicine, and the availability of portable ultrasound scanners provide a unique opportunity to address this problem. This technology will provide the opportunity to employ ‘real time transmission’ of ultrasound images (telesonography) from the pre-hospital setting, and during transportation to the ED. Through sonography can quickly be determined whether air or free fluid is present in the abdominal or pleural cavities and may provide additional diagnostic information to guide therapy. The utility of this information will depend on the transport time as well as the training level of the provider in the ambulance or helicopter. Furthermore, ultrasound examination could improve triage in cases of more than one patient in disaster medicine. In addition, many biomarkers are used in many clinical scenarios, in the emergency department, ward, clinic and in the near future in the patient’s home (using telemedicine platform).

Stroke Biomarkers

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Following ischemic insult the brain tissue becomes necrotic in a few minutes within the ischemic core. Around the core, in the so-called penumbra, the tissue undergoes a number of biochemical processes which eventually lead cells to dye (by programmed cell death or autophagy), or to survive to regain the function, hours or days following the onset. While the necrotic area can be identified by neuroimaging, the extent of salvageable tissue.

Ideal biomarkers candidates should reflect the different components of the ischemic cascade and provide clinicians with indication of the extent of salvageable tissue.

Several molecules have been proposed as potential stroke biomarkers. Antibodies to subunits of the glutamate NMDA-receptors, neuron-specific enolase, myelin basic protein, glial fibrillary acid protein, S100ß, or caspase-3 are markers of injury or related glial activation, and may also predict risk of hemorrhage transformation (S100ß) or stroke versus mimics (caspase-3). Thrombomodulin, D-dimer, fibrinogen, fibronectin von Willebrand factor, soluble glycoprotein V1, thrombin-activable fibrinolysis inhibitor or vascular adhesion protein-i are thought to reflect hemostasis and endothelial dysfunction, which typically occur in the perinfartual area. Blood concentrations have been shown to change following stroke or have potential value in identifying patients at risk for hemorrhage following tPA administration. Several markers of post-ischemic brain tissue inflammation have been also proposed, including C-reactive protein, matrix metalloproteinase 9, interleukin 6, adhesion molecules or tumor necrosis factor α. The redox-sensitive molecular chaperone PARK-7 and a number of lipid peroxidation products, including malondialdehyde and oxidized low-density lipoprotein, have been studied as markers of oxidative stress with potential prognostic and diagnostic value.

Common, major limit to all these potential markers is the lack of specificity for the ischemic stroke. In addition, few biomarkers may exhibit a delayed time course. For most of them the Blood-Brain Barrier may restrict the release so to limit the relationship between extension of the damage and peripheral concentrations.
AHF physiopathology in the first hours in ER: need for new IV vasodilators treatment as soon as possible

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Acute heart failure (AHF) remains a major public health problem because of its high frequency, significant burden of mortality and morbidity and substantial few improvements in therapy over last decades. Current pharmacotherapy for AHF consists primarily of diuretics associated with inotropic agent or vasodilators in selected subset.

Vasodilator therapy, as suggested in many guidelines, should be considered in AHF patients with high or normal SBP on admission and avoided in those with low systolic blood pressure (SBP). The ultimate ESC guidelines state that vasodilators “are probably most useful in patients with hypertension and should be avoided in patients with a systolic blood pressure <110 mmHg”.

Data from Acutely Decompensated Heart Failure National Registry (ADHERE) demonstrated that patients with AHF are most commonly hypertensive (over three-fourths) at the time of admission and often have preserved, not depressed, left ventricular contractile function. In fact only minorities of those admitted with AHF have systolic dysfunction and reduced SBP.

This findings were also confirmed in Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE).

Complex pathophysiological component of the hemodynamic alteration may contribute to symptoms and to the poor prognosis of patients with AHF.

The most important mechanism, called “afterload mismatch”, is the interaction between a progressive decrease of systolic function and an acute increase of vascular resistance. This leads to a decrease of cardiac output and at the same time to a filling pressure increase in left ventricle.

Due to an increase of congestion, the lower O2 saturation and the systemic O2 desaturation contributes to insufficient myocardial O2 supply with the possibility of myocardial ischemia, this mechanism could be amplified by concomitant artery disease and by increasing of myocardial oxygen demand from wall stress consecutive to the afterload mismatch.

Moreover several mechanism contribute to multi-organ failure related to AHF:

a) the increase of fluid exudation in the lung and the reduction of O2 saturation may lead to pulmonary vasoconstriction resulting in a further increase of right ventricular pressure.

b) the impairment of circulatory system may result in metabolic acidosis which further compromise cardiac performance.

c) a further increase of leak of fluid into alveoli may be a consequence of inflammatory and neurohormonal activation as the result of their effect on cardiac and renal function as well as pulmonary membranes.

d) finally, reduction of forward perfusion, increase of venous pressure and neurohormonal-inflammatory activation may lead to a renal injury that result in worsen heart failure.

Overall changes in vascular tone, both on the arterial side and venous side, are significant contributors to AHF and may be the main determinant of the AHF syndrome in patient with AHF and elevated SBP.

As consequence of these complex hemodynamic alterations in AHF the use of vasodilator therapy in acute setting can improve both hemodynamics and symptoms and is particularly recommended.

Conclusions: Treatment of AHF with vasodilators is associated with dyspnea relief and improvement of clinical outcome. However the administration of these drugs should be made with caution considering the possibility of coronary hypoperfusion and myocardial ischemia, worsening renal function and inappropriate reduction of SBP resulting in hemodynamic instability. As consequence it is recommended a careful SBP monitoring and a careful titration of the dose according to changes in SBP.

References

Galectin 3 in diabetic patients

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Galectin-3 is member of the lectin family which shows an ubiquitous localization not only within the cell but also in the extracellular space. This dual localization of galectin-3 determines two different modes of interaction with proteins. Firstly, extracellular galectin-3 interacts with the β-galactoside residues of several extracellular matrix- and cell surface-glycoproteins via the carbohydrate recognition domain; this is the classical lectin-glycoconjugate interaction. Secondly, interactions of intracellular galectin-3 occur via peptide-peptide associations mediated by its N-terminal domain. These structural properties enable galectin-3 to bind a variety of proteins and, hence, to exert multiple functions, which make it a broad-spectrum biological response modifier. In fact, galectin-3 exerts several AGE-independent effects, including the modulation of immune/inflammatory function, with both pro-inflammatory actions, prevailing in acute settings and favoring the acute phase of inflammation, and anti-inflammatory effects, which predominate under chronic conditions and favor the resolution of inflammation. The latter effects include the induction of alternative macrophage activation, negative regulation of T-cell activation, and activation of myofibroblasts with promotion of fibrosis. In addition, galectin-3 is involved in the uptake and removal of irreversibly modified molecules such as AGEs and ALEs, thus suggesting that it may have a role in diabetes and its complications. Unfortunately, there is a paucity of data from diabetic humans. These data show that galectin-3 correlates with cardiovascular risk factors, heart failure and mortality in diabetic and non-diabetic individuals and that galectin-3 levels are elevated in obesity and correlate negatively with HbA1c in subjects with type 2 diabetes. Studies in experimental animal models have suggested that galectin-3 may act as an opponent of RAGE in protecting renal and vascular tissues from these damaging by-products. In fact, galectin-3 ablation accelerated glomerulopathy induced by streptozotocin-induced diabetes, aging and AGE injection and also renal disease and atherosclerosis promoted by high fat diet. Conversely, lack of galectin-3 was associated with amelioration of diet induce NASH in these animals. These data suggest that the role of galectin-3 in diabetes and its long-term complications is uniquely complex, consistent with the multifunctional nature of this lectin.

Clinical study coordinators responsibilities for research in “Emergency and Critical Care Medicine” in Germany

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According to Fisher et al. “research coordinators are vital to a robust and efficient system of clinical research. They are the protocol managers, participant educators, and liaisons for the sponsors and institutional review boards (IRB).” Responsibilities of clinical study coordinators are quite diverse. One can distinguish between three main fields of activities: activities before the start of the clinical trial, during the clinical trial and after the close out of the trial. The profession of a clinical study coordinator generally does not require a distinct degree. It is often pursued by experienced nurses. On occasion a bachelor or even master degree is requested, as the proportion of administrative and regulatory activities is increasing and becoming more complex.

A clinical study coordinator has to work with several parties having various, sometimes diverging interests: sponsor, contract research organizations, public authorities, clinical (principal) investigators, study nurses and of course patients. While doing so a clinical study coordinator has to be compliant with all the requirements imposed by the sponsor or by general guidelines as GCP or the declaration of Helsinki. All too often these various interfaces create tensions in clinical practice.

In emergency medicine the patient is particularly worthy of protection, because the trial related interviews and interventions are conducted in the acute situation in which the patient has acute symptoms and acute physical problems. In this situation the clinical study coordinator sometimes has to manage the balancing act between patient interests and interests of the sponsor or principal investigator. A survey among clinical trial coordinators has shown that many of them solve their ethical concerns by being “selfish altruistic”.

Selfish altruism is described as a mechanism that allows clinical trial coordinators to reduce the conflicts between research and care, to maintain their professional identity and to exert pressure on the patient for participating in the trial and then being compliant with the trial protocol.

In Germany, research in emergency medicine is far less common than in the United States. In many cases the structures and processes are not adjusted to the requirements of research. Bringing research into clinical practice often means breaking new grounds for principal investigators and clinical study coordinators.

In my lecture I want to highlight both the responsibilities of a clinical trial coordinator in theory and in clinical practice. Therefore I want to give examples regarding past or ongoing clinical trials in our emergency department and the associated activities and responsibilities.

References

A new device for the prompt diagnosis of acute urinary infections in ED

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MBS srl (a spin-off of Roma Tre University, Rome, Italy) has developed and patented an alternative method for bacterial counting, called Micro Biological Survey (MBS) method. The MBS method is based on colorimetric survey performed in mono-use disposable reaction vials in which samples can be inoculated without any preliminary treatment. The analyses can be carried out by untrained personnel and anywhere where they are necessary, without the need for any other instrumentation than a thermostatic optical reader that can automatically detect the colour change, providing an estimate of the bacteria count in the sample.

In a previous study (The Open Emergency Medicine Journal, vol. 6, 2013 (in press)) we have carried out a preliminary validation study, in accordance with ISO Standards, of the quantitative MBS method to explore the possibility of its use as microbiological POCT in Urinary Tract Infections (UTIs). Precision, variance, uncertainty, linearity and accuracy were determined for testing of all bacterial species by the MBS method, demonstrating that the MBS results were in good agreement with the reference method of colony count on PCA for the bacterial species most commonly present in UTIs.

In the present study, we have carried in vitro experiments using urine samples supplemented with some antibiotics most frequently used for the treatment of UTIs (amoxicillin/clavulanic acid, ciprofloxacin, and trimethoprim/sulfamethoxazole). The antibiotics were added in the concentration range reached in urine during therapy. We have also utilized a new automatic device produced by MBS srl to automatically detect the colour change due to the presence of contaminating bacteria.

At the bacterial concentrations significant for UTI (10^9-10^10 bacteria/ml), the POCT device detected the presence of pathogenic bacterial species (Enterobacter cloacae, Pseudomonas aeruginosa, Escherichia coli and Staphylococcus aureus) within 12 hours, revealing at the same time the sensitivity to one or more of the above mentioned antibiotics. In the hand of untrained practitioners, the MBS device provides in a short time a presumptive indication of UTI and a preliminary assessment of antibiotic resistance/sensitivity.

This new device could therefore represent an innovative POCT, and this study will progress further with testing of patients admitted in Emergency Department with a diagnosis of UTI.

### A new protocol to treat hyponatremia based on pathophysiological assessment: NaCl replacement in solutes deficit and use of tolvaptan in water excess.

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**Introduction:** Hyponatremia (PNa <135 mEq / L) is the most common electrolyte disorder encountered in Emergency Department, although it is often undiagnosed, is a negative prognostic factor and an independent predictor of mortality in hospitalized patients (1). Several studies have demonstrated the importance of a quantitative therapeutic approach, based on the identification of the pathophysiopathological alteration (2). The aim of our study was to assess the efficacy and safety of a protocol for the treatment of hyponatremia based on early recognition of the pathophysiopathological mechanism that caused it. A secondary goal was to evaluate the efficacy and safety of Tolvaptan treatment.

**Materials and methods:** Patients with PNa ≤130 mEq/L admitted at the Emergency Medicine Department of the “Maggiore della Carità” Hospital of Novara, were enrolled and divided in three groups on the basis of clinical and laboratory data: A, hypovolemic patients with deficit of Na (that were treated with Normal Saline, NaCl 0.9%); B, euvoletic patients with deficit of Na (treated with 3% NaCl); C, water excess (treated with Tolvaptan 15 mg qd) (3). Patients were treated until the normalization of the values of Na plasma concentration and the regression of symptons were achieved. Physical examination, bioelectrical impedance vector (BIVA) evaluation (4), blood and urine tests were performed at the beginning of treatment (T1) and were repeated after 4 (T2), 12 (T3), 24 (T4) and 48 hours (T5). At the end of the study, two investigators re-evaluated the balance of salt and water relative to the first 12 hours of treatment (from T1 to T2). The analysis of these data allowed us to identify patients whose initial assessment of the state of volume was incorrect; on this basis, patients were switched to the correct group of hypovolemic deficit of Na, euvoletic deficit of Na or water excess. This ex-post evaluation was considered as our “gold standard” and was used to identify, between clinical and laboratory data collected at T1, some possible predictors useful for a correct classification of hyponatraemic patients: for this purpose we performed an analysis of association using clinical elements, plasma copeptin concentration (5), and BIVA.

**Results:** 14 patients (43%) were treated with 0.9% NaCl (group A), 8 (24%) with 3% NaCl (group B) and 11 (33%) with Tolvaptan (group C). The comparison of the medians of PNa at different times did not show statistically significant differences between groups, so the time-course of PNa correction was the same in all patients. The difference between expected and measured PNa (ΔPNa) among the three groups was not statistically significant (p = 0.165). To confirm this result we performed Passing-Bablok linear regression on all patients combined into a single group without detection of statistically significant differences in ΔPNa (intercept 17.96 with CI-38 to 53; slope 0.85 with CI 0.59 to Δ1.28).

The re-evaluation of patients according to the fluid and electrolytes balance (performed retrospectively, using the data collected during the first 12 hours of treatment) identified 4 patients for which water excess was not recognized at T1 (two of them were wrongly assigned to group A and two to group B). At this point: 12 patients (36.4%) had hypovolemic hyponatremia, 6 (18.2%) euvoletic hyponatremia and 15 (45.4%) water excess. This assessment allowed us to better evaluate the association of clinical or laboratory indicators with one of the three groups.

The only element that showed a statistically significant difference in frequency of distribution in the three groups of patients, redefined as reported above, was the presence of oedema (8.3% in hypovolemic hyponatremia, 50% in normovolemic hyponatremia and 73.7% in water excess, p = 0.003). The concomitant presence of at least 2 of 3 signs of dehydration (dry mucous membranes, axillary skin and positive pinch test) has not been shown to be useful for volume assessment; also jugular turgor seems not to be useful because the distribution of this finding was not different in the three groups. The differences in copeptin plasma concentration did not reach statistical significance between the three groups (median value 42.7 in hypovolemic hyponatremia, 23.2 in normovolemic hyponatremia and 17.8 in water excess, p = n.s.). Finally the BIVA method was useful to identify patients with water excess (78.6% of water excess patients were correctly identified by BIVA evaluation).
Conclusions: As expected, in hyponatraemic patients the presence of peripheral oedema can be considered an indicator of water excess and may help the clinician to address the patient to Tolvaptan treatment. The presence of two or more signs of dehydration (dry mucous membranes and axillary skin, positive pinch test) seems to be useful to exclude water excess but we did not find any statistically significant difference between groups. The bioelectrical impedance vector analysis may be useful to confirm water excess but this method does not identify correctly patients with dehydration. In our study, copeptin has not proved to be useful in helping the assignment of hyponatraemic patients in one of the three groups. Finally, our results confirm that quantitative approach for the correction of hyponatraemia, due to salt depletion, is effective and safe as has been the administration of Tolvaptan in water excess.

References

Decision Making and Lab tests in starting thrombolysis in stroke patients

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Stroke is the second cause of death after cardiovascular disease and the first cause of long term disability in the world. Its incidence increases with age reaching the maximum value in the ultra 80 old age.

The 85% of stroke is ischemic stroke and the causes are large artery atherosclerosis, small artery disease, cardioembolism, in older patients (> 55 years), hypercoagulable states and non atherosclerotic vasculopathies in younger patients (< 55 years). When an ischemic stroke occurs a clot occlude an artery and an hypoperfusion occurs in the area below the artery. In this area there is a core of irreversible infarction and a “penumbra” that is a zone of reversible ischemia around the core, salvageable in first few hours after ischemic stroke onset.

The rationale of the thrombolysis is to save the penumbra zone. Several trials have demonstrated that great benefits are obtained when thrombolysis is started within 90 minutes of symptom onset.

For thrombolysis Tissue plasminogen activator (rt-PA) is used, it binds to fibrin in a thrombus, converts plasminogen to plasmin and it’s cleared rapidly from circulation plasma by liver. There are inclusion and exclusion criteria that show when is possible do thrombolysis in patient with ischemic Stroke. Thrombolysis is an acute therapy that need few laboratory tests and few focal actions to make decision to do it, but need an acute stroke team with experience and organization for the care of stroke patients.

Despite the clear inclusion and exclusion criteria for the use of rt-PA there are some circumstances where data to support its use is limited such as pediatric stroke, stroke patients older then 80 years, adults who do not meet current criteria for rt-PA, and more trial are need.

In our experience, from May 2006 to August 2013, ninety-nine patients were thrombolysed: 59% had an improvement of their neurological examination with slight or not significatly disability.

Thrombolysis is the “gold standard treatment” in acute ischemic stroke, acute stroke multidisciplinary team are important for its use because “time is brain and time lost is brain lost”.

Acute child gastroenteritis in ED: how to approach

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Acute gastroenteritis accounts for millions of deaths each year in young children, mostly in developing communities. In developed countries it is a common reason for presentation to general practice or emergency departments and for admission to hospital.

The most common causes of acute gastroenteritis in children are viral, self-limited, and need only supportive treatment. However, bacterial, protozoal and helmintic GE can occur, particularly in developing countries.

Antibacterial therapy should be restricted to specific bacterial pathogens and disease presentations. In general, infections with Salmonella Typhi, Shigella spp. and Vibrio cholera should usually be treated with antibacterials, while antibacterials are only used in severe unresponsive infections with Salmonella non tifoiea, Yersinia, Aeromonas, Campylobacter, Plesiomonas spp., and Clostridium difficile. Antibacterials should be avoided in enterohemorrhagic Escherichia coli infection.

The most frequent and dangerous complication is dehydration, which may be associated with electrolyte disturbance and metabolic acidosis.
In 2008, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society of Paediatric Infectious Disease (ESPID) developed evidence-based guidelines for the management of acute gastroenteritis (AGE) in children in Europe.

Optimal management with oral or intravenous fluids minimises the risk of dehydration and its adverse outcomes. Therapy with synbiotic plus an oral rehydration solution shortened the duration of acute diarrhoea in children by approximately one day compared to oral rehydration solution only.

For intravenous rehydration, new evidence is available regarding rapid or ultrarapid and large-volume vs. standard-volume rehydration; as the new evidence is not consistent, until more data are available, the administration of 20 mL/kg seems appropriate.

Convincing evidence has accumulated showing that ondansetron reduces the risk for vomiting; however, a clearance on safety in children is needed. New data, although mainly from outside of Europe, have reconfirmed that either smectite or racecadotril is an effective adjunctive therapy to oral rehydration.

Prevention is the key to controlling gastroenteritis, and recently licensed, highly effective rotavirus vaccines will have a major effect on public health.

Cardiogenic shock 2013

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Cardiogenic shock (CS) is the leading cause of death in patients hospitalized for acute myocardial infarction. In spite of the increasing rates of use of primary percutaneous angioplasty mortality is still well above 50%. Risk stratification using both clinical and laboratory markers allows for early adoption of support measures that can potentially avoid or limit CS onset. Likewise prompt detection of multigorgan failure is essential. Although acute impairment of left ventricular function is the initial precipitating mechanism in CS, its pathophysiology is complex and involves several other circulatory disorders that contributing to tissue hypoperfusion and end-organ failure. Beyond early reperfusion treatment no fundamental improvements have been made in the pharmacological treatment of CS. The role of intra-aortic balloon counterpulsation, the mainstay for mechanical circulatory support in CS during decades, has recently been challenged by the results of a large randomized clinical trial. Full mechanical circulatory support is theoretically appealing, but more randomized trials are needed to assess their value in different strategies in CS. Finally new emerging therapies will be reviewed.

How to properly detect ACS in chest pain patients in ED: an Italian Registry Proposal

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Every year patients with chest pain who arrive at the Emergency Department represent 5% of the total number of accesses.

From here the importance to collect data to properly detect acute coronary syndromes.

In the last years the literature has recognized the importance of using clinical data in cardiological areas, but there isn’t a similar approach in ED, especially regarding chest pain.

Chest Pain Clinical Database in the Emergency Department is an Italian Registry Proposal, with the goal to collect data about patients with chest pain who arrive at the Emergency Department.

The definition of chest pain is extremely important and difficult: we want to enrol patients with typical chest pain suggestive of ACS.

We can utilize different scores and definitions, but the clinical judgement is the best approach for the definition.

In the Italian Database, data will be classified in areas of interest: age, sex, race, hemodynamic parameters, risk factors, therapies administered in ED, final diagnosis, areas in which patients are treated.

There are some points to focus on: these patients are different from those of cardiological trials. They are old and have a lot of comorbidities. From here a different adherence to guidelines regarding medical and invasive treatment.

Another growing class of new patients is represented from those with a history of CAD treated at home with antiplatelet drugs: often these patients arrive at the Emergency Department with chest pain, anemia and an increase of Troponin. This population needs a different treatment in the acute phase and after discharging.

Troponins have always represented a solution and at the same time a big problem in the life of ED doctors: there are several types of troponins with different sensibilities and it is extremely important to understand the meaning of troponins in the global clinical context.

About treatment in ED, we think it will be interesting to collect data about drugs delivered in various ED and then to compare them and discuss results with cardiologists.

There are some international guidelines to adhere to, but we have several realities in relation to backgrounds and internal protocols. This is an important point, because in the literature there aren’t any data about drugs administered in ED.

The statistical analysis will give specific informations in different realities: it will be possible to compare data and from here to try to be able to have equal treatments in different Emergency Departments.
Why do we need hemodynamics assessment in septic patients

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Cardiovascular derangements during sepsis lead to hypoperfusion and to development of multiple organ failure; therefore the initial management of sepsis in the emergency department (ED) is crucial to prevent this evolution. In the early phases of sepsis the hemodynamic profile is characterized by increased capillary leak and low systemic vascular resistance, that results in a decreased venous return to the heart. The cardiovascular response is characterized by tachycardia and elevated cardiac output, both sympathomediated, that attempt to restore the arterial blood pressure toward normal values. In some cases this hemodynamic response is inadequate to achieve the homeostasis and hypotension persists. The cardiovascular monitoring during the early phases of sepsis is crucial to evaluate the development of severe sepsis and septic shock and to lead clinical interventions. Close hemodynamic monitoring helps physicians to choose right therapy and timing. Different methods of hemodynamic monitoring are available, most of them involving invasive procedures and admission in intensive care units (ICU). Currently, the recommended procedures in severe sepsis and septic shock are arterial cannulation for continuous blood pressure measures, central venous and pulmonary artery catheterization to assess intravascular volume, central venous oxygen saturation and cardiac output; all these parameters are mandatory in order to achieve the early goal-directed therapy (EGDT). EGDT has been shown to reduce mortality in patients with severe sepsis/septic shock, however, implementation of this protocol in the emergency department is sometimes difficult. These methods require expertise, carry the risks related to blood vessel catheterization and are performed in ICU. However, the hospital gateway for patients affected by severe sepsis and septic shock is usually the ED, where it would be desirable to start the clinical and therapeutic managing. We used a noninvasive device to assess hemodynamic patterns in patients admitted to our ED in sepsis or septic shock. No risks of infections or vascular complications are related to this non invasive method. As reported and widely acknowledged septic patients are a challenge for the emergency physician. It is crucial to make an accurate diagnosis as soon as possible in order to implement clinical and therapeutic protocols, in the attempt to positively affect the outcome of septic patients. Moreover, another task required to the ED physician is also a risk stratification in order to define the need of hospitalization and/or the admission in the right division, based on the severity of clinical conditions. Accordingly, it would be interesting to demonstrate that noninvasive hemodynamic monitoring might offer prognostic information in the attempt to stratify the risk of these patients thus starting a prompt and appropriate clinical and therapeutic protocol in ED.

The role of the observation unit in today’s healthcare system

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Emergency department (ED) represents the fundamental gateway for critically ill. This primary goal of the ED is increasingly questioned by the overcrowding which occurs when available resources for patient care in the ED, hospital or both are not commensurate to critical patients requests and an extreme volume of patients crowded the ED treatment areas, forcing the ED to operate beyond its capacity. In these conditions the emergency system might crash because of 1) inappropriate boarding 2) delays in time-sensitive diagnostic and treatment decisions, 3) patients leaving without completion of care, 4) patient and provider dissatisfaction, 5) diverting ambulances, as well as 6) poor outcomes. Among the other problems crowding prevents the full application in our ED of the Observation Unit. The causes of crowding are multifactorial according the widely accepted theory combining input, throughput, and output factors. The primary determinants of ED overcrowding seem to originate outside the ED. Of these, the two most important are an increasing volume of high-acuity old patients affected by several diseases and insufficient inpatient bed capacity. Consequently ED might experience new solutions to face the unavoidable overcrowding thus allowing the Observation Units to work properly. In order to address the issues of ED overcrowding, we developed a 20-24-bed inpatient-based emergency observational care unit (EOCU) implemented without any significant additional resources amount. The main tasks of EOCU has been to take care of patients after having charged in ED and to look for an hospital admission. The goal of this presentation was to examine how and whether the development of the EOCU has impacted on the ED efficiency. The attempt has been increasing and improving active patient care capacity through the implementation of a remotely situated acute care unit, which pushes the boundaries of traditional ED management beyond that conceived for emergency room-based observations units. The first important result has been that the activity in the EOCU has been limited over time, in fact patients have been charged in the EOCU for less than three days. A further goal of the present study has been to show that the dedicated managing of patients waiting in ED for a hospital admission might have a positive effect on the Emerging Room activity showed by a significant decrease in the waiting time from triage to the visit. The improved Emergency Room performance is also confirmed by the significant reduction of patients who left the Emergency Room without being seen. Overall our data show that the improvement of the ED overcrowding seems due to a slight increase of the rate of patients discharge at home and mainly to a substantial increase of patients admitted to other hospitals.

Acute heart failure, aging and muscular deconditioning: a path from emergency department toward cardiac rehabilitation

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Acute heart failure is defined as the appearance de novo or the exacerbation of a complex multifactorial syndrome, characterized by an inability of the heart to pump blood adequately as compared to the peripheral tissue demands. The epidemiological data on its prevalence are quite alarming. Currently heart failure affects 0.4-2% of the adult population in the European Union with a 4 years-mortality of 50%. It accounts for 5% of the total hospitalizations and affects 2% of the cost of the National healthcare system. Its high cost is mainly caused by the high frequency of re-hospitalizations (40% within 12 months). In this alarming scenario becomes more and more important early recognition of the disease and its proper management from the emergency department to the hospital discharge, possibly addressing patients to structured programs of Cardiac Rehabilitation. One of the most significant disability in relation to the quality of life produced by the natural history of the heart failure is represented by the reduced tolerance to physical activity mainly due to the bed-rest syndrome always present as a corollary to this disease and enhanced by the repeated hospitalizations of these patients. For the above reasons currently both European and American guidelines recommend exercise as a non-pharmacological therapy in the treatment of heart failure patient. Physical training through a complex action on several pathophysiological mechanisms underlying heart failure, as autonomic nervous system balance, central haemodynamic, vascular and musculoskeletal function has a favourable impact by reducing the rate of hospitalization, death and by improving functional capacity and quality of life for patients affected by heart failure. Unfortunately, as already said, however, these patients undergo repeated hospital admissions due to continuous exacerbations and this problem becomes particularly acute in the elderly population. Consequently the attempt to define easy and valuable indexes able to give information on the effectiveness of physical training programs in order to optimize the physical treatment thus attempting to reduce the incidence of re-hospitalization, seems mandatory. A further issue strictly linked to the managing of acute heart failure in the Emergency setting is represented by the continuously rising age of patients. It is evident that this condition significantly affects the ED overcrowding. The continuous increases in life expectancy and the improvement of medical technologies causes a shift toward a very old population of patients with heart failure (≥75 years). Most studies on the role of the heart failure patient rehabilitation was carried out on a sample of patients definitely younger. For this reason it would be desirable to test new training protocols that are tailored to older patients as well.

**Translation Research in Emergency Medicine**

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**Background:** One of the most important assumptions which are at the basis of the translational research is that early diagnosis and early treatments can be “optimized” using genetic, biological and phenotypic information. The ability to facilitate rapid and accurate diagnoses and treatment, ultimately affecting long-term clinical outcomes, provides a compelling rationale for the role of emergency departments (EDs) in the translational research focused on development of human disease-specific innovative biomarkers and assay methodologies for the early diagnosis, monitoring, evaluation, and prediction of diseases and of patient responses to therapies. Risk-defining biomarkers are especially evaluated and used at the ED levels - cardiac biomarkers such as, troponin, copeptin copeptin assay, copeptin cand brain natriuretic peptides; urinary biomarkers of nephron damage (NGAL, KIM-1, and serum cystatin C; biomarkers in the management of sepsis (procalcitonin); MicroRNA-134 as a potential plasma biomarker for the diagnosis of acute pulmonary embolism. The up–to–date map from the clinicaltrials.gov website of ongoing studies on biomarkers (all medical conditions) conducted at the emergency departments level, reveals a list of 93 studies. Unsurprisingly, these studies concentrate particularly in the evaluation and treatment of conditions commonly presented to the ED. These not only include cardiovascular(CV) disorders, but also respiratory, allergic and infectious diseases. Most of these trials are concentrated in North America and Europe, with little representation from other continents, in contrast to the globalisation of clinical research characterising non-emergent indications.

**Conclusions:** EDs are involved in translational research mainly by providing biomarker studies conducted with rigor, and for this purpose guided by a full time staff of experienced ED physicians, scientists and clinical fellows, with the ultimate objective to impact on health-care longer term outcomes with reduced health-care utilization.

**Galectin-3 immunotargeting in human diseases**

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- Galectin-3 (Gal-3), α-β-galactosyl binding lectin first discovered in macrophages (MAC-2) plays a regulatory role in several biological functions, some of which are critical for cancer. Gal-3 in fact, directly regulates apoptosis, cell-cycle, nuclear splicing of pre-mRNA, cell-ECM interactions, epithelial differentiation and morphogenesis, immuno-response and tumor growth and progression. Moreover, the recent discovery of Gal-3-mediated profibrotic function is a very important finding with potential implications in translational medicine. The role played by Gal-3 in cardiac fibrosis and remodeling, in fact, has been extensively demonstrated, as well as the prognostic value of soluble Gal-3 in the management of patients with heart failure. However, Gal-3 is a potent activator of fibroblasts isolated from a broad range of tissues, including heart, kidney, liver
and lung, and for this reason it may likely play a potential role in a more general pan-organ fibrosis. As a consequence the possibility to use Gal-3 as a marker for prognostication of different chronic diseases (i.e renal and liver fibrosis and idiopathic pulmonary fibrosis) should be investigated. Furthermore, immunotargeting or functional block of Gal-3 may potentially open new therapeutic avenues for several chronic diseases with extracellular matrix remodeling.

We show here the molecular bases of Gal-3 profibrotic activity in liver, kidney and lung idiopathic fibrosis (IPF), together with some original data on Gal-3 expression in vivo during the evolution of chronic hepatitis to liver cirrhosis.

In cancer, Gal-3 has important diagnostic and prognostic value. The high prevalence of benign thyroid nodules in the adult population, compared to the relatively low incidence of thyroid cancer, make the preoperative diagnosis of thyroid cancer very difficult. Gal-3 immunotargeting is currently in the clinical practice for the preoperative characterization of thyroid nodules. We demonstrated that Gal-3 expression is restricted to malignant transformed thyroid cells compared to normal and benign thyroid conditions. Application of a Gal-3 test-method on FNA-derived cytological substrates allows a better selection of patients candidate for surgery. In our hands up to 71% of unnecessary thyroid surgical procedures for benign nodules can be avoided.

A galectin-3 based immunoPET strategy for thyroid cancer imaging in vivo has been also recently developed by our group. These diagnostic methods are going to change consistently the clinical management of patients bearing thyroid nodules in the next future.

Original and unpublished data on galectin-3 expression in a large serie of neuroblastic tumors (NTs) will be also discussed. We discovered a direct correlation among Gal-3 expression and NTs differentiation, with relevant prognostic implications. (Supported by A.I.R.C.)

Biomarkers in Short Observation Unit solutions for overcrowding in ED

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In the emergency department (ED) the usefulness of biomarkers is crucial, in particular in the short observation unit. When evaluating patients with acutely heart failure (AHF) in the ED, prompt diagnosis and appropriate treatment is the key to superior outcome. Part of the intricacy of caring for patients with AHF is managing the co-morbidities that may complicate their management. Brain Natriuretic Peptide (BNP) is the first biomarker to detect AHF to distinguish patients referring to ED with shortness of breath. The BACH trial demonstrated the diagnostic role of Mid-regional pro-atrial natriuretic peptide (MR-proANP) to identify patients with AHF and the prognostic role of MR-proADM in the same cohort of patients. Galectin 3 has been demonstrated to be linked with a poor outcome in patients with AHF. An important situation in AHF management is the development of Cardiorenal syndrome, for this reason to detect in time Acute Kidney Injury prior to serum Creatinine increase exists for both urine and plasma Neutrophil gelatinase Associated Lipocalin (NGAL). In septic patients the diagnostic use of Procalcitonin (PCT) is demonstrated in literature but it’s also interesting to drive antibiotic therapy with the daily value of PCT, in this setting it’s important the dosage of biomarker to have a prompt diagnosis and good outcome, to permit the use of correct therapy. Usually in Short Observation Unit there are a lot of patients with chest pain, in this kind of patients detect in time high sensivity troponin and copeptin and is very important, to permit a fast rule out. There is no generally univocal agreement in determining which patients should be discharged, admitted to an ordinary ward or to the intensive care unit (ICU). In this attempt biomarkers become a helpful tool to predict mortality and risk stratification. In a previous study we demonstrated the utility of PCT and Mid-regional pro-adrenomedullin (MR-proADM) in the risk stratification of critically ill patients presenting for fever in the ED. MR-proADM has been demonstrated to be of utility in guiding initial disposition of undifferentiated ED patients with acute dyspnea and might therefore be helpful to improve resource utilization and patient care. A multimarker approach could aid physician in promptly identifying the origin and the severity of the underlying disease. During hospitalization the daily use of biomarkers help physicians to evaluate patients should be discharged, admitted to an ordinary ward or to ICU.

Biomarkers research in Emergency Medicine: what do we need in septic patients?

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Biomarkers are valuable tools in the differentiation of sepsis patients from those with non-infective inflammatory syndrome, although their clinical use is far from optimal. The actual shortcomings in their use reflect weaknesses in our knowledge of the whole pathophysiology and management of sepsis. Resolving these limitations is of foremost importance in order to overcome the main cause of death in Emergency Departments.

The first flaw is definition of sepsis. Although sepsis is an immediate concept, its definition is an ongoing work. This uncertainty, in turn, affects comparability of research, development of diagnostic tools as well as clinical practice. There is, anyways, a general agreement that the global definition or concept of sepsis as a single, homogeneous disease process is inadequate and therefore either a more technical or pragmatic definition is needed.
The second need is to develop a pathophysiology-related choice of the biomarkers. Extracellular (i.e. surface receptors) are promising biomarkers, while those deriving from intracellular signaling of virtually all microorganisms encompasses classes of receptors (TLR, CD281 – CD 290, NLR, CLR and RLR) shared also by DAMPs (danger associate molecular patterns). Therefore, the difference between sepsis and non-infective conditions relies only on the magnitude of the injury.

A gold standard for its diagnosis is eagerly needed. Sepsis is the most frequently misdiagnosed condition in medical practice and likely in research, being both based on clinical judgment and microbial growth from cultured specimens. A definite diagnostic tool would strengthen all research on biomarkers. Sepsis is a complex syndrome and modern technology could provide some solutions to look for a panel of possible invading microorganisms.

Inter-individual genetic variability can deeply affect the response to different agents. To know in advance the variants that might affect plasma levels of biomarkers and the effect of therapy might shed more light in this complex conundrum.

At the end, funding of sepsis research projects would benefit the healthcare system in a medium term reducing length of stay, improve the proper management of antimicrobial agents, and therefore reducing the prevalence of multidrug resistant bacteria.

**Fluid management in trauma patients**

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A proper approach to fluids administration management in patients with trauma entails to analyze how fluids are partitioned within a healthy subject and during inflammation. The human body is approximately 60% water, divided between the extracellular space (20% of body weight) and the intracellular space (40% of body weight) by the energy-dependent pumps system of cell membrane. The extracellular fluid (ECF) is divided further into the intravascular and extravascular spaces by the capillary membrane and the oncotic pressure caused by plasma proteins. The traditional Starling’s law has been recently revised by the deeper knowledge of the role that the intercellular junctions and composition of the intraluminal layer have in the microvascular endothelium (1) has for the leakage of fluids to extravascular space.

Trauma yields a diffuse hyperinflammation through a large release and activation of many inflammatory mediators that affect the energy produced by cells, open the intercellular gaps and alter the intraluminal layer’s structure (2). Fluids translocation from the intravascular to the extravascular spaces reduces tissue perfusion and oxygen diffusion to cells and it strictly hinges on fluid management at the emergency department (ED) or in the early stage of treatment in the intensive care unit (ICU).

To complete the analysis to fluids balance in trauma patients a relevant factor to be considered is the amount of the absolute hypovolemia induced by the blood loss and its effects on thermoregulation, coagulation and acid-base equilibrium in the blood. Indeed the occurrence of hypothermia, coagulation disorders and metabolic acidosis (lethal triads) (3) ought to be prevented making early measures for damage control resuscitation (DCR) (4) at the admission of emergency department (ED) or even in prehospital frame (5). Central hypovolemia per se has been proved to elicit a microcirculatory response in tissues even in healthy subjects adequately compensated and with an intact autoregulation (6). After trauma the blood loss and fluids translocation have cumulative effects on tissues perfusion giving rise to a clinical setting of reduced organ function onwards to a lasting damage. Therefore for an appropriate fluids management the assessment of the equilibrium point between blood volume lost to be re-infused and microvascular overload to be avoided it becomes primary considering also that trauma yields a very decreased capacity to hold fluids in microcirculation. As it was amply proved that adult (7) and children (8) with sepsis-induced inflammation admitted in the ICUs with fluid overload have a reduce survival than those with fluid restriction, after trauma the early management of fluid administration at the accident site or at ED becomes crucial. This topic was also matter of a recent prospective observational multicenter study on major trauma transfusion (PROMMTT) (9).

The estimation of blood volume lost on trauma scene can give a useful information for blood transfusions particularly if the emergency care providers are well trained on this topic (10). When trauma patients are admitted in the ED, the evaluation of clinical signs and hemodynamic instability, as suggested by the Advanced Trauma Life Support (ATLS) protocol (11), can be usefully integrated by a decisional algorithm based on multiparametric monitoring (12).

Because the extravascular fluid accumulation elicited by trauma affect the organs in their function, a close monitoring of the organ dysfunctions indicators allows the physician to define the extent of inflammation and hint volume of fluids to be administered. Some suggested B-type natriuretic peptide might be helpful in guiding fluid therapy (13) despite its correlation with fluid balance during resuscitation is not so strong to allow this biomarker could be considered alone as a guide for fluid administration. Nevertheless because high values of the natriuretic peptide associate to an aggressive fluid administration it can be used as an indicator of overloading (14).

Along with indirect biomarkers of fluid overload a new frontier of researcher has been opened consisting on the development of new instrumentation based on optical and impedentiometric technologies for the measurement of the water content within tissues. These instruments could provide an bench-to-bedside evaluation of tissue water content as a real-time guide for fluids infusion.

The goal of early treatment in trauma patients is not to normalize the hemodynamic parameters but to make the patient comes alive as soon as possible to the operating theatre or to interventional radiology (15). To reach this objective maintaining tissue perfusion acceptable a common practice is an aggressive administration of fluids of any kind. This empiric mode of treatment for uncontrolled bleeding and massive hemorrhage is defined as the replacement of the blood volume with crystalloid solutions conventionally followed by 10 or more units...
of packed RBC in the first 24 h to restore oxygenation of the tissues. This approach is dilutive by nature and entails many potential risks on coagulation (16). Many studies showed that massive fluid administration results in an increase of complications (17) including hemodilution with hyponatremia, hypothermia, worsening of tissue inflammation in multiple organs that yielded a damage correlated to the amount of fluids (18,19) and worsening of bleeding (20). Aggressive early crystalloid resuscitation adversely affects also the outcomes in adult blunt trauma patients (19). A recent study on the prehospital settings showed that trauma patients without hypotension the administration of even more than 500 mL crystalloid resulted in a worse outcome, suggesting that a prehospital moderate infusion of crystalloids could be justified only presence hypotension (21). The hazard of massive transfusion was also confirmed by PROMMTT study who highlighted that the administration in a short time (within 30 minutes the ED arrival) of more than 4 units resuscitative fluid increased more than twofold the in-hospital mortality at 6 hours in severe trauma patients (22). As resuscitative fluids they considered all kinds of fluids infused including crystalloid, colloids, red blood cells (RBC) and plasma. To reduce the amount of fluids resuscitation an European guideline recommends to maintain a target systolic blood pressure of 80 to 100 mmHg until major bleeding has been stopped following trauma without brain injury (23). The so-called ‘permissive hypotension’ with of low-volume fluid resuscitation achieving a mean arterial pressure of 65 mmHg or more avoids the adverse effects of an early aggressive resuscitation while maintaining a level of tissue perfusion that, although lower than normal, is adequate for short periods. Low-volume approach however has some limitations. It is contraindicated in brain and spinal injuries because of need to maintain a perfusion pressure higher than normal to ensure the oxygenation of an injured central nervous system, in elderly patients and in patients suffering from chronic arterial hypertension. Although the use of a vasopressor cannot substitute fluid resuscitation it helps to rapidly achieving a target blood arterial pressure. Which target of the Hb concentration physician has to achieve is another major issue to be pointed out. Although the optimal Hct or Hb concentration required to sustain haemostasis in bleeding patients remains unclear, from the results of studies concerning the harmful effects of blood transfusions and the effects of the Hb level on cerebral oxygenation in patient with brain injury (24) a Hb target of 7 to 9 g/d could be recommended.

Currently many evidences suggest that warm fresh whole blood (WFWB) is the safest way to restore the blood loss (25,26). The additional leucocytes and pathogen inactivation of whole blood has further improved its clinical safety, although with some loss of the active principles. Though WFWB is more available in combat support hospitals, the possibility that coagulation function is maintained at room temperature for 72 hours makes feasible its availability also at large civilian trauma centers (27). For replacement of depleted blood volume with the more available packed RBC the DCR protocol recommends to transfuse fresh frozen plasma before RBC in a high ratio for every unit of packed RBC, while minimizing infusion of crystalloids (28).

What kind of fluids and how much to give remain open questions for trauma resuscitation from hemorrhagic shock. Concerns for hyperchloremic acidosis elicited by normal saline (NaCl) and the proinflammatory properties of lactated Ringer’s solution induce to use alternative choices in crystalloid solutions composition. The hypertonic saline effectiveness observed in patients with brain injury resulted less effective in a randomized trial on trauma patients (29). Indeed because this trial refers to pre-hospital fluids administration with uncontrolled volumes the results are most probably affected by the effects on excessive volume expansion elicited by hypertonic saline hindering its efficacy. Recently hyperosmolar reconstituted lyophilized plasma proved to be effective to respect physiologic and hemostatic properties and required much less volume of fluids that may reduce the adverse effects of large-volume resuscitation (30). Use of low volumes colloids during high ratio DCR was associated to better survival than use resuscitation with higher volumes of crystalloids (31).

In conclusion, to realize an adequate view of the prehospital and the ED fluid management in trauma patients we should consider besides the short term effects on mortality, the long-term effects on morbidity. The effects of a wrong strategy of fluid administration can be delayed to the ICU’s and can be likely related to a water overload inside the organs resulting in dysfunction and finally damage.

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Galectin-3 monitoring utility in heart failure patients

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Galectin-3 is a member of the galectin family and has been implicated in various pathophysiological processes, like inflammation and fibrosis. Experimental data obtained in cell and animal models of cardiac hypertrophy and remodeling suggested that galectin-3 is associated with increased tendency towards heart failure. Galectin-3 is secreted by macrophages and turns quiescent fibroblasts into myofibroblasts and as such plays a critical role in myocardial fibrogenesis. Although galectin-3 is mainly localized in the cytoplasm, it may partially translocate to the nucleus, while it may also be membrane-bound. As a result, galectin-3 is secreted into the circulation. The circulating galectin-3 can reliably be measured with an ELISA. In the general population, galectin-3 is associated with cardiovascular risk factors, and predicts mortality as well as new onset heart failure and renal failure. Several clinical studies in acute and chronic heart failure have shown that circulating galectin-3 is a strong predictor of outcome. Its prognostic usefulness has been shown to be independent from renal function, diabetes, LVEF, and natriuretic peptides. In addition to other biomarkers, e.g. natriuretic peptides, it offers incremental prognostic value. This may be explained by the observation that natriuretic peptides and galectin-3 are markers of different phenomena: while natriuretic peptides mainly respond to (over-) loading of the heart, galectin-3 rather reflects tissue fibrosis and remodeling. Changes in galectin-3 over time strongly predict outcome and may be used to monitor patients at risk. Further, near term hospitalization can accurately be predicted by galectin-3. Finally, galectin-3 may be of particular interest in specific subgroups of patients with heart failure, such as patients with heart failure with preserved ejection fraction or patients with the cardiorenal syndrome. In this presentation, recent data on the use of galectin-3 as a biomarker in heart failure is summarized.
Which antiplatelet treatment for which patients with acute coronary syndrome in ED?

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Platelet activation and aggregation play a central role in determining the clinical consequences of dynamic coronary thrombosis, which is a key feature of the pathophysiology of acute coronary syndromes (both with and without ST-segment elevation- STE). As a consequence, it has been proved that pharmacological platelet inhibition is highly beneficial in the whole spectrum of patients with acute coronary syndromes (ACS), being associated with a marked reduction of cardiovascular events both at short- and long-term. In the past 25 years several antiplatelet drugs, targeted to inhibit different pathways of platelet activation, have been tested alone or in combination. Key results are the following: 1- Aspirin (with or without a loading dose) is highly effective both in patients with or without ST-segment elevation in the presenting electrocardiogram; 2- The addition of a P2Y12 receptor inhibitor (typically clopidogrel) to aspirin potentiates the anti-thrombotic efficacy of the antiplatelet regimen; 3- The inhibition of the final pathway of platelet aggregation mediated by the GPIIB/IIIA receptor exposure on platelet surface is beneficial in high-risk patients managed with an invasive strategy particularly when this strategy is applied immediately (primary PCI for STE-ACS); 4- The substitution of clopidogrel with newer and more potent P2Y12 platelet receptor inhibitors (prasugrel and ticagrelor) is effective in the all spectrum of acute coronary syndromes both receiving or not receiving GP IIb/IIIa inhibitors. Whether the benefit of antiplatelet therapy is greater when started at first medical contact rather than when a decision is taken about the choice between an invasive or conservative strategy is still a matter of debate. For STE-ACS patients immediate administration of a loading dose of aspirin is recommended at the time of ECG diagnosis, which is now increasingly obtained in the pre-hospital setting. In remaining cases, aspirin should be administered in the Emergency Department. A number of studies, both observational and randomized, have evaluated the role of GPIIB/IIIa inhibitors administered in the pre-hospital setting in comparison with the administration in the catheterization laboratory. The results of these studies are mixed, but meta-analysis of randomized trials failed to show a clear benefit of early administration, being associated with an increase of major bleeding. The efficacy of clopidogrel pre-treatment in comparison with clopidogrel administered after diagnostic coronary angiography has been less extensively evaluated. Observational studies reported a benefit in favor of pre-treatment; however, the only randomized comparison between a 600 mg loading dose given pre-hospital or at the time of percutaneous intervention showed no significant differences in coronary patency rates among the two groups. Prasugrel has been shown to be more effective than clopidogrel in STE-ACS for whom primary PCI was planned. In TRITON-TIMI 38, randomisation could take place without knowledge of coronary anatomy, just after informed consent was obtained. It is however unknown the number of patients who received study drugs before primary PCI, the proportion of those receiving them outside the hospital or in the Emergency Department, and the time difference between the two modalities of administration. More importantly, it is also unknown whether early administration of prasugrel was more effective than late administration. Similar considerations apply to ticagrelor, which has been shown to be superior to clopidogrel in the PLATO trial. In this case however, a randomized trial (ATLANTIC) is currently recruiting patients. The results of this study will assess the value of the pre-hospital administration of ticagrelor in comparison with the administration at the time of primary PCI. Diagnosis and risk stratification of NSTE-ACS patients is typically performed in the Emergency Department and the Coronary Care Unit. A loading dose of aspirin is recommended when the clinical suspicion is high. When the diagnosis is ascertained, clopidogrel should administered as soon as possible with a loading dose of 300 mg. In fact it has been shown that incidence of cardiovascular events is significantly decreased since 24 hours from the start of therapy. The infusion of a GP IIb/IIIa inhibitor (small molecule) may be initiated when the ischemic risk is high and the bleeding risk is low. It is unknown whether, when given early, prasugrel is more effective than clopidogrel given the fact in TRITON-TIMI 38 treatment was started after coronary angiography only in patients with coronary anatomy suitable for PCI. On the contrary, ticagrelor was compared with clopidogrel in the PLATO trial according to the recommended early initiation of treatment. Since the superiority of ticagrelor over clopidogrel was apparent, ticagrelor might be the preferred P2Y12 receptor inhibitor suitable for NSTE-ACS patients to be started even in the Emergency Department.

Sepsis and septic shock: a pilot study on the prognostic value of noninvasive hemodynamic monitoring

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Cardiovascular derangements during sepsis lead to hypoperfusion and to development of multiple organ failure; therefore the initial management of sepsis in the emergency department (ED) is crucial to prevent this evolution. Different methods of hemodynamic monitoring are available, most of them involving invasive procedures and admission in intensive care units (ICU). Currently, the recommended procedures in severe sepsis and septic shock are arterial cannulation for continuous blood pressure measures, central venous and pulmonary artery catheterization to assess intravascular volume, central venous oxygen saturation and cardiac output; all these parameters are mandatory in order to achieve the early goal-directed therapy (EGDT). These methods require expertise, carry the risks related to blood vessel catheterization and are performed in ICU. However, the hospital gateway for patients affected by severe sepsis and septic shock is usually the ED, where it would be desirable to start the clinical and therapeutic managing.
We realized an observational study in an teaching ED, in Rome, based on clinical data collection, hemodynamic assessment and clinical scoring, to evaluate the prognostic value of early noninvasive hemodynamic monitoring in patients with sepsis and septic shock admitted to ED. Twenty-seven patients in sepsis and septic shock, admitted to the ED of our hospital, were included in the study. The inclusions criteria were those used for the diagnosis of sepsis and septic shock according to the 2001 International Sepsis Definition Conference. Clinical data were collected for each patient including age, sex, site and the type of infection, serum procalcitonin levels, SOFA score, use of vasopressor and/or inotropic agents, complete list of the other drugs. Cardiovascular parameters were detected by Nexfin® (BMEYE B.V., Amsterdam, The Netherlands) providing a continuous noninvasive monitoring, by ECG tracing and capillary pulse derived blood pressure measurement. This device, using a pulse contour method, derived the value of blood pressure, heart rate, cardiac output, stroke volume, left ventricle contractility index (dp/dTmax) and systemic vascular resistance.

Overall death rate was 48%. The analysis of means between survivors and non survivors showed a significant statistical difference for stroke volume (74,00 vs 53,21 ml; p=0,002), cardiac output (6,69 vs 5,04 lpm; p=0,012), cardiac index (3,65 vs 2,83 lpm/m2; p=0,018), left ventricle contractility index (870,81 vs 565,83 mmHg/s; p=0,004) and lactates (1,8 vs 2,7 mmol/l; p=0,04). Stroke volume has a positive association with survival, the mortality rate is reduced of 40 % for each centiliter of increase in stroke volume (p=0,006). The percentage of deaths is 72% among patients with dp/dT max < 636,5 mmHg/s (median of value’s distribution) vs 24% in patients with dp/dT max higher than the median value (OR 8,1; 95%CI 2.29; 28,9; χ²: 0,001).

Conclusions: Noninvasive hemodynamic monitoring is a reliable tool for the early management of patients in sepsis and septic shock, in the ED. In these patients stroke volume and dp/dT max noninvasive measured have shown a positive correlation with survival.

Using high sensitivity cardiac troponin assays in the emergency department

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High sensitivity cardiac troponin (hscTn) assays have the potential to markedly improve the identification of patients with acute cardiac injury in the Emergency Department. However, understanding how to use these assays optimally to distinguish those with acute disease from those with more chronic cardiovascular comorbidities takes some degree of clinical sophistication and some understanding of how to use hscTn assays appropriately.

It should be understood that with hscTn assays, most patients will have detectable levels of cTn. Indeed the absence of detectable levels or very low levels without a change over a couple of hours may be a good way to exclude acute disease. Ruling in acute disease however will be more challenging and will require not only elevated values of hscTn but also a changing pattern of those values. Unfortunately, the metrics for the definition of a changing pattern of values will be assay dependent and have not yet been optimally defined. Preliminary data suggest that near the 99th% URL that both percentage and absolute values will be helpful but with more elevated values, absolute values are likely to be better clinically. However, the criteria in use for elevated values are very likely to be less than changes that can occur spontaneously due to conjoint biological and analytical variation. Thus, there will be a tension between the sensitivity and specificity of elevations for the diagnosis of acute disease. The reasons for this and the determinants of these criteria will be discussed in some detail. In addition, the situations that may confound the diagnosis of acute myocardial infarction, including stable coronary artery disease and heart failure will be considered.
3D and 4D echocardiographic assessment in early phase of AHF: do we need it?

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Acute heart failure (AHF) is defined as the rapid onset of symptoms and signs secondary to abnormal cardiac function and it is life threatening and requires urgent treatment. For those working in Emergency Room question is – 'Where is the place for echocardiography in general?' According to ESC Guidelines for the diagnosis and treatment of AHF – Echocardiography is an essential tool for the evaluation of the functional and structural changes underlying or associated with AHF, as well as in the assessment of acute coronary syndromes. 3D/4D Echocardiography become a standard acquisition which should be routinely use to simplify the diagnostic problem in AHF.

The usefulness of 3D Echocardiography (EAE/ASE Recommendations for Image Acquisition and Display Using Three-Dimensional Echocardiography) are: the evaluation of cardiac chamber volumes and mass, which avoids geometric assumptions, the assessment of regional left ventricular (LV) wall motion and quantification of systolic dys synchrony, presentation of realistic views of heart valves, volumetric evaluation of regurgitant lesions and shunts with 3DE color Doppler imaging, 3DE stress imaging.

Study limitations for 4DE in AHF patients are that because 3DE/4DE analysis requires a “full volume” acquisition, there are practical problems in capturing the full extent of very large ventricles, which may require modified views and which can be underestimated by this technique. Another limitation of 3DE/4DE is its sensitivity to the heart rate variability, which constitutes the acquisition of full volumes in patients with arrhythmias such as atrial fibrillation difficult. For the same reasons patients in very severe HF who are unable to withstand a 5-s breath-hold, which is necessary for the dataset acquisition, cannot be investigated. This limitation is expected to be overturned by the next generation of proper real-time 3D acquisitions on just 1 beat.

Anemia in acute heart failure: is it important?

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Anemia is frequent in individuals with cardiac failure (HF), with an estimated prevalence of 5 to 55%, also as a function of time and extension of the hemodynamic involvement. In the OPTIMIZE-Heart Failure trial on 48,612 patients, 51.2% had Hb < 12.1 g/dl, whereas 25% ranged between 5 and 10.7 g/dl. Anemia was present in about 9% of pts with class I HF (NYHA), while > 70% in class IV. Onset of anemia was an independent predictor of morbidity and mortality, with an increase of the RR of death of nearly 20% for any 1 g/dl decrease of Hb.

In the PROTECT trial on acute decompensated heart failure and volume overload, a rapid increase of hemoglobin during the first week of treatment predicted a favourable outcome, likely through better decongestion in response to therapy.

On the other hand, clinical trials on anemia in chronic renal failure (CRF) yielded controversial results. The CREATE trial (2006) on 603 pts with estimated glomerular filtration rate (eGFR) of 15-35 ml/min and baseline Hb of 11.0-12.5 g/dl included 32% patients with HF. In two groups with target Hb of 13.0 – 13.5 and 10.5 – 11.0 g/dl, no differences were noted between cardiovascular endpoints, left ventricular mass index and eGFR, while quality of life was better in the former group, although more pts. were on regular dialysis treatment. In the CHOIR trial (2006) 23% of 1632 pts. with eGFR 15-50 ml/min and baseline Hb < 11.0 g/dl had HF. No differences were found between two treatment groups with target Hb of 13.0 – 13.5 and 10.5 – 11.0 g/dl, respectively, in terms of a composite endpoint of death and 3 cardiovascular events. Similarly, a secondary endpoint including progression to end stage renal disease, quality of life and hospitalization did not differ in the two groups. Overall, in 10 interventional studies published between 2001 and 2006 on n = 29,626 pts with HF (552–6563), prevalence of anemia ranged between 5 and 47% (median 17%), turning out again to be an independent risk factor of mortality.

Treatment of anemia with rhEPO should soon expand to cardiac ischemia and decompensated HF, with a remarkable potential in the amelioration of symptoms and cardiovascular endpoints.

Innovative approach to traumatic patients in the ER

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Thoracic trauma is frequent in multiple traumatized patients. According to the current annual report of the TraumaRegister® of the German Trauma Society (DGU) 56% of 10766 documented severe trauma patients with Injury Severity Score (ISS) ≥16 points showed thoracic injuries with an Abbreviated Injury Scale (AIS) ≥ 3 points [1]. Beside rib fractures, lung contusion and pneumothorax (PTX) are the main consequences of blunt chest trauma. In hospital, significant PTX is detected in 37 to 59% of the cases [2]. Primary routine diagnostics in shock trauma room include clinical examination and chest x ray (CXR). However, a significant percentage of PTX maintains undetected by these methods and is first distinguished by CT scan. These occult PTXs count for 2 to 15% [3-5], in some studies even 50% [6]. The initial, secure and fast detection or exclusion of PTX has a high impact on the physician, especially when continuous monitoring and immediate treatment of PTX through chest tube placement can not be guaranteed [2, 7, 8]. Therefore the "S-3 guideline on treatment of patients with severe and multiple injuries of the DGU" recommends to expand radiologic diagnostics by thoracic ultrasound when suspecting thoracic trauma. If significant clinical signs are
present a thoracic CT scan with i.v. contrast agent is advised, alternatively even primary [2]. However, circumstances as mass casualty incident (MCI) could rapidly restrict clinical established diagnostics by limiting available resources.

In the preclinical setting, thoracic ultrasound is conceivable but is not yet used regularly and is depending on the skills of the examiner. Consequently, an anytime available, examiner independent, easy to use and fast method with high diagnostic accuracy in terms of a point-of-care device to rule out PTX would be desirable [7]. Therefore a micropower impulse radar-based tool – the PneumoScan™ engineered by PneumoSonic Inc. (Cleveland, OH, USA) is investigated to exclude PTX in the context of shock trauma room treatment of severe injured patients. Based on micropower impulse radar (MIR), the PneumoScan™ is a portable, battery-powered, CE-certified (CE-certificate 561036) diagnostic tool, commercially available via PneumoSonic Inc. (Cleveland, OH, USA). It emits ultra short electromagnetic impulses with a frequency of 500 megahertz to six gigahertz [9]. The radar impulses are specifically reflected by different tissues of the human body and can be analysed and distinguished by the device. The spatial accuracy amounts approximately five millimetres [10]. PneumoScan™ can detect a pneumothorax to a depth of eight centimeters. In the presentation already published data [11] concerning the performance of the device will be reviewed and preliminary data from an ongoing examination will be demonstrated.


Heart transplant experience in Czech republic

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Heart transplantation (HTX) has become an accepted treatment for selected patients with end-stage heart failure. There are two transplant centres in Czech republic – Prague, since 1984 and Brno since 1992, in which more than 1000 heart transplantations were performed. In Brno centre there were transplanted 412 adult patients till the end of 2012.

Pharmacotherapy after heart transplantation includes the problems of immunosuppression and interactions of immunosuppressant drugs and their adverse effects.

Posttransplant complications include infections, metabolic disorders (hypertension, hyperlipidemia, diabetes mellitus), ulcer disease, hematological disorders, nephropathy, hepatopathy, neuropathy, osteoporosis and development of malignancies, especially cutaneous and lymphomas. Nevertheless the survival after heart transplantation is very good: one year 85%, five years 70% and 10 years 50%.

The main task for present time is
1. Introduction of new and more potent immunosuppressant drugs with less adverse effects
2. Non-invasive assessment of allograft rejections

1. The new immunosuppressive agents known as inhibitors of proliferation: sirolimus (rapamycin) and its derivative RAD (everolimus) act by the mechanism of TOR (target-of-rapamycin) inhibition. They allow to minimize the dose of calcineurin inhibitors and thus reduce the nephrotoxicity without compromising effectiveness of immunosuppression. They have a further protective effect against CMV infection and antitumour and antiproliferative activity. Reasons for conversion to sirolimus or everolimus in patients after heart transplantation are: chronic calcineurin nephrotoxicity, graft vasculopathy, refractory rejection, myopathy, cyclosporine neurotoxicity, malignancy.

2. Diagnosis of rejection without endomyocardial biopsy.

The non-invasive methods include echocardiography – tissue Doppler imaging, densitometry, contrast echocardiography, strain and strain rate or determining the levels of certain humoral mediators: interleukin, brain natriuretic peptide, troponin T or directly determining the release of donor DNA in the blood of the recipient.

The main task for future is to find alternatives to classical transplantation: xenotransplantation, stem cell transplantation or development of new ventricle assist devices.
Brazilian Heart Failure Network

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Acute Decompensated Heart failure (ADHF) is the leading cause of hospitalization in patients over 65 years old in Brazil and a rise in its incidence has been observed. This has been attributed at least in part to the population ageing in our country. To cope with this, the Brazilian Society of Cardiology founded the Heart Failure Department in 2001. In 2005 the I Latin American Guidelines for the management of ADHF was launched and was updated in 2009 and 2012. A Brazilian registry on acute heart failure, the BREATHE study, which comprises 57 centers all over the country, has just ended the inclusion period. Preliminary data shows high in-hospital mortality (12%) and high readmission rates. The most frequent etiology of heart failure in Brazil is ischemic heart disease (30%) but Chagas disease plays an important role, accounting for 11% of the cases. Chagasic HF patients have worse outcomes than non-chagasic. Regarding HF treatment most patients were treated with intravenous (IV) loop diuretic and 14% were on IV inotropes. The rate of IV vasodilator use was incredibly low, accounting for only 6% of the cases. Considering the importance of such medications in the treatment of ADHF, all efforts should be implemented in order to increase awareness among emergency department physicians and as a result, improve the outcomes of ADHF in our country.

How to optimize the management of patients with acute diarrhea

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Diarrhoea is an alteration of normal bowel movement characterized by an increase in the water content, volume or frequency of stools. A decrease in consistency and an increase in frequency of bowel movements to >3 stools per day have often been used as a definition for epidemiological investigations. Diarrhoea needs to be classified in acute or chronic (using a limit of 4 wk to separate the two conditions) and in watery, fatty, inflammatory, on the basis of the faeces characteristics. Duration of diarrhoea is important, because acute forms are usually due to infectious agent, intoxication, or food allergy; however, acute diarrhoea may be a symptom of the onset of chronic organic or functional disease. Also important is a chemical/physical examination of the stools: secretory diarrhoeas, mostly acute and due to infections are by far the most important subtype of diarrhoeas in terms of frequency, incidence and mortality. In developing countries, they represent the primary cause of child mortality. Moreover, acute diarrhoea is frequently reported in old age with a prevalence of 3.9%-14.2%.

Infectious diarrhoeas are of viral aetiology in more than 70% of cases, while bacterial aetiology occurs in 1.5%-5.6% of cases. Depending on the pathogenetic mechanism, infectious bacterial diarrhoeas can be divided in cytotoxic (pathogens stimulate secretory function by activating intracellular enzymes) and cytotoxic (pathogens damage directly epithelial cell). C. difficile is an important nosocomial pathogen and the most frequently diagnosed cause of infectious hospital acquired diarrhea. Disruption of the bowel microflora, generally by antibiotics creates an environment that allows its proliferation.

Clinical classification of diarrhoea and an understanding of the main pathogenic mechanisms that bring it about are vital for a diagnostic and therapeutic approach. Obtaining a thorough history, including both clinical and epidemiological features, should be the first step in evaluating a patient who presents with any significant diarrheal illness. The most common risks with diarrheal illnesses are dehydration: thus, the critical initial treatment must include rehydration. Symptomatic and aetiological therapy should be adopted to improve the patient’s clinical condition.

Probiotic agents have been studied for the management of diarrheal disease. Probiotics are defined as live microorganisms of human origin and they have been shown to have immunomodulating properties and enhance the mucosal barrier. They are involved in production of essential nutrients of the colonic mucosa, beneficial effect on intestinal immunity, recovery of the disturbed gut mucosal barrier and prevention of microbial translocation, elimination of toxins and eradication of microbial pathogens, production of steroids from cholesterol and reduction of its pool in circulation, participation in regulation of intestinal functions.

Hypertensive emergencies in pregnancy

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Hypertensive disorders are the most common medical complications of pregnancy, affecting 5% to 10% of all pregnancies. The spectrum of the disease ranges from mild hypertension with minimal clinical significance to severe hypertension and multiorgan dysfunction. Gestational hypertension is defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg after the 20th weeks without proteinuria and without symptoms. A diagnosis of preeclampsia can be made when hypertension is accompanied by proteinuria,
and symptoms of the involvement of one or more organ systems. Basing on the severity of hypertension and proteinuria as well as the involvement of other organ systems, preeclampsia may be subdivided into mild and severe forms. Severe preeclampsia is defined as a systolic blood pressure $\geq 160$ mm Hg or a diastolic blood pressure $\geq 110$ mm Hg together with severe proteinuria ($\geq 5$ g/24 hrs), cerebral symptoms, thrombocytopenia, pulmonary edema, oliguria. At mature gestational age delivery should not be delayed. In earlier gestational ages, if the patient maintains a stable maternal and fetal course, may be expectantly managed until 34 weeks. In these cases, blood pressure control is essential. As in other forms of hypertension, urgencies may be managed with oral treatment and blood pressure reduced in 24-48 hours. Hypertensive emergencies are conversely characterized by acute organ involvement and/or deterioration and an IV treatment is mandatory.

Medications should be given orally or intravenously in order to maintain blood pressure between 140 and 155 mmHg systolic and 90 and 105 mmHg diastolic.

The most commonly used intravenous medications are labetalol and hydralazine and oral rapid-acting nifedipine. Care should be taken not to drop the blood pressure too rapidly so as to avoid reduced renal and placental perfusion.

Worsening maternal or fetal status warrants delivery, regardless of gestational age. Expectant management is associated with an increased risk of DIC, intracranial haemorrhage, renal failure, retinal detachment, pulmonary edema, liver rupture, abruptio placentae, and death. The HELLP Syndrome (hemolysis, elevated liver enzymes, and low platelet count) is a severe form of preeclampsia. The initial management of this syndrome should be the same as that for severe preeclampsia. Expectant management of HELLP syndrome poses a significant risk of abruptio placentae, pulmonary edema, adult respiratory distress syndrome, ruptured liver hematoma, acute renal failure, DIC, eclampsia, intracerebral hemorrhage, and maternal death. Therefore, expectant management past 48 hours is not warranted. Eclampsia is severe form of preeclampsia characterised by the onset of seizures. Eclampsia is major cause of maternal and perinatal morbidity/mortality. The management of eclampsia included supportive care to avoid injury, maintain oxygenation, control blood pressure and move toward delivery. Magnesium sulphate should be used for prevention of recurrent seizures.

Hyponatremia in congestive heart failure: prognostic value and treatment

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Hyponatremia (a serum value of sodium $<135$ mEq/L) is the most common serum electrolyte disorder. In congestive heart failure (CHF) admitted patients has been observed in 18-30% while the prevalence seemed to be lower in out-patients. Hyponatremia is generally divided into: a) sodium and water excess; b) water excess and c) sodium and water excess. In CHF hyponatremia results from a non-osmotically mediated increase in arginine vasopressin (AVP) levels in response to arterial underfilling. The stimulation, in fact, of $V_2$ receptor in the collecting ducts of the nephron leads to increase water reabsorption and dilutional hyponatremia.
Hyponatremia has been proved to be a powerful predictor of survival in out-patients or admitted to hospital CHF patients. The association between hyponatremia and worse prognosis at 1-year mortality was demonstrated in the EFFECT study and confirmed into the Seattle Heart Failure Model, in which a serum sodium<138 mmol/l had a negative predictive value at 3-year follow-up. Finally, in the MAGGIC meta-analysis that included 14776 CHF patients with preserved or reduced left ventricular ejection fraction, the risk of death appeared to increase linearly with serum sodium levels<140 mEq/L and was predictive independently in both preserved/reduced EF. Although the powerful predictive value of hyponatremia was still verified after adjustment for other variables of clinical relevance such as age, gender, renal function, diabetes and ischemic heart disease, in the MAGGIC meta-analysis the group of CHF patients with hyponatremia presented a worse clinical profile, identifying a more compromised patients. Recently, the relationship between cardiovascular mortality and serum sodium in CHF patients should be depicted as an ‘U-curve’ in which not only hyponatremia but also hypernatremia (value>145 mmol/L) has a negative predictive value at 5-year follow-up.

The possible mechanisms of developing hypernatremia in CHF regard the use of loop diuretics caused by a reduction of diuretic-induced free water clearance, parenteral nutrition or an impaired feeling of thirst.

Treatment of hyponatremia in CHF should be considered that is a chronic form with hypervolemia and normally benefit with fluid restriction. Serum sodium concentration would increase by 1.2 mEq/l per 24 h only if the amount of daily intake is less than daily urine output and insensible losses. Although fluid restriction is effective in managing hypervolemic hyponatremia, the long-term compliance, particularly in out-patient, is poor. The availability of vasopressin receptor antagonists (vaptans) seemed to change the field of hyponatremia. The most studied, tolvaptan, an oral selective V$_2$ receptor antagonist, determined in CHF patients a reduction of body weight, an increase in urine volume, a decrease in clinical edema and a normalization of serum sodium. The correction of serum sodium has been confirmed in a larger experience and occurred after 4-day maintaining at 30-day follow-up but after the discontinuation of tolvaptan hyponatremia recurred. Although these positive preliminary experiences, the EVEREST Trial, including 4333 CHF patients (only 8% with hyponatremia) failed to demonstrated an improvement in cardiovascular death and hospitalization for heart failure at 10-month follow-up. However, this trial confirmed the normalization of serum sodium in patients with hyponatremia, the reduction of edema and the quick relief of dyspnea.

These results seemed to suggest to test vaptans in hyponatremic CHF patients hoping that the correction of sodium concentration might ameliorate the clinical prognosis together with symptoms.

References

Lessons learnt from February 2013 airplane accident in Fiumicino

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Nowadays airport plane crashes are statistically the most probable serious emergencies, because more and more people today choose airplanes as means of transport.

The disproportion between the resources available at once and the needs of medical assistance for this kind of accidents emphasize the necessity of excellent organization to exploit those resources in the best way, and, more important, limit the confusion which may occur in such circumstances.

In case of air crash, the medical organization in the airport provides that a medical team (doctor-paramedic) shall immediately reach the place of the accident, in accordance with what has been established by the ICAO set of regulations for airport emergency.

The procedures provide that, after the alarm phase, all the necessary communication about the accident will be given to the First Aid staff, both inside the airport and in the nearby area.

In case of air accident according to the airport manuals there will be a Triage (through START method) on the side crash, then the rescue and transport of the injured by airport ambulances and bus to the advanced medical station (activated and located inside the airport), where the conditions of the injured are stabilized before they are evacuated to the hospitals concerned.

The authors will relate about their experience and how they faced the critical states of the rescue operation in the air crash at Fiumicino airport on the 2 February, 2013.
Ultrasound evaluation for abdominal pain in the emergency setting

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The term acute abdomen is used to refer to severe pain of sudden onset and rapidly worsening clinical manifestations, that has a poor short term prognosis unless urgent specific measures, often of a surgical nature, are taken. Presentations at the Emergency Department for abdominal pain account for 30% of the total patients seen at this Department. The most common causes of acute abdomen are: acute appendicitis (25-30%), acute diverticulitis (10-15%), bowel obstruction (5-10%), acute cholecystitis (5%), acute pancreatitis (3%), kidney stones. In these situations, although they are considered abdominal emergencies, the physician has more time for diagnostic workup and surgical treatment is often unnecessary. True abdominal emergencies are much rarer (prevalence is ≤1%) but in these conditions immediate diagnosis and treatment are mandatory. They include rupture of an aortic aneurysm, traumatic or non traumatic hemoperitoneum (due to rupture of the spleen, extrauterine pregnancy, hemorrhagic corpus luteum), bowel ischemia, visceral perforation, acute peritonitis. In acute abdomen, when the vital functions are often affected (circulation, breathing, consciousness), making it difficult to take the clinical history, US has high sensitivity and specificity: aorta aneurysm (sensitivity 95%, specificity 100%), pneumoperitoneum (sensitivity 85%, specificity 100%), endoperitoneal effusion (sensitivity 95%, specificity 100%). These are “time sensitive” diseases in which only timely recognition and treatment can improve the prognosis, that is otherwise very poor.

The guidelines for correct management of the acute abdomen include a clinical examination, blood tests and instrumental investigations (direct abdominal X-ray, US, CT). A global approach to the acute abdomen may regard US as necessary in all cases, followed by CT in cases with negative or inconclusive results. This approach guarantees maximum sensitivity (about 95%) in emergencies, and limits exposure to ionizing radiation.

Such guidelines are even more important in the pediatric population because still more care needs to be paid to the risks of biological damage induced by ionizing radiation.

US is essential in procedures like paracentesis.

In conclusion, US in the Casualties Department is an essential investigation that allows:
- Appropriate diagnosis
- Appropriate hospital admission
- Appropriate discharge
- Management of the clinical risk
- Prevention of error
- An improved doctor-patient relationship

Enkephalin for diagnosis of AKI

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The incidence of Acute Kidney Injury (AKI) is very high in Emergency Department. Novel biomarkers for the early detection of AKI in critically ill patients have not been established in clinical routine, as they are not sufficiently accurate, influenced by inflammation and/or detectable only in urine. Opioid receptors are highly expressed in the kidney, but it is not known, whether Enkephalin is associated with kidney function. A novel immunoassay has been developed that enables the measurement of Pro-Enkephalin A (pro-ENK) as a stable surrogate marker for the not reliably detectable Enkephalin.

101 consecutive patients admitted to the emergency department with suspected sepsis were enrolled in order to evaluate the association of plasma pro-ENK with sepsis severity and outcome in baseline and serial measurements, and with renal dysfunction.

We explored the clinical utility of plasma pro-ENK assessments using a novel immunoassay in patients with sepsis. AKI was diagnosed according to the RIFLE criteria. Plasma samples for pro-ENK measurement were obtained on admission and for the next four days. The 7-day mortality rate was recorded.

Admission pro-ENK was associated with the diagnosis of AKI, (pro-ENK median [IQR]: AKI: 238.3 [103.9-662.8] pmol/L; no AKI: 70.90 [42.90-105.2] pmol/L; p<0.001) and with severity of kidney dysfunction (negative correlation with creatinine clearance: r=-0.74; (p<0.0001); significant association with RIFLE criteria comparably to NGAL). As opposed to NGAL, in the septic patients with no AKI, pro-ENK levels were essentially in the normal range. Pro-ENK was also associated with 7-day mortality (pro-ENK median [IQR]: survivors: 75 [47-124] pmol/L; non-survivors: 209 [77-499] pmol/L; p<0.001) and had a higher prognostic power compared to creatinine clearance (creatinine clearance median [IQR]: survivors: 56 [29-81] mL/min; non-survivors: 33 [15-69] mL/min; p=0.071). Decline of pro-ENK below 100 pmol/L from admission to day 1 after admission was associated with a change in survival rate from 56% to 100%.

Conclusions: Plasma pro-ENK in sepsis patients is strongly correlated to acute kidney dysfunction, predictive for short-term mortality and not influenced by sepsis/inflammation. pro-ENK as a plasma marker can be measured easier, quicker and more reliable than urine markers in critically ill patients.
Mature Adrenomedullin for the management of patients with sepsis in ED

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The incidence of death among patients admitted for severe sepsis or septic shock is high. Adrenomedullin (ADM) plays a central role in initiating the hyperdynamic response during the early stage of sepsis. Pilot studies indicate an association of plasma ADM with severity of the disease.

101 consecutive patients admitted to the emergency department with suspected sepsis were enrolled in order to evaluate the association of serial measurements of Adrenomedullin with sepsis severity and outcome (28 day mortality).

We explored the clinical utility of plasma ADM assessments using a novel sandwich immunoassay in patients with sepsis. Sepsis was defined by fulfillment of at least two systemic inflammatory response syndrome (SIRS) criteria plus clinical suspicion of infection. Plasma samples for ADM measurement were obtained on admission and for the next four days. The 28 day mortality rate was recorded.

Admission ADM (aADM) was associated with severity of disease (correlation with APACHE II: r = 0.46; p = 0.0001). aADM was also associated with 28 day mortality (aADM median [IQR]: survivors: 50 [31-77] pg/ml; non-survivors: 84 [48-232] pg/ml; p < 0.001) and was independent from and additive to APACHE II (p = 0.02). Cox regression analysis revealed an additive value of serial measurement of ADM over baseline assessment for prediction of 28 day mortality (p < 0.01). aADM was negatively correlated with mean arterial pressure (r = -0.39; p = 0.0001), and it strongly discriminated those patients requiring vasopressor therapy from the others (aADM median [IQR]: no vasopressors 48 [32-75] pg/ml; with vasopressors 129 [83-264] pg/ml; p = 0.0001).

Conclusions: In patients admitted with sepsis, severe sepsis or septic shock plasma ADM is strongly associated with severity of disease, vasopressor requirement and 28 day mortality.

Update on the SIRS/SEPSIS GREAT trial

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Early diagnosis of sepsis still plays a key role in improving prognosis for a disorder with a case mortality of more than 20%. In this context, biomarkers are the most promising tools to achieve such goal. On the other hand unnecessarily administration of antimicrobial treatment in non-infective SIRS can lead to drug induced side effects as Clostridium difficile colitis, allergic reactions as red man syndrome, life threatening risk of infections caused by multiresistant bacteria increasing global costs.

Multicenter prospective observational study to determine the accuracy of a multimarker-panel of biomarkers in early ruling in/out of sepsis among SIRS patients.

All adult patients with at least two SIRS criteria (according to 1991’s criteria) newly hospitalized were considered. In all patients, blood samples for biomarkers determinations, and at least two sets of blood cultures, were obtained within 4 hour from admission. Correspondingly, and where indicated any other suspect biological fluid was analysed according to current guidelines. Exclusion criteria were pregnancy, blood drawn for biomarkers after 4 hour from MW admission, refusal to provide written informed consent. Beyond biomarkers, variables considered in the study were all SIRS criteria, routine laboratory test and all indicators concurring to the Charlson, SOFA and APACHE II scores.

Clinical work-up aimed at discriminating sepsis among SIRS patients based on clinical and/or radiological signs of infection, blood cultures, and cultures of the suspected site of infection. At the end of follow-up nSiSIRS patients were those with no reasons to continue to suspect an infection and an established alternative diagnosis, while sepsis patients were either those in which pathogens were identified in biological fluids (microbiological sepsis patients), patients, or those just with clinical and/or radiological signs of infection, without pathogens identification (clinical sepsis patients). Such endpoint was issued by the physician in charge of the patient and subsequently validated by a Data Review Committee (composed by two other internal medicine/ED specialists not involved in the clinical work-up of the patient), which posed the final diagnosis. Both diagnosis were carried out blinded to biomarkers results and any disagreement were resolved by discussion. All-cause mortality was recorded at 7 and 30 days.

Receiver Operator Characteristic (ROC) curves were used to identify the relationship between biomarkers and the final diagnosis (nSiSIRS or sepsis). Youden index was used to identify the best cut-off values for each variable. Binary logistic regression analysis (forward conditional method) was developed first assuming as independent variables the biomarkers alone and then, the biomarkers together with SIRS criteria and laboratory routine test (namely complete cell blood count, glycaemia, kidney, liver function test, and lactate).

Results: Ongoing.

Need/Speed Trial: a new panel of biomarkers in the early rule in/rule out of sepsis in patients with systemic inflammatory response syndrome

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The incidence of death among patients admitted for severe sepsis or septic shock is high. Adrenomedullin (ADM) plays a central role in initiating the hyperdynamic response during the early stage of sepsis. Pilot studies indicate an association of plasma ADM with severity of the disease.

101 consecutive patients admitted to the emergency department with suspected sepsis were enrolled in order to evaluate the association of serial measurements of Adrenomedullin with sepsis severity and outcome (28 day mortality).

We explored the clinical utility of plasma ADM assessments using a novel sandwich immunoassay in patients with sepsis. Sepsis was defined by fulfillment of at least two systemic inflammatory response syndrome (SIRS) criteria plus clinical suspicion of infection. Plasma samples for ADM measurement were obtained on admission and for the next four days. The 28 day mortality rate was recorded.

Admission ADM (aADM) was associated with severity of disease (correlation with APACHE II: r = 0.46; p = 0.0001), aADM was also associated with 28 day mortality (aADM median [IQR]: survivors: 50 [31-77] pg/ml; non-survivors: 84 [48-232] pg/ml; p < 0.001) and was independent from and additive to APACHE II (p = 0.02). Cox regression analysis revealed an additive value of serial measurement of ADM over baseline assessment for prediction of 28 day mortality (p < 0.01). aADM was negatively correlated with mean arterial pressure (r = -0.39; p = 0.0001), and it strongly discriminated those patients requiring vasopressor therapy from the others (aADM median [IQR]: no vasopressors 48 [32-75] pg/ml; with vasopressors 129 [83-264] pg/ml; p < 0.0001).

Conclusions: In patients admitted with sepsis, severe sepsis or septic shock plasma ADM is strongly associated with severity of disease, vasopressor requirement and 28 day mortality.
Given the complexities of the sepsis response, the different times at which individual biomarkers are elevated, and the fact that most, if not all, markers currently available or under research are also raised in other inflammatory conditions, it is unlikely that any single marker will ever be of use to diagnose sepsis.

We reviewed the literature for prospective observational trials to detect the most useful biomarkers or combination of biomarkers for an early diagnosis of sepsis in patients suffering from systemic inflammatory response syndrome. The most useful panel will be implemented in a large multicenter trial (Need/Speed Trial).

We searched PubMed, MEDLINE, and Google Scholar for all adult trials published in the past 2 years.

Surprisingly most of the homogenous biomarkers panels used in clinical trials have not suggested any predictive benefit over single biomarker alone.

Conclusions: The future direction of research is most likely a greater focus on combinations of markers with clinical signs in heterogeneous models.

Why IV vasodilators in early phase of AHF: Europe experience

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The number of admissions for AHF has the same frequency as those for Acute Coronary syndromes. Although the acute phase mortality is quite low and similar with ACS, medium and long term mortality are almost five fold. Mortality rates are higher in forms associated with severe congestion and/or low output. Beyond the immediate goals the AHF therapy should fulfill as many of the following criteria: prompt improvement or cessation of dyspnoea, improvement of short and long term mortality, decrease of in-hospital stay, improve the neurohumoral profile, decrease the end organ damage as measured by different biomarkers, decreases the need for diuretic and inotropic support, has an accessible price.

Unfortunately in the last years several AHF trials were negative. Novel agents are emerging with promising results. The experience gained from the development of the current therapies in ACS showed us that appropriate timing of intervention is a prerequisite for success. To support this opinion there is data showing lower mortality rate with earlier administration of a vasoactive agent in AHF patients. The novel emerging agents are serelaxin, cinaciguat, CD-NP, adenosine regulating agents, stresscopin, istaroxime, cardiac myosin activators.

Relaxin-2 is a naturally occurring peptide with systemic hemodynamic, and renal adaptive changes during pregnancy. In the pre-Relax and Relax development program, the most outstanding results were a sustained and significant dyspnea relief, reduction of cardiovascular and total death at 180 days. It reduced the iv diuretics use, signs and symptoms of congestion, and worsening of heart failure. Serelaxin decreased the length of hospitalization. The magnitude of changes was proven in both preserved and reduced EF patients. In those receiving serelaxin the value of BNP and troponin was lower than in the placebo group. An early change in biomarkers of cardiac injury and organs dysfunction was associated with a better survival, as a proof of benefit from immediate vasodilator therapy. The subgroup analysis showed a more consistent benefit in older patients, no previous HF hospitalizations, no beta blocker therapy, signs of inflammation, more severe renal impairment. The phase two trial SIRIUS II showed promising results in both clinical and hemodynamic parameters. Also is seems there can be a short term mortality benefit. This immediate positive effects are expected to result in a long term benefit in both survival and rehospitalisations Early and effective therapy is needed in AHF to avoid myocardial function loss and end organ damage. This approach is expected to improve short and long term adverse outcomes.

From Italian guidelines: managing sickle cell anaemia

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Sickle cell disease (SCD) is a world-wide distributed hereditary anaemia, due to a point mutation, i.e. insertion of valine in place of glutamic acid on the β-globin chain, resulting in the generation of pathological Hb S.

In Europe immigration from developing countries has increased the prevalence of SCD through the second half of the 20th century, so that thousands of subjects (often young or very young) are requiring care by National Heath Systems; as a related consequence, referral of affected patients to the Emergency Depts is progressively growing.

In light of the upcoming Italian guidelines, management of acute events of SCD, in particular vaso-occlusive crises (VOC), acute chest syndrome (ACS) and acute anaemia will be discussed.

In principle, all patients who come to the Emergency Dept with suspected or definite diagnosis of SCD should be considered as yellow codes triage and immediately treated with major analgesic drugs since pain is one of the main symptoms. In SCD patients, the pain is the result of different components and its management requires a combination of NSAID and opioids.

Transfusion strategy is also important in management of acute sickle cell related events not only to restore sufficient haemoglobin levels in patients with acute exacerbation of the anaemia, but also to rapidly reduce the Hb S concentration in order to prevent further sickling and decrease VOC complications such as ACS or stroke.
ACS is the second most frequent complication of SCD in young adults, and may be underdiagnosed despite being associated with a relatively high mortality. The treatment of ACS must include effective pain control, oxygenation, hydration, antibiotic therapy and early transfusion or transfusional exchange.

**Conclusions:** Acute complications of SCD, such as vaso-occlusive crises and ACS, need prevention, rapid identification and adequate treatment in order to avoid chronic invalidating complications. Specific skill, experience and awareness of the problem are important factors in determining the prognosis of these patients. In the next years, a National network and specialized centers will probably be needed to achieve better management of these patients.

**Galectin-3 in Metabolic Syndrome Patients: The MeGa 3 Study**

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Galectin-3 (Gal-3) seems to play a significant role in the pathophysiology of heart dysfunction. Actually, Gal-3 is supposed to be associated with activation of fibroblasts and macrophages, leading to cardiac remodeling. Gal-3, being expressed in adipocytes, is also involved in abdominal obesity and/or insulin resistance. The aim of our study was to evaluate the association between circulating Galectin-3 levels and heart remodeling; also, to verify the influence of sleep related breathing disorders on the circulating Galectin-3 levels.

MeGa 3 Study is designed as an observational, prospective, multicentric, international study. Over 700 patients (pts) with metabolic syndrome (criteria for metabolic syndrome (MetS) were defined according to the International Diabetes Federation definition), are supposed to be included in the study.

Standard clinical examination/assessment; transthoracic echocardiography and polysomnography were performed to all our patients. Assessment of left and right-heart function was done according to standard 2-dimensional (2D), Doppler and Tissue Doppler echocardiographic methods. Circulating Gal-3 was analyzed using chemiluminescence method by Triage Point of Care Meter in Central lab in Rome, Italy. According to the Gal-3 concentration, our pts were divided into 2 groups (Gal-3≥25 ng/mL and Gal-3<25 ng/mL).

We are presenting preliminary data derived from our current sample of 53 pts (mean age 54.4 ±9.9 years; male 32, female 20) with MetS. All pts had abdominal obesity, arterial hypertension and at least one more criteria for MetS. All of them had preserved left ventricular systolic function, measured by ejection fraction (EF). We found diastolic dysfunction (I and II grade) in 39 pts. Mean level of Gal-3 was 20.7±18.6 ng/mL. Our groups were similar in demographic and clinical characteristics, except in BSA (p= 0.039) and NGAL (p=0.000). There was significant negative linear correlation between Gal-3 concentration and left ventricular ejection fraction (r= -0.300, p=0.030). Pts with Gal≥25 ng/mL had significantly lower EF compared to those with Gal<25 ng/mL (57.1±10.4 vs. 63.8±5.3, p=0.008). Gal-3 significantly correlated neither with other echocardiographic parameters of left ventricular function, including diastolic dysfunction nor with other metabolic characteristics (glucose level, glucose HbA1c, body mass index, waist and chest circumference, total cholesterol, LDL and HDL cholesterol, triglycerides) of our pts. According to regression model, NGAL was found to be the strongest independent predictor of left ventricular EF (β=-0.402). We also established significant negative correlation between Gal-3 and oxyhemoglobin saturation (p=0.010, r=−0.515).

**Conclusions:** Our results reveal that circulating Gal-3 as a biomarker of cardiac fibrosis might indicate the impairment of left ventricular systolic function in pts with MetS. We also found that higher Gal-3 is associated with lower oxyhemoglobin saturation suggesting the relationship between Gal-3 and sleep related breathing disorders.

**Procalcitonin in Sepsis**

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Globally sepsis and its complications are a major cause of acute illness and death in patients with community-acquired and nosocomial infections. The ACCP and SCCM defined sepsis as systemic inflammatory response caused by infection. However, the major challenge remains as how to prove that there is infection? Culture best identifies it but in only about 30% of patients with sepsis. Moreover false positivity of cultures further complicates the situation. Clinical signs of sepsis, such as fever, tachycardia, and leucocytosis, are non-specific and overlap with signs of systemic inflammatory response syndromes of non-infectious origin making detection of sepsis a clinical challenge. Thus, delay in diagnosis and treatment of sepsis is responsible for increased mortality.

Thus to prove the presence of infection, biomarkers like Procalcitonin (PCT) are useful. It is a protein with sequence identical to that of the prohormone of calcitonin. Under normal metabolic conditions, hormonally active calcitonin is produced and secreted in the C-cells of the thyroid gland after specific intracellular proteolytic process of the prohormone PCT. Thus, under normal conditions the PCT levels in the circulation are very low (< 0.05 ng/mL). Bacterial infections induce an ubiquitous increase of CALC-1 gene expression and a constitutive release of PCT from all parenchymal tissues and differentiated cell types throughout the body. So significant concentrations of PCT can be detected in the blood of patients with severe bacterial infection/sepsis. One major advantage of PCT compared to other parameters is its early
Gastric asthma presentation in ED

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Bronchial asthma is an ancient and multifactorial disease that has been recognized for centuries. But it is not full defined. The classic phenotype of asthma is an atopic subject with typical symptoms, with typical pathophysiological hallmarks, and with bronchial hyperreactivity. Genetic and environmental factors characterize the clinical pictures, determining several asthma phenotypes. Among these, “gastric” asthma is an unrecognized disease with an unsuspected frequency.2

Estimates of the incidence of gastroesophageal reflux (GER) in asthmatic patients vary between 30% and 89%; the consensus is that 50-60% of asthmatic patients are suffering from GER.3 This data is of particular importance considering the frequency of bronchial hyperreactivity about 10-15% and that of GER variable from 11 to 36%.4

Evidence emphasizes the role of GER as enhancing or triggering factor of “gastric” asthma, so defined by Mays.5 Gastroesophageal disorders and mainly GER with or without esophagitis are known to produce in predisposed individuals a spectrum of clinical symptoms, similar to allergic reactions to foreign substances. These manifestations are clinically indistinguishable from anaphylactic reactions consequent to the activation of IgE-sensitized mast cells by specific substances.6,7 In subjects with hyperreactivity, the studies demonstrated that GER is to be considered an effective trigger not only of bronchial asthma,8 but also of other diseases, such as rhinitis, pruritus, acquired chronic urticaria with or without angioedema.9–10

A neuroimmune mechanism, known as “neurogenic inflammation”, usually operating in asthmatic disease, plays a major role in “gastric” asthma.11

In a modern view, it is assumed that the mediators are released from immune cells and from airways nerves, and are involved in the pathophysiological mechanisms of “gastric” asthma. The sensory nerves (C fibers) play an important role in asthmatic inflammation by amplifying symptoms. Neural reflexes lead to the release of neuropeptides, such as substance P (SP), neurokinin A (NKA) and calcitonin gene-related peptide (CGRP).11–13 These neuropeptides act on target cells in the airways to increase inflammation. Neuropeptides may cause vasodilatation, microvascular leakage, and mucus secretion, as well as smooth muscle contraction.11,12 The neuropeptides released by sensory nerves have potent effect on the network of inflammatory cells.11–13

For instance, mast cells are known to release nerve growth factor (NCF) or brain derived neurotrophic factor (BDNF), which are potent regulators of neuropeptide synthesis.14 In this regard, it should be specified that the pathogenetic mechanism involve also the eosinophils and their cytotoxic mediators. They play a pivotal role in ongoing allergic or allergic-like inflammation by contributing to the late-phase reaction.15–16 The chronic inflammatory process associated with the release of cytokines and growth factors leads to structural changes, such as goblet cell hyperplasia, sub-epithelial fibrosis, and smooth muscle hypertrophy and hyperplasia-processes that are more difficult to reverse than the acute processes.17 Early and effective treatment is therefore essential to prevent long-term damage that could initiate the remodeling stage (which can be irreversible).18

Regarding whether asthma causes GER or GER causes asthma, the question is not relevant. “Gastric” asthma may occur only when there is the coexistence of two essential and inseparable conditions represented by the constitutional airway hyperreactivity and a pathologic GER.19 In the absence of one of these two conditions, gastric asthma is highly improbable.

Obesity and exercise contribute to emphasize the gastroesophageal disorders.20–22

The recognition of gastric abnormalities is very relevant for therapeutic aspects also when they are in a subclinical phase. Once recognized and identified, this singular form of bronchial asthma, also antiasthmatic strategies should be reviewed, also when gastroesophageal disorders are often silent or not adequately considered.23–25 In fact many drugs normally used in the treatment of bronchial asthma can promote or enhance GER, which successively can be a high risk for gastric asthma development.26–27

The GER treatment and long-term follow-up can induce the disappearance of clinical symptoms related to esophagitis and decrease or eliminate bronchoconstriction caused by GER.28–29 This and the other facts discussed here should be emphasized and properly considered as an exacerbating trigger in the pathogenesis of bronchial asthma.30 The linkage between bronchial asthma and GER represents a clinical reality, that has gradually established over time. A more complete understanding of the complex pathogenesis of bronchial asthma will improve the prognosis of this disease that may be sometimes a severe life-threatening condition.
References

Why do we need to blockade RAAS in AHF?

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Renin angiotensin aldosteron blockade is an established treatment in patients with chronic heart failure due to both systolic and/or diastolic dysfunction. The first clinical trial CONSENSUS I confirmed, that treatment with enalapril is beneficial. The CONSENSUS trial was the first
study to show prognostic improvement by an ACE inhibitor. Patients in NYHA class IV heart failure were treated with enalapril or placebo. After study completion (average 183 days) all patients were offered open-label enalapril therapy.

The beneficial effect was confirmed by many other heart failure trials and the recommendation for ACE inhibitor is IA in all published guidelines. If the patients have dry cough after ACE-I – angiotensin receptor blockers are recommended. A combination of both is recommended only if the patients do not tolerate aldosterone blockade.

Less information is known about acute heart failure. If the patients are treated with an ACE-I, it is recommended to continue the treatment or if a renal impairment appears to lower the dose of ACE-I.

The largest acute heart failure registry ADHERE included 105,338 patients, 73% had hypertension, 57% coronary artery disease and 44% diabetes mellitus. At admission 41% were receiving ACE inhibitor, at discharge 66%. More than 50% were admitted with systolic blood pressure higher than 160 mmHg and 30% have had renal impairment.

In the AHEAD registry more than 8,600 patients are included, 5,859 are first hospitalizations. Mean age is 69.5 years for men and 75.0 years for women. 75.2% have hypertension, 46.6% diabetes mellitus and 30% renal insufficiency. 950 patients have heart failure, diabetes mellitus and renal insufficiency. 86% are treated with diuretics at discharge, 78% with ACE-I or AR blockers.

Mild to moderate renal insufficiency (creatinine above 180-220 umol/l) was a frequent exclusion criterion in chronic heart failure clinical studies, terminal renal insufficiency in acute heart failure trials. So we are still missing clinical data about renin angiotensin blockade in patients with moderate to severe renal impairment.

**Development of a Framework for Real-time Earthquake Loss Estimation for the city of Messina**

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Earthquake loss estimation can play a fundamental role in the sustainable development of a given region, providing local governments and other decision makers with valuable information fundamental to the creation of risk mitigation actions. These may include the development of post-disaster emergency and recovery plans, structural retrofitting/strengthening campaigns, creation of insurance pools or strategic urban planning. Such measures are especially important in the Mediterranean region, where an aging, mostly gravity-designed building stock is exposed to a high level of seismic hazard. This study is focused on the city of Messina, which has its past marked by devastating earthquakes, such as the magnitude 7.1 (Mw) event that occurred on the 28th of December of 1908, causing around 100,000 casualties. The present work therefore investigates the seismic behavior and geographical distribution of the existing building stock in Messina, and proposes a new vulnerability and exposure model. The latter datasets will be incorporated within a newly developed framework to estimate human and economic losses. This framework will build upon OpenQuake; the open-source software for seismic hazard and risk assessment.

The creation of a loss model for a city requires compiling information regarding the location and value of the exposed building stock, material and geometric characteristics of a set of building typologies and selection of a group of attenuation models. In addition, a module will be developed to process input data regarding the spatial distribution of ground motion in the affected area, which will then be used by OpenQuake to estimate the associated losses and damage.

The development of the exposure model relies on cadastral information from the local government, national Census data and population distribution datasets (GRUMP). For the calculation of the vulnerability functions, non-linear dynamic analysis will be employed to test a number of representative structures against a set of ground motion records, compatible with the local tectonic environment. Finally, a module compatible with OpenQuake will be developed to produce a large number of ground motion fields based on seismic hazard input data, usually released shortly after the occurrence of seismic event by organizations such as the United States Geological Survey (USGS) or the Istituto Nazionale di Geofisica e Vulcanologia (IGNV).

The development of the vulnerability model, exposure model and loss estimation framework will allow not only the rapid assessment of losses due to an eventual earthquake, but also the investigation of possible earthquake scenarios near Messina. The main outputs of this platform will comprise human and economic loss statistics, loss maps, collapse maps, spatial damage distribution and loss disaggregation according to the various building typologies.

**Conclusions:** The development of the earthquake loss assessment platform for the city of Messina will enable the rapid estimation of human losses and distribution of damage within the affected region, which is a critical tool in order to trigger emergency rescue operations and initiate post-disaster recovery plans.

**Adrenomedullin as a novel therapeutic target in sepsis: experimental data**

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Adrenomedullin (ADM), a circulating vasodilatory peptide, plays an important role in the progression of sepsis. Elevated plasma ADM concentrations are associated with bad outcome. Modulating the ADM system could be a new approach to reduce mortality from septic shock.

High-affinity anti-ADM antibodies with different epitope specificities were developed and assessed for their antagonist activity in vitro and their mortality-reducing effect in a CLP mouse model. Additionnally, the effect of one of these antibodies on clinical and laboratory variables was investigated in a resuscitated CLP mouse model.
Monoclonal antibodies were developed against three moieties of ADM. Affinity constants were determined, and their ability to reduce ADM-induced cAMP response in a bioassay was analysed. Antibodies were injected in CLP mice at baseline and the 14-day mortality rate was recorded. In a resuscitated CLP mouse model, an anti-N-terminal ADM antibody was injected at baseline and blood and tissue samples were harvested after 24 h and analysed.

An anti-ADM antibody directed against the N-terminus substantially increased survival of mice in a CLP model, whereas other antibodies with similar affinities but other epitope specificities were much less potent. The efficacious antibody only partially inhibited ADM agonist activity in vitro. In the resuscitated CLP mouse model, the anti-N-terminal ADM antibody reduced the norepinephrine infusion rates required to achieve hemodynamic targets, increased urine flow, improved creatinine clearance, which coincided with reduced expression of the inducible nitric oxide synthase and formation of peroxynitrite (nitrotyrosine immunostaining) in kidney and aorta, ultimately resulting in attenuated systemic inflammation and tissue apoptosis.

**Conclusions:** An anti-N-terminal ADM antibody, as opposed to antibodies with other epitope specificities, strongly reduced mortality in CLP mice. During resuscitated murine septic shock, this antibody improved catecholamine responsiveness, blunted the shock-related impairment of energy metabolism, reduced nitrosative stress and attenuated systemic inflammatory response, which was ultimately associated with reduced kidney dysfunction and organ injury.

**Do we still need echocardiographic assessment in acute heart failure (AHF) in ED?**

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For patients presenting to the emergency department (ED) for breathlessness, the following 4 things need to be done: 1) Identify the cause for the breathlessness, 2) Initiate the appropriate treatment, 3) Decide on need for admission, and 4) Identify any associated significant co-morbidities which may contribute to the symptoms. If the main diagnosis is that of acute heart failure (AHF), underlying pathologies that cause or aggravate heart failure (HF) and assessment of volume status of the patient should also be sought.

**Review of literature**

A thorough history and physical examination should be obtained to ascertain the causes of breathlessness. However, the signs and symptoms gleaned from both are neither sensitive nor specific enough for the diagnosis of heart failure. While findings from traditional investigations, such as cardiomegaly and pulmonary congestion on chest radiography; or myocardial infarction or ischaemia, left ventricular hypertrophy, and atrial fibrillation as seen on electrocardiogram, may be suggestive of HF, they too are not entirely specific for the condition. Clinical uncertainty is significantly associated with increased morbidity and mortality, especially if the diagnosis of AHF is missed.

Two dimensional echocardiography (Echo) can be used for detecting left ventricular systolic and diastolic dysfunction. It can evaluate myocardium, valvular, and pericardial abnormalities as the cause of heart failure. However, Echo may not able to differentiate if the abnormalities present are acute or chronic. Moreover, it is operator dependent and not readily available at the ED.

Brain natriuretic peptide (BNP) < 100 pg/ml and N-terminal (NT) proBNP < 300 pg/ml have been shown to have more than 95% specificity in ruling out AHF in the ED setting. The use of BNP/NT-pro BNP reduces the number of unecessary Echos. A BNP level of > 400 pg/ml “rules in” HF with specificity exceeding 90%. BNP and NT-proBNP are also useful for prognosticating AHF.

**Conclusion:** In the era of BNP, Echo should be performed in the inpatient setting. Echocardiography is needed for assessment in AHF in ED if 1) The patient does not respond to empirical AHF treatment and deteriorates (e.g., becomes hypotensive), 2) Non-cardiac diagnoses like pulmonary embolism or pericardial tamponade are suspected, or 3) Surgically correctable causes (e.g., acute mitral or aortic regurgitation or ventricular septal rupture, as suggested by presence of a new murmur on auscultation) are suspected.

**The role of nursing in clinical trials**

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The International Council of Nurses defines Nursing practice as follows “Nursing encompasses autonomous and collaborative care of individuals of all ages, families, groups and communities, sick or well and in all settings. Nursing includes the promotion of health, prevention of illness, and the care of ill, disabled and dying people”. Nurses should assume their role according to their training and experience. Among the most important functions are caring, communication, collaboration, education, research and management.

Due to several factors like ageing population, limited medical resources, increasing technology and the health care costs, research plays an increasingly important role in clinical practice.
Clinical trials are the mainstay of evidence based medicine. According to Royal Decree 223/2004, February 6, 2004 of The Spanish Agency of Drugs and Health Products, a pharmacological clinical trial is “any research in humans to determine or confirm clinical effects; pharmacological, pharmacodynamic of one or more drugs under study with the purpose of establish safety or efficacy”. To assess its quality, medical research has to follow the ethical principles of the Declaration of Helsinki and the Good Clinical Practice.

Research nurses can assume several responsibilities in clinical trials as management, coordination and patient care. One of the main tasks is the surveillance of the proper compliance of the informed consent. Furthermore, other important tasks are the maintenance of the integrity of the protocol; assist the investigator in the study visits; performance of the protocol procedures; work with monitors during monitoring visits, collaborating with other departments, and data management.

Currently, due to the increasing number of clinical trials in Spain, the role of the research nurse is becoming more important. The help of the specialized research coordinator improves quality of data collection and facilitates the logistic of studies, and as a consequence, study efficiency is clearly enhanced. However, there is no such academic speciality in Spain. For all those reasons it would be convenient to support the creation of the speciality in research coordination.

An ER model for optimal approach to women victims of violence

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Receiving domestic violence victims in ER is a relatively common occurrence for the medical staff, who is however rarely willing to intervene effectively.

This leads to an underestimation of the cases of violence and actual errors in the care of the victims, resulting in secondary damage to health. Important issues are often not tackled, sequelae are not considered and the experience of the victims themselves is minimised with a serious impact on their mental health, including removal from further health proceedings.

The underestimation encumbers a full understanding of the phenomenon and contributes to reduced communication with judicial authorities, which damages the court case of the victims.

Our experience in handling cases of domestic violence has developed over several years: in 2012 we visited 356 patients (344 females and 12 males) and devised a model approach to patients in the Emergency Room that is not limited to health service but rather accompanies the victims step by step, through the intra-hospital care up to their discharge, with the constant presence of a contact person supporting their needs.

In joining the triage patients are given an access code: a VIP code aimed at protecting their anonymity and privacy (similar to the access Pink Code adopted in Tuscany Region).

After that, an individual path of tutoring is started by experienced health staff, specialised in Counselling or trained in specific courses, who immediately activate all the health and psychosocial resources available.

Actions under the VIP code include:
1. Specific Triage and Screening protocol of un-declared violence.
2. Intervention of specialised staff (staff on the payroll of the Centre, volunteer staff that is detached from the workplace, hospital volunteers), who will follow the patient throughout the diagnostic or therapeutic process, even in case of prolonged hospitalization.
3. Acquisition of consent to data processing.
4. Accurate anamnesis and medical record of the aggression.
5. Complete and topical physical examination.
6. Acquisition of forensic evidence.
7. Biological investigations.
8. Photographs or anatomical drawings.
11. Request of expert advice.
12. Activation of network and relationships with other services and local structures of social health.
13. Assessment of a dangerous situation with SARA method.
15. Discharge of the victim, admission to care-centre or hospital.
16. Check of the procedure.

In case of doubt, the anti-violence centre booklet is provided.

Results are definitely positive. If we compare the present situation to that before the adoption of this care model, the percentage of properly treated cases has increased from 6% to 36 %, the staff has improved its handling of complex situations and the satisfaction of patients, institutions and services has considerably increased.
How to properly manage acute atrial fibrillation in the ER

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The European Society of Cardiology (ESC) has issued its Atrial Fibrillation guideline in 2010, covering all major aspects in diagnosis and therapy of this prevalent arrhythmia [1]. However, already in 2012, there was a necessity to publish an “Atrial Fibrillation update” document [2], due to the fastly emerging evidence in this field. The new particular aspects that required revision were:

- Anticoagulation risk stratification (CHADS-VASc score)
- Use of novel oral anticoagulants (NOACs)
- Pharmacological cardioversion (Vernakalant)
- Oral long-term antiarrhythmic therapy (Dronedarone), and
- Left atrial catheter ablation

The topic on pharmacological cardioversion was in the focus since – for the first time in many years – a new antiarrhythmic drug (Vernakalant) was introduced, being an addition to the previously existing 4 “old” cardioverting drugs (Flecainide, Propafenone, Ibutilide, and Amiodarone).

In the setting of the Emergency Department / Emergency Room (ER), time to cardioversion is an important issue. This is especially relevant when the ER is crowded, requiring a waiting period of 12-24 hours for amiodarone to convert. In this context, the mean time-to-conversion of 11 minutes for Vernakalant is noteworthy.

Another important aspect for the ER is the question regarding presence or absence of structural heart disease in any given patient. This can be difficult to evaluate in many ER’s due to, e.g., lack of time or expertise. Amiodarone is known to be safest even in structural heart disease, which may explain its extensive use, however having Vernakalant in the therapeutic armamentarium offers the ER physician a safe option in the ER setting even in patients where the doctor is in doubt.

References
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Approach and management of spider bites in an Italian Emergency Department: a clinical case

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Background: Patients’ presentation with signs and symptoms due to spider bite are not uncommon in the Emergency Department (ED). The management of definite spider bite requires good information on effects of spiders in the region where the subject lives. Currently, expertise on spider bite recognition and treatment are still lacking.

Clinical case: ST (woman, 22 years old) presented to the ED of the Melegnano Hospital (Milan), referring a spider bite in the lateral neck. At the visit she was showing an itchy rash with a diameter of about 1 cm. The patient denied systemic symptoms. She was employed in sorting Ecuador fruit. The woman brought the spider with her. Immediately, given the possible geographic origin of the spider, the inability to recognize it between common spiders of our areas and the minimal symptoms reported by the patient, the poison control Centre of reference was contacted. It was suggested to monitor the patient, to deal local symptoms with cortisone and antihistamine and to send the spider to the nearest natural sciences Centre for identification. The patient hasn’t developed systemic symptom or worsening of the local lesion. After 3 hours, the expert identified the spider as *Nuctenaea umbratica* (spider native, non-hazardous, Image 1) and the woman was discharged with an indication to take antibiotics and antihistamine therapy. A new visit was advised if major symptoms were occurring (weakness, muscle cramps, difficulty breathing, nausea, vomiting, headache, anxiety, high blood pressure, tachycardia, diaphoresis, increased salivation, abdominal rigidity and over the next two to three days pulmonary oedema, bronchitis, hardening of ‘grip area’).

Conclusions: The class *Arachnida* of the phylum *Arthropoda* comprises an estimated 100,000 species worldwide. However, only a handful of these species can cause clinical effects in humans because many are unable to penetrate the skin, whereas others only inject prey-specific venom. In Italy there are only a few poisonous spiders (*Latrodectus tredecimguttatus* and *Loxosceles rufescens*).

The most important problem is the identification of possible adverse effects of bites of imported spiders that reach the Peninsula by air travel or transport of vegetables. Otherwise, attribution of clinical effects to different spiders is problematic because of poor case definition and paucity of clinical evidence. The effects of medically important spiders are sometimes underestimated and simultaneously there is misattribution of effects to harmless spider groups. The use of anti-venom is based on clinical experience, which has led to discrepancies in the proportion of patients treated (Table 1).

### Table 1 Hypothesis of a algorithm of management for patient reporting spider bite in the emergency room.

**RICE:** rest, ice, compression, and elevation.
Figure 1 The walnut orb-weaver spider (*Nuctenaea umbratica*) is very wide and flattened, with a leathery skin. Its color ranges from red brown and grey brown to black with a dark, yellowish to yellow-greenish leaf-like fleckled marking on its opisthosoma, where small dents are visible. These are the onsets of muscles that flatten the abdomen. The spider hides during the day outside of buildings in wall crevices, or under loose bark. They are very common in Central Europe. This spider has a flattened body, helping it to secrete itself in cracks and crevices. Walnut orb-weaving spiders are capable of concealing themselves in very confined spaces. This tends to act as a defensive advantage and increases the amount of locations an orb-web can be effectively constructed. This spider is capable of biting humans, causing itchiness and a burning sensation followed by a red patch with white lumps.

Antioxidant Protection After Myocardial Infarction is Related to Ventricle Remodeling and Oxygen Uptake

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Background: Oxidative stress is common among the patients with heart failure. Objective was to examine relationship between oxidative stress and severity of left ventricle dysfunction after myocardial infarction, by setting antioxidant protection. Then correlating those results with echocardiographic and cardiopulmonary capacity parameters.

Methods: Study consisted of 65 post myocardial infarction patients (minimum 6 months after MI), 34 with diastolic and 31 patient with systolic dysfunction of left ventricle. During hospitalization all patient went through echocardiographic examination and regular checkups 6-18 months later. Checkups included measuring concentration of erythrocyte superoxide dismutase (SOD) and glutathioneperoxidase (GPX) prior and after cardiopulmonary exercise test. The control group consisted of 20 healthy individuals.

Results: Significant decrease of SOD was detected among the control group compared to healthy individuals ($t$=-11, df=64, $p<0.01$), while base GPX level remained unchanged. However, exercise test caused major GPX level increase ($z$=-2.614, $p<0.01$) while SOD didn't vary. There was no correlation between basic level of antioxidant enzymes and most echocardiographic indicators of left ventricle function. Base GPX value difference is significant among group of patients with and without remodeling of left ventricle ($t$=-2.404, $p<0.05$). Base GPX value is significant predictive indicator of ventricle remodeling (OR =0.98) and has significant influence on maximal oxygen uptake during the test ($p=-0.32$, $p<0.05$).

Conclusion: Antioxidant protection varied in post myocardial infarction dysfunction of the left ventricle, possibly favoring its remodeling and affecting the cardiopulmonary capacity of the patients.

Utility of pyrogenic interleukins (IL-6, IL-2, IL-1β, TNF-α) and APACHE II score in risk stratification of critically ill febrile patients in Emergency Department

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Background: Fever is a common symptom in the Emergency Department (ED) and it is highly suggestive of microbial infection. Fever is an adaptive defense that is necessary for the protection and survival of the host in the presence of pathogenic agents. The signaling pathways regulating fever are complex and still remain unclear. TNF-α, IL-1β, IL-2 and IL-6 are considered critical proinflammatory cytokines for the febrile response and they are important mediators of the systemic host response to infection. These cytokines are produced mainly by activated monocytes and macrophages and their elevated serum levels have been found in septic patients, but the precise physiologic and pathophysiologic role of systematically present cytokines is still unclear. MR-proADM and PCT may be helpful to the febrile patient’s care in the ED: data from literature support the prognostic role of MR-proADM and PCT in that setting and their correlation with the APACHE II score. The combined use of the two biomarkers can predict a subsequent hospitalization of febrile patients. The aim of our study was to evaluate the prognostic value of pyrogenic interleukins in febrile patients in the ED in association with MR-proADM, PCT and the APACHE II score.
Study Design: This was an observational, multicentric study. We enrolled 128 patients referred to the ED with high fever and a suspicion of severe infection such as sepsis, lower respiratory tract infections, urinary tract infections, gastrointestinal infections, soft tissue infections, central nervous system infections, or osteomyelitis.

Materials and Methods: After ED admission, each patient was clinically examined by the emergency physician, a blood sample for biomarkers and interleukins was collected, the APACHE II score was calculated and a case report form completed.

Results: Preliminary results shows that in all patients there was a significant stepwise increase in median values of interleukins in accordance with PCT values and MR-proADM values; we found a correlation between the Apache II score and some interleukins. Statistical analysis is in progress and final results will be able soon.

Conclusions: Our preliminary data support the prognostic role of pyrogenic interleukins in febrile patients in ED. The rational use of these molecules in addition to PCT and MR-proADM could lead to more accurate risk stratification, and optimization of the treatment, with consequent benefit to the patient and considerably reduced costs.

Mouth edema A case of ACE inhibitors angioedema

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64 years old man presents to the ED with tongue edema appeared about 2 hours before and treated at home with betamethasone 2 mg x os without benefit.

Remote medical history: essential hypertension; previous visits to the ED with similar episodes, the last of which 6 months before.


Tongue and submandibular region edema with erythematous skin.

Home Therapy: atenolol 100 mg/day, lisinopril 5 mg/day.

Deny drug allergies.

A few months earlier, in the course of investigations aimed at framing the possible cause of the episodes of angioedema, the patient has performed:

- PRICK TEST and PATCH TEST who showed no awareness of the tested substances
- Total IgE dosage 126.23 KIU/l (n.v. <150)
- Specific allergic IgE Dosage: all class 0 (n.v. <0.34)
- C3 96 mg/dl (n.v. 90-180)
- C4 29 mg/dl (n.v. 10-40)
- C1 INH 348 mg/l (n.v. 195-345)

In the ED, it were administered:

- Methylprednisolone 40 mg iv x 2
- Chlorphenamine 10 mg in normal saline 100 cc
- Omeprazole 40 mg in normal saline 100 cc
- Adrenaline 2 mg aerosol
- Betamethasone 8 mg iv
- Acetated Ringer’s solution 500 ml iv

At the end of the therapy it was observed a slight decrease of the tongue edema.

After a further observation period, the patient was discharged to home with the advice to discontinue ACE inhibitor therapy on suspicion that it may be the cause of the angioedema episodes.

The main side effects of ACE inhibitors are cough and angioedema, the latter occurs in 0.1-1% of patients (1). There are also rare reports of intestinal angioedema (2,3). Angioedema from ACE inhibitors is often not recognized by physicians (4), as demonstrated by the fact that administration of ACE inhibitors was continued in more than 50% of patients who experienced these symptoms (5). Patients who have experienced angioedema and continue to receive ACE inhibitors have an increased frequency of recurrent angioedema compared to patients in whom therapy is discontinued (4). The accumulation of bradykinin in the tissues would be responsible for this adverse effect. It’s known that ACE inhibitors may act as antigens that bind IgE or basophils or mast cells. This complex then induces the cell degranulation causing the release of bradykinin and other vaso-active agents (6).

References


Carbon Monoxide Poisoning in Pregnancy

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Case Report: A 31 years old at 35 weeks gestational age came to emergency room for headache and nausea. Her vital signs were normal but in emogas analisy CoHb was 24 mmHg.

The patient was then treated with 12L/O2 and sonography confirm the presence of fetal heart tone. The treatment with hyperbaric oxygen was started after 3 hours of ammission to hospital. She was discharged in good health two days later. She gave birth a healthy baby.

Discussion: Carbon monoxide is still the most common unintentional poisoning in the Western Countries. In emergency medicine it is essential to consider this diagnosis every time a patient in found in state of unconsciousness in an environment with possible exposure to CO, as well as in patient presenting whit non specific syndromes. Poisoning during pregnancy is an uncommon event, but wrong diagnosis can have dramatic effect on the fetus.

Conclusion: Carbon monoxide poisoning is a leading cause of toxicological morbidity and mortality, for the early identification monoxide poisoning, in our hospital has been proposed a protocol for diagnostic, treatment and follow-up of patient with medium or severe intoxication.

We emphasize the importance of early diagnosis and focus not only on the neurological sequelae but also on cardiac sequelae in the medium and long term.

We introduced:
– blood gas analisy in TRIAGE;
– ECG, the echocardiographic monitoring,dosage of cardiac biomarkers (cardiac troponin1 and natriuretic peptide type B) before treatment,

6 hour after treatmente, to 3 mouns and 1 years later

Prognostic value of Pro Adrenomedullin in patients with Community-acquired Pneumonia in Emergency Department

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Background: Community-acquired Pneumonia (CAP) is one of the major reasons for admission to hospital, with a relatively high mortality (5%-15%). CAP presents to physicians as a wide spectrum of illness. The recognition of patient at low risk of complications can reduce inappropriate hospitalization. Otherwise, early identification of patients at high risk of deaths allows initiation of appropriate therapy and admission to an intensive care setting. The severity assessment of CAP is dependent on the clinical judgment, but this can result in under or overestimation of severity. Severity scoring systems have been developed to help the clinician to identify patients with poor prognosis at an early stage (PSI score, CURB-65). A new diagnostic and prognostic approach relies on evaluation of biomarkers as an expression of the host’s inflammatory response against the microorganism. Several new biomarkers have been demonstrated to be independent prognostic factors for mortality. Adrenomedullin is a 52-aminoacid peptide, potent vasodilator, synthesized principally by the endothelium as a part of Pre-Pro-Adrenomedullin, a larger precursor molecule. It plays an important role in the immune response and has bactericidal activity. MR-pro-adrenomedullin (ProADM) is a stable fragment of ADM degradation, used for its better viability. Levels of ProADM are raised in sepsis.

Study design: We realized a monocentric observational study, enrolling 59 patients referred to the “Policlinico Tor Vergata” ED, in Rome, between December 2012-January 2013.

Materials and methods: CAP was defined as presence of recent clinical symptoms or signs (fever, cough, dyspnea, sputum production or abnormal auscultatory findings) associated with radiological chest evidence of infiltrate. We tested ProADM levels, PCR, PCT, routine blood test. PSI and CURB 65 scores were calculated. The patients were evaluated after 2 and 4 weeks. The ethics internal committee approved the study and written informed consent was obtained from all patients.

Results: MR-pro-ADM median values were 1,19 nmol/L. The values were higher in dead patients (2,57 nmol/L) than in survivors (1 nmol/L). ProADM levels increased with severity of CAP, classified according to PSI score (p value 0,001) and according with CURB 65 (p value 0,01). ProADM levels correlated with with length of stay.

Conclusion: Our findings suggest a possible role of MR-pro-ADM in the severity assessment of patients with CAP in ED.
Diagnostic and Prognostic Utilities of B-type Natriuretic Peptide, Neutrophil Gelatinase-associated Lipocalin, and Procalcitonin in Critically Ill Patients With Suspected Sepsis.

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Background: Sepsis is a severe syndrome characterized by an immune response to different types of infections. In Emergency Department (ED) discriminating local infections from sepsis is important to start promptly an adequate treatment. Procalcitonin (PCT), the propeptide of Calcitonin, is secreted in response to inflammatory related cytokines and it is useful to classify infection’s severity. Neutrophil gelatinase-associated lipocalin (NGAL) is an emerging biomarker for early detection of acute kidney injury (AKI). Brain Natriuretic Peptide (BNP) has been recently studied in sepsis as an early biomarker of myocardial dysfunction.

Study Design: We investigated the diagnostic and prognostic utilities of B-type natriuretic peptide (BNP), neutrophil gelatinase-associated lipocalin (NGAL), and procalcitonin (PCT) in critically ill patients with suspected sepsis, for whom sepsis was diagnosed clinically or based on PCT concentrations.

Materials and Methods: BNP, NGAL, and PCT concentrations were measured at admission in 340 patients and were followed up at discharge in 109 patients. They were analyzed according to the sepsis diagnosis, severity, and clinical outcomes.

Results: Clinical sepsis and PCT-based sepsis showed poor agreement (kappa = 0.2475). BNP and NGAL showed significant differences between the two groups of PCT-based sepsis (P = 0.0001 and P < 0.0001), although there was no difference between the two groups of clinical sepsis. BNP and NGAL were significantly different according to the PCT staging and sepsis-related organ failure assessment subscores (P < 0.0001, all). In the receiver-operating characteristic curve analysis, both BNP & PCT showed an equal ability to predict in-hospital mortality (P = 0.0001). BNP and PCT at admission were significantly higher in the non-survivors than in the survivors (P = 0.0002). In the survivors, both NGAL and PCT at discharge were significantly lower than those at admission (148.7 ng/mL vs. 214.5 ng/mL, P < 0.0001; 0.61 ng/mL vs. 5.56 ng/mL, P = 0.0012).

Conclusions: Combined use of BNP, NGAL, and PCT seems to be an objective and reliable approach for the diagnosis, staging, and prognosis prediction of sepsis. Follow-up measurements of these biomarkers would be necessary to predict clinical outcomes in septic patients.

Efficacy of fast Troponin I in prediction of ACS: rule-out and rule-in in Emergency Department

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Background: Chest pain is a major problem in emergency medicine and it represents 5% of all visits to the emergency department (ED). Chest pain can have many causes and the emergency physician (EP) needs quick tools in order to recognize acute coronary syndrome (ACS) and to allow its early diagnosis and risk stratification. In this clinical context biomarkers play a key role. “Joint European Society of Cardiology and American College of Cardiology Task Force for the Universal Definition of Myocardial Infarction (MI)” recommends the use of Troponin T (cTnT) or Troponin I (cTnI) as a specific marker for myocardial injury. The increase in Troponin concentration is a necessary and sufficient criterion for diagnosis of acute myocardial infarction (AMI) in an appropriate clinical picture. New tools, such as Troponin fast in point of care (POC), are emerging to help EP in early diagnosis or in ruling-out.

Study Design: This study evaluated the diagnostic performance of cTnI of POC assay compared to a central laboratory cTnI assay for detecting myocardial injury and diagnosing AMI in order to perform a rapid diagnosis, reduce length of stay (LOS) in ED, and improve the rule-out of patients without ACS.

Materials and Methods: We enrolled 90 patients, from February to April 2013, presenting at the ED with chest pain. We measured cTnI at the central laboratory (Beckman Coulter cTnI Assay System) on admission (T0) and 4-6 hours post-admission. Each patient also underwent evaluation by the electrocardiogram (EGK) and POC Triage® MeterPro (Alere Triage® Cardio3 Panel), a fluorescence immunoassay for quantitative measurements of CK-MB, next generation cTnI, and B-type Natriuretic Peptide (BNP).

Results: In comparison to laboratory cTnI, Cardio3 Panel had a sensitivity of 100% and specificity of 88.7%. Between laboratory and Cardio3 cTnI, at T0 we found an acceptable agreement of k=0.769 (95%CI=0.620 to 0.918) while we found a lower agreement of k=0.619 (95%CI=0.345 to 0.894) with second determination of laboratory cTnI. Moreover, there was a slight agreement with other biomarkers of ischemic heart disease as CK-MB.

Conclusions: cTnI is a sensitive biomarker for detection of myocardial injury. Our study demonstrated that POC Triage point of care is able to detect ACS faster than laboratory cTnI and this allows a rapid rule-out of patients admitted to ED with chest pain without ACS.
Galectin-3 in Metabolic Syndrome Patients: The MeGa Study

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Background: Galectin-3 (Gal-3) has a significant role in the pathophysiology of heart dysfunction. It is associated to activation of fibroblasts and macrophages, leading to cardiac remodeling. Because it is expressed on adipocytes, it is also involved in abdominal obesity and/or insulin resistance.

Study Design: The study evaluates the association between circulating Galectin-3 levels and heart remodeling, and it also verifies the influence of sleep related breathing disorders on the circulating Galectin-3 levels.

Materials and Methods: The MeGa Study is an observational, prospective, and multicentre international study. So far, standard clinical examination/assessment, transthoracic echocardiography and polysomnography were performed to all our 53 patients (mean age 54.4 ±9.9 years; male 32, female 20) with MetS. Assessment of left and right-heart function was done according to standard 2-dimensional (2D), Doppler and Tissue Doppler echocardiographic methods. Circulating Gal-3 was analyzed using bioMerieux VIDAS® Gal-3, an automated quantitative test for use on the VIDAS instruments using the ELFA (Enzyme-Linked Fluorescent Assay) technique. According to the Gal-3 concentration, our pts were divided into 2 groups (Gal-3 ≥ 25 ng/mL and Gal-3 < 25 ng/mL).

Results: All 53 pts had preserved left ventricular systolic function, measured by ejection fraction (EF). In 39 pts we found diastolic dysfunction (I and II grade). There was a strong negative linear correlation between Gal-3 concentration and left ventricular ejection fraction (r = -0.300). The Gal-3 mean level was 20.7±18.6 ng/mL. Pts with Gal-3 ≥ 25 ng/mL had significantly lower EF compared to those with Gal-3 < 25 ng/mL (57.1±10.4 vs. 63.8±5.3, p = 0.008). Gal-3 was not significantly correlated neither with other echocardiographic parameters of left ventricular function, including diastolic dysfunction, nor with other metabolic characteristics of our pts. According to regression model, NGAL was found to be the strongest independent predictor of left ventricular EF (r = -0.515). We also established a significant negative correlation between Gal-3 and oxyhemoglobin saturation (r = -0.515).

Conclusions: Our results reveal that circulating Gal-3, used as a cardiac fibrosis biomarker, might indicate the impairment of left ventricular systolic function in pts with MetS and Gal-3. It is also associated with lower oxyhemoglobin saturation suggesting the relationship between Gal-3 and sleep related breathing disorders.

Performances of two different procalcitonin assays for an early rule-in rule-out and prognosis of sepsis in patients suffering from SIRS

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Background: Procalcitonin (PCT) accuracy for sepsis diagnosis has been extensively studied in ED and ICU with conflicting results. Their findings were biased due to selection criteria, methodological quality, patient’s clinical spectrum, admission category, procalcitonin assay and cut-off used. This study aimed at comparing two different PCT methods.

Study Design: Prospective observational study.

Materials and Methods: This study included SIRS patients newly admitted to a medical ward from February till May 2012. Cases were diagnosed as sepsis or non-infective SIRS using clinical examination, cultures of the biological fluid, and imaging during a 7 days follow-up. Survivor at 7 and 30 days were also assessed. Samples for PCT were collected within 4 hour from admission. The first procalcitonin assay (PCT-L) was analyzed by the Liaison™ Brahms PCT™ from Diagnostica, Berlin, Germany and calibrated with Liaison Brahms PCTCal (Low/High). The test is based on immunomagnetic separation and subsequent reading of chemiluminescent isoluminol bound to a second mouse anti catalalcin antibody. The range of measurement is 0.1-500 ng/mL and the analytic sensitivity is < 0.032 pg/mL.

The second procalcitonin assay (PCT-K) is based on the principle of time-resolved amplified cryptate emission (TRACE) technology (Kryptor instrument, Brahms, Henningsdorf Germany). This assay has an analytical sensitivity of 0.019 ng/mL and a function assay sensitivity of 0.06 ng/mL.

Their role in predicting diagnosis and survival have been investigated by receiver operating characteristic (ROC) curve, Youden index, relative risk and binary logistic regression.

Results: Among the 60 sepsis patients (microbiological and clinical sepsis), the most common sites of infection were lung (67%), urinary tract (17%), abdomen (5%), and skin (8%). In one third of septic patients cultures resulted positive. The sepsis group had significantly higher levels of PCT. The area under ROC was 0.72 and 0.78 for PCT-L and PCT-K, respectively. The positive and negative predicting value in early rule in/out of sepsis were 93 and 35% for PCT-L (cut-off 0.5 ng/ml) and (cut-off 0.1 ng/ml) were 90 and 54% for PCT-K. Accuracy was 55 and 78% for the PCT-L and PCTK, respectively. Survival at 730 days were not significantly different according to the PCT method with the specified cut-off values.
Conclusions: In medical ward patients, PCT-K has a higher accuracy in sepsis diagnosis than PCT-L assay. Neither PCT-L nor PCT-K holds prognostic value on survival.

**Metabonomics Analysis of Plasma Reveals the Lactate to Cholesterol Ratio as an Independent Prognostic Factor of Short-Term Mortality in Acute Heart Failure**


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Mortality in acute heart failure (AHF) remains high, especially during the first days of hospitalization. New prognostic biomarkers may help to optimize treatment. The aim of the study was to determine metabolites that have a high prognostic value.

**Study Design:** Prospective metabolomics cohort survival study with classical biochemistry validation.

**Materials and Methods:** We conducted a prospective study on a training cohort of AHF patients (n = 126) admitted in the cardiac intensive care unit and assessed survival at 30 days. Venous plasmas collected at admission were used for 1H NMR–based metabolomics analysis. Differences between plasma metabolite profiles allow determination of discriminating metabolites.

A cohort of AHF patients was subsequently constituted (n = 74) to validate the findings.

**Results:** Lactate and cholesterol were the major discriminating metabolites predicting 30-day mortality. Mortality was increased in patients with high lactate and low total cholesterol concentrations at admission. Accuracies of lactate, cholesterol concentration and lactate to cholesterol (Lact/Chol) ratio to predict 30-day mortality were evaluated using ROC analysis. The Lact/Chol ratio provided the best accuracy with an AUC of 0.82 (P = 0.0001). The acute physiology and chronic health evaluation (APACHE) II scoring system provided an AUC of 0.76 for predicting 30-day mortality. APACHE II score, Cardiogenic shock (CS) state and Lact/Chol ratio ≥ 0.4 (cutoff value with 82% sensitivity and 64% specificity) were significant independent predictors of 30-day mortality with hazard ratios (HR) of 1.11, 4.77 and 3.59, respectively. In CS patients, the HR of 30-day mortality risk for plasma Lact/Chol ratio ≥ 0.4 was 3.26 compared to a Lact/Chol ratio of 0.4 (P = 0.018). The predictive power of the Lact/Chol ratio for 30-day mortality outcome was confirmed with the independent validation cohort.

**Conclusions:** This study identifies the plasma Lact/Chol ratio as a useful objective and simple parameter to evaluate short term prognostic in AHF and could be integrated into quantitative guidance for decision making in heart failure care.

**Intracranial haemorrhages: observational study in an Emergency Room**

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**Background:** Intracranial haemorrhages (ICH) are a group of potentially life-threatening pathologies with a very high morbidity and mortality. Antithrombotic therapy and head trauma are important risk factors for these events.

**Study Design:** We performed an observational study enrolling all consecutive patients with ICH admitted to the Emergency Room (ER) of IRCCS Policlinico Hospital of Milan from January 1st, 2010, to March 31st, 2013.

**Materials and Methods:** 530 patients with ICH were enrolled (52% males, mean age 70.4 yrs).

**Results:** At arrival to the ER, 33% of patients was registered as red codes, 48.8% as yellow codes and 18.1% as green codes. A significant number of patients (202, 38.1%) was on antithrombotic therapy. Of these, 65 (12.2%) were treated with Vitamin K antagonists (VKA), 139 (26.2%) with anti-aggregants (AA), 18 patients (3.3%) with heparin (15 low-weight molecular heparin, 3 unfractioned heparin), while 18 patients had a combined therapy (anticoagulants+antiaggregants or 2 antiaggregants). An elevated number of patients (162, 30.6%) had a history of head trauma in the hours or days before the arrival to the ER. The different types of haemorrhages are reported in table 1 (17 patients had more than one type).

<table>
<thead>
<tr>
<th>Type of ICH</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subdural haemorrhage</td>
<td>136</td>
<td>25.7</td>
</tr>
<tr>
<td>Intraparenchymal haemorrhage</td>
<td>303</td>
<td>57.2</td>
</tr>
<tr>
<td>Subarachnoid haemorrhage</td>
<td>97</td>
<td>18.3</td>
</tr>
<tr>
<td>Extradural haemorrhage</td>
<td>11</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Of the 530 patients, 16 died in the ER (3.0%). Surgical operation or admission to Neurosurgery Unit for observation and eventual surgery was indicated for 198 (37.3%) patients, while 205 (38.7%) were admitted to medical divisions in the absolute absence of surgical indications. 99 (18.7%) were admitted to the Intensive Therapy Unit. Only 11 patients (2.1%) were discharged and sent home directly from the ER and 1
refused the admission to the Hospital. In patients receiving VKA, therapy was performed in 47/65 subjects (72.3%) with vitamin K, factor VII, prothrombin complex concentrate, fresh frozen plasma in various combinations. In total, 43 patients were treated with vitamin K, 21 with prothrombin complex concentrate, 15 with factor VII, 1 with fresh frozen plasma, 3 with the complex including prothrombin, factor VII, and c+s proteins. INR values at arrival to the ER are reported in table 2. 95% of patients had an INR > 1.5.

### Table 2

<table>
<thead>
<tr>
<th>INR value</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR &lt; 2</td>
<td>11</td>
<td>16.9</td>
</tr>
<tr>
<td>INR between 2 and 3</td>
<td>30</td>
<td>46.1</td>
</tr>
<tr>
<td>INR &gt; 3</td>
<td>24</td>
<td>36.9</td>
</tr>
</tbody>
</table>

**Conclusions:** Intracranial haemorrhages are a group of life-threatening pathologies whose clinical presentation and prognosis can be worsened by the assumption of anti-thrombotic therapy. In patients treated with VKA, reversal therapy with prothrombin complex concentrate is necessary but still underused.

## Acute heart failure as first clinical presentation of primary dilated cardiomyopathy

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**Background:** Primary dilated cardiomyopathy (DCM) represents 90% of all primary heart muscle diseases in general cardiology practice with incidence 0.73-6.95 pts/100.000 and prevalence 8.3-36.5 pts/100.000. Dilated left ventricle (LV) and depressed LV ejection fraction in absence of congenital heart disease, coronary artery disease, valvular or pericardial diseases are key diagnostic features. Clinically, DCM presents with symptoms of heart failure (HF) in the majority of patients, less frequently with the symptoms of rhythm and conduction disturbances, thromboembolism, and sudden cardiac death (20-50). Acute HF (AHF) may also be the index event in less than 20% of patients. Furthermore, DCM is associated with the high mortality (15-50% in five years), risk for sudden death, and it is a most common indication for heart transplantation and prolonged hospitalization.

**Study Design:** DCM patients admitted to the Department of Cardiology, University Medical Center, Belgrade, Serbia between January 1997 and august 2003 were analyzed retrospectively.

**Materials and Methods:** The criteria for entering the study included DCM patients with all forms and manifestation of HF, including AHF. Demographic data, risk factors for development of CVD, family history and history of previous viral infection were obtained. Clinical examination parameters included heart rate, systolic and diastolic blood pressure, gallop rhythm, cyanosis, jugular veins congestion, pulmonary congestion, heart sounds and murmurs, hepatomegaly, cardiac edema and ascites. Laboratory and cardiology work-up methods used were: ECG, chest X-Ray, echocardiography and cardiac catheterization with selective coronary angiography. The total of 227 parameters were analyzed with cross-section of survival performed in 2004.

**Results:** A 126 patients with DCM were analyzed, with average age of 54.71 ± 13.23 years, 76.2% men. Average follow up was 91.2 months (4-582 months), average duration of DCM was 63.3 months (4-180 months). AHF as a first clinical manifestation of DCM occurred in 18.4%. Fatal outcome was revealed in 22 patients, 140 patients survived to the end of 2004. The most common cause of death were cardiac arrest (45.5%), followed by progressive HF (27.3%) and respiratory failure (9.2%). Pulmonary embolism, unknown cause of death, lung neoplasm, and diabetes were cause of death in 4.5% of patients. No correlation between AHF and fatal outcome was revealed. Lower systolic and diastolic blood pressure correlated with longer survival in these patients (p < 0.05 and p < 0.05 retrospectively). Patients with DCM who had a higher NYHA functional class had significantly shorter survival (p < 0.05). Atrial fibrillation or flutter statistically significant increased relative risk for fatal outcome (p < 0.05). Myocardial fibrosis (echocardiography), (excluding septum) was associated with shorter survival of patients (p = 0.02). High right atrial pressure correlated with shorter survival (p = 0.01).

**Conclusions:** AHF as a first clinical manifestation of DCM occurred in 18.4%. Cardiac arrest and progressive HF were most common causes of fatal outcome. Lower systolic and diastolic blood pressure correlated significantly with longer survival. Higher NYHA functional class, atrial fibrillation or flutter, myocardial fibrosis (excluding septum) and high pressure in the right atrium correlated with shorter survival. No correlation between AHF and fatal outcome was revealed.

## Small bowel intussusception due to malignant melanoma of unknown primary. Two cases report and literary reviews


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Abstract: Malignant melanoma is characterized by forming metastases in the gastrointestinal tract, especially in the small bowel. The gastrointestinal tract is a frequently site of malignant melanoma metastases (35.6%). The diagnosis is often delayed because of an unspecific clinical presentation (frequently as chronic iron deficiency anemia, rectal bleeding or an intestinal obstruction). We present two case report about a diagnosed melanoma of unknown primary, whose clinical presentation was only an intestinal obstruction.

Case Report A: A 51-years old man patient was admitted to the General Surgery Department with acute abdominal pain since a week. In last two days he had been suffering from fever, persisting vomiting, worsening of abdominal pain and no stool passage. The X-ray confirmed an intestinal obstruction. During the hospital stay the clinical condition got worse, with several vomiting episodes, drop off Hb, acid-base imbalance. Patient underwent laparotomy as surgical emergency. The histopathologic exam diagnosed an intestinal melanoma of unknown primary. A lymph node package in right axilla was palpable as a fixed tumor painful with a wooden texture. The histopathological exam described it as other metastasis. In order to exclude all typical melanoma localization, it was performed ophthalmological, otorhinolaryngological (negative) and oncological videate. This one suggested a diagnostic improve with MRI and PET scan: "many pathological sites: lymph nodes, bladder, liver, vertebral column, medulla". Oncologist diagnosed malignant melanoma IV staging (according to American Joint Committee on Cancer). The patient died 8 weeks later medical treatment beginning, because of cachexia and CNS recurrences.

Case Report B: A 89-years old man patient was admitted to the General Surgery Department with acute abdominal pain and no stool passage since some days. Abdominal X-ray underlined the increase of colic air-fluid level with fecal obstruction. During the hospital stay were performed CT scan: "long tract of intestinal obstruction, with distal fulcrum, and a polyloid neof ormation in the intestinal lumen. The worsening of clinical presentation imposed laparotomy as surgical emergency. It was performed a resection of 20 cm of first ileal tract (under the Triet’s ligament) including the lesion and appropriate margin of healthy intestine and the mesentry with lymph nodes. The histopathological exam confirmed a diagnosis of intestinal melanoma of unknown primary. The Braf gene, in this case was mutated. A week later the dismissing, the patient return to the Hospital because of a intestinal obstruction, resolved with a stomach probe.

Conclusions: Tumour was evidenced as surgical emergency due to extended ileal intussusceptions on 22%. Melanoma of unknown primary could result after a differential diagnosis and a complete physical exam of the patient. The clinical features lay on an emergency surgical treatment. As first step of diagnostic item, abdomen cavity ultrasounds are useful to diagnose intussusceptions, but it is necessary complete with CT and PET imaging. When clinical presentation is intestinal obstruction, surgery is the only treatment opportunity, the only possibility to achieve a certain diagnosis.

80-Lead EKG and New Biomarkers for Physiopathological Myocardial Cells Process

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Background: Chest pain caused by Acute coronary syndrom (ACS) is one of the most common reasons of patients admission to the emergency department (ED). ACS, divided in ST-Elevation (STEMI) and Non ST-Elevation (NSTEMI/UA), needs to be distinguished from other cardiac and non cardiac diseases causing chest pain.

Study Design: The aim of this study was to evaluate the diagnostic and prognostic role of new biomarkers such as Troponin I (TnI) and High Sensitivity Troponin T (hsTnT). We also analyzed the diagnostic and prognostic validity of the (80 lead) HeartScape 3D EKG System compared to the 12 lead EKG. Final diagnosis was adjudicated using all diagnostic data.

Materials and Methods: Patients presenting with chest pain at the ED were divided into four groups: STEMI, NSTEMI, Low Risk and High Risk. This differentiation was done by using the two biomarkers (TnI, hsTnT), 12 and 80-lead EKGs, and clinical judgment. We also performed a follow up phone call 30 days after hospital discharge to study the prognostic role of this method.

Results: In the whole population studied 31 patients received the final diagnosis of STEMI, 15 of STEMI, 2 of instable angina and 72 was discharged or hospitalized with a different diagnosis.

In the STEMI group we found positive TnI at first relevation in 54.8% of patients while the HS-TnT was positive at the same time in the 81.4% of the subject examined.

In the NSTEMI group at time zero the 80-leads-EKG provide significant additive information for the MI diagnosis in 26.4% of patients with a normal 12-lead EKG. In this group the HS-TnT was positive in 83.3% of patients while the TnI results diagnostic only in 80% at first measurement.

In the group of patient without diagnosis of cardiac MI 80-leads-EKG was normal in 90.9% of the case. HS-TnT results falsely positive at first measurement in 18.52% of patients while TnI results altered only in 2.8%.

Conclusions: The use of HS-TnT allows a quicker diagnosis of Acute Coronary Syndrome (ACS) in the ED. This can be also especially important in cases of rule out.

The 80-lead EKG coupled with HS-TnT has in this attempt more advantage comparing to 12-lead EKG. This helps in the shortening the time between patient arrive and final disposition.

Technique and outcome about a new laparoscopic treatment: pelvic organ prolapse suspension (P.O.P.S.)

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Conclusions:

Our study is the first to address the prognostic impact of thrombocytopenia in the setting of ED. Our results show that the severity of thrombocytopenia at the time of ED admission represents an independent risk factor for bleeding and in-hospital mortality. Detection of bleeding risk and mortality.

Materials and Methods:

We enrolled 54 women with symptomatic pelvic organ prolapse. The interview and some investigations were part of routine preoperative and postoperative assessments. We used Longo ODS score to assess obstructed defecation syndrome and Wexner score to evaluate impairment of fecal incontinence. We staged uterine prolapse by a speculum, using “Half way system” . All patients underwent preoperative cytology of the cervix and ultrasound examination of the uterus to detect abnormalities. Urodynamic studies, including uroflowmetry, cystometrometry, pressure flow studies and residual urine volume, were reserved patients affected by urinary disorders.

Background:

In critically ill patients, thrombocytopenia represents the most common coagulation abnormality. In the setting of intensive care unit (ICU), thrombocytopenia has been associated with an increased risk of bleeding, blood product transfusion, progression to multi-organ failure, longer length of stay, and mortality. Thrombocytopenia is frequently observed in patients evaluated in the Emergency Department (ED); however, no data regarding its incidence, prevalence, and prognostic impact in this clinical setting are currently available.

Study Design:

We conducted a retrospective observational study on patients admitted to the ED of “Città della Salute e della Scienza” Molinette Hospital, Corso Bramante 88, 10126, Turin, Italy. Our aims were: 1) To describe the epidemiological characteristics of thrombocytopenic patients in the ED; 2) To evaluate the impact of thrombocytopenia on diagnostic and therapeutic management; 3) To evaluate the prognostic role of thrombocytopenia on bleeding risk and mortality.

Materials and Methods:

We enrolled 54 women with a mean age of 55.2 and a BMI of 28.3. Patients underwent stapled trans anal rectal resection (S.T.A.R.R.) too at the same time to correct the residual rectal prolapse. We evaluated these patients after 1 year follow-up and we confirmed the validity of our treatment. We had no relapses, the preliminary results were excellent. We appreciated the simplicity of this technique versus traditional treatments and we observed an important reduction or a completely disappearance about pre-operative signs and symptoms.

Conclusions:

In conclusion we believe that the procedure proposed by us, given the results, was excellent in patients with the vagina walls elongated and that retain a good trophism.

Prognostic impact of thrombocytopenia in the emergency department

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Background:

In critically ill patients, thrombocytopenia represents the most common coagulation abnormality. In the setting of intensive care unit (ICU), thrombocytopenia has been associated with an increased risk of bleeding, blood product transfusion, progression to multi-organ failure, longer length of stay, and mortality. Thrombocytopenia is frequently observed in patients evaluated in the Emergency Department (ED); however, no data regarding its incidence, prevalence, and prognostic impact in this clinical setting are currently available.

Study Design:

We conducted a retrospective observational study on patients admitted to the ED of “Città della Salute e della Scienza” Molinette Hospital (Torino, Italy). Our aims were: 1) To describe the epidemiological characteristics of thrombocytopenic patients in the ED; 2) To evaluate the impact of thrombocytopenia on diagnostic and therapeutic management; 3) To evaluate the prognostic role of thrombocytopenia on bleeding risk and mortality.

Materials and Methods:

We enrolled 1218 patients with a platelet count at admission lower than 150x10^9/L during four non-consecutive months in 2012. There were not exclusion criteria.

Results:

The study population was heterogeneous for demographic data, comorbidity, etiology of thrombocytopenia, and clinical severity at admission. The incidence of bleeding and hypovolemia, as well as the need of transfusional support and mechanical, surgical or endoscopic haemostasis progressively increased with the severity of thrombocytopenia. Moreover, severe thrombocytopenia (<20x10^9/L) was associated with higher ICU admission rate and longer in-hospital length of stay. In-hospital mortality in our population was 10.0%, whereas was as high as 22.9% in patients with severe thrombocytopenia. Multivariable logistic regression showed that thrombocytopenia, after adjustments, remained associated with an increased risk of major and minor bleeding, and of mortality. In particular, mortality risk increased by 12% every 10x10^9/L reduction in platelet count at admission.

Conclusions:

Our study is the first to address the prognostic impact of thrombocytopenia in the setting of ED. Our results show that the severity of thrombocytopenia at the time of ED admission represents an independent risk factor for bleeding and in-hospital mortality. Detection of thrombocytopenia in ED patients may be an useful tool for prognostic stratification of ED patients.
Background: ST2, an interleukin-1 receptor family member up-regulated in the setting of cardiomyocyte strain, in literature has prognostic value in patients with acute myocardial infarction, chronic severe heart failure, in outpatients. The predictive value of ST2 levels in Acute Heart Failure (AHF) patients is unknown. We studied the clinical correlates of ST2 levels and evaluated its prognostic use in patients with Acute Heart Failure at admission in Emergency Room (ER).

Study Design: In a prospective, blinded international study, 171 emergency department (ED) patients with AHF were evaluated with testing for BNP, ST2. The primary endpoint was death at 30 days after rehospitalization. The primary endpoint of the study was 30 days mortality or rehospitalization, the latter obtained by phone call follow up. The study enrolled subjects between April and July 2013 at two tertiary care academic medical center members of the Global Research on Acute Conditions Team: the Massachusetts General Hospital (Boston, MA), and Sant’Andrea Hospital (Rome, Italy). All study procedures were approved by local institutional review boards. Biomarkers of myocardial stretch included BNP (Alere Triage BNP, San Diego, CA), and soluble ST2 (Presage ST2, Critical Diagnostics, San Diego, CA). Biomarkers of renal function included blood urea nitrogen (BUN), serum creatinine, and estimated glomerular filtration rate (eGFR; estimated using the simplified Modification of Diet in Renal Disease equation).

Results: In this cohort with mean age of 76.23 ± 10.84 years and median ST2 level of 106.7 ng/ml (interquartile range 74.49-164.69), 37 deaths occurred and 5 patients rehospitalized. The median value of ST2 in AHF patients with events is 105.75 [82.07,194.92] vs no events 112.14 [67.01 - 167.55] (p<0.002). The ROC Curve for events at 30 days showed an AUC 0.71 (p<0.002) with a cut of value of 84.10 (Sens 75%, Spec 64%). The values of ST2 was not affected by eGFR value and age. The multivariate Cox regression showed that ST2 value in patients with AHF is an independent factor to predict mortality (p<0.003) with a value of 142.71 ng/ml. BNP has no prognostic value in his cohort of patients.

Conclusions: ST2 evaluation at ER admission in patients with AHF is an high independent predictive value for 30 days events (mortality or rehospitalization). The value of ST2 is not affected by eGFR and age, it suggested to be a specific marker of myocyte injury and stretching.

A complex case of Chronic Carbon Monoxide Intoxication. Case Report

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Background: Mild, moderate or severe CO intoxication (COI), damaged tissues and organs. Acute CO intoxication (ACOI) is caused by one single less than 24-h-long exposure; chronic CO intoxication (CCOI) is induced by multiple exposures (more than 24-h-long each), with low CO concentrations and low COHb levels (9.65±2.46% D&L Penney). Therefore CCOI diagnosis is difficult and requires an high suspicion index.

Case Report: SD, male, 30 yo, Senegalese, smoker, non Italian speaker, was brought by ambulance into the AE Dept. complaining of nausea, asthenia and widespread muscular pain. The presence of a brazier at his house was reported. A first neurological and cardiopulmonary examination did not show any abnormalities. Chest Xr were normal, Arterial Blood Gas (ABG) indicated Oxygen Partial Saturation (SO₂) at 99%. Carboxyhemoglobin (COHb) at 9.9%, EKG showed ST elevation in V1-V3. The patient (pt.) referred temporary loss of consciousness, but denied any chest pain. COCOI was suspected in spite of low COHb levels and the pt. was admitted into the ER. The man confirmed prolonged exposition to the brazier’s heat. O₂ therapy was started. Blood tests indicated CK 24.500 U/L (nv < 200), TnI 0.13 ng/dL (nv < 0.006), WBC 12.000. ABG in 2 hours showed COHb at 6%. Cardio ECOX revealed apex hipokinesia. The pt. then referred having experienced chest pain during the previous night. Therapy with high rate fluids, NaHCO₃, ASA, clopidogrel and LMWE was initiated. The pt. was subjected to hyperbaric treatment during which he developed left lower limb plegia and acute urine retention, so a bladder catheter was placed. Neurological symptoms subsided 24 hours after the hyperbaric treatment. Brain CT scan and brain and spine MRI after neuro consult resulted regular. TnI normalized. After 36 h of IC the pt. was sent to a Medical Dept. and discharged in a week without symptoms or consequences.

Discussion: In this case, the clinical findings and the history of exposition were enough to suspect CCOI, but misdiagnoses are common when exposition is unknown or symptoms are the same as other diseases. The most frequent mistakes are: no diagnosis (60%) flu (15%), depression (8%), psychosomatic condition (8%). Particularly, when no loss of consciousness is reported it is harder to make the correct diagnosis, because minor conditions seem to be more likely. Chronic exposure to CO (CECO) commonly causes headache, drowsiness, nausea, dizziness, vomit. When checked, CO levels, even if normal, may be significant in CECO, and CCOI may be confused with other diseases, especially with smokers.

Conclusions: CCOI diagnosis is basically made of two main steps: finding a probable CO source and searching for CECO symptoms. Both must be pursued, especially when chances of CECO are high; for example in winter, with lack of building maintenance or when similar symptoms are registered in many patients living in the same environment. In these cases, CCOI must be considered even if COHb levels seem to be quite normal.
Role of fast-focused sonography assessment of ICV size in septic shock

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Background: An 81-years old woman presented to the Emergency Department for high fever (39°3C) preceded by chills, malaise and acute mental deterioration with onset in the last few hours. Her past medical history was unremarkable except for hypertrophic cardiopathy with paroxysmal atrial fibrillation, treated with amiodarone and warfarin. On physical examination she appeared dyspnoic, with SpO2 86% when breathing O2 at 4 l/min by mask; non pathologic remarks to the respiratory tract; tenderness in the epigastric region of the abdomen; she appeared confused and disoriented about time and space (GCS = 11-12), without neurological focal signs or neck stiffness. Oral mucosa was dry; no jugular turgidity was present. Blood pressure (BP) 100/60 mm Hg; ECG showed sinus rhythm with ventricular rate of 90/min and normal morphology. Chest x-rays gave normal findings. BP quickly fell until became non measurable. Diuresis, monitored by vesical cathether, was absent (anuric). The patient was then referred to the Unit of Medicina d’Urgenza. Laboratory findings at presentation and in the following two days were: leucocytes up to 27.260 with neutrophils 93,5%, hemoglobin 12.2 g/dl, BUN up to 88 mg/dl, creatinine up to 3 mg/dl, AST 762 UI/l, ALT 317 UI/l, LDH 685, GGT 449, C reactive protein (CPR) 29,47 mg/dl, PT/INR 1,8-2,0 after withdrawal of warfarin. Arterial blood gas specimen revealed metabolic acidosis of moderate degree, with lactate 8,46 mmol/l. Blood and urine samples were collected for culture since the first access to the Emergency Ward; both registered the growth of Escherichia Coli with broad antibiotic sensitivity, but resistant to amoxicillin and florochinolones. The patient was started empirically on piperacillin/tazobactam 2,25 g X tid and levocoxacin 250 mg daily, the second stopped after the results of cultures. Ultrasound study of thorax and abdomen, performed in ED, showed no pleu-r/pericardial effusion nor pulmonary consolidation, hyperkinetic ventricular walls with cavities near empty, inferior caval vein (ICV) totally empty (non detectable), normal appearance of liver, kidneys and spleen, biliary tracts not dilated, absence of ascites. A septic shock with multiorgan failure (hepatic, renal, cerebral) was diagnosed and the patient was started, besides antibiotics, on fluid challenge with hourly infusion of 2 → 1 l saline/Ringer lactate and Haemaccel in the proportion of 4:1. After three hours (4 liters of fluids infused) a second bedside US evaluation was able to detect ICV, whose diameter was 1 cm with total inspiratory collapse. Systolic BP raised to 40 mm Hg. The patient, yet anuric, was therefore considered to be still hypovolemic and received further volume replacement with 0,5 liters of Haemaccel and 2 liters of Ringer lactate plus sodium bicarbonate 8 ml/hour. Two hours later BP raised to 85/50, whereas a third US control showed expansion of ICV, whose size reached 2,1 cm with inspiratory collapse of 50%. Here dopamine was added at 4 mcg/Kg/min; after two hours BP was normal (110/70). In the next days general and neurological conditions improved rapidly, sepsis healed (hemo and urine cultures became negative, CPR fell to 0,4 mg/dl) and MOFS resolved (creatinine 1,2 mg/dl, normal value of AST/ALT). The patient was discharged on day 11.

Discussion: During septic shock mechanism of hypotension and peripheral hypoper-fusion are various. Careful clinical evaluation is topic for a correct management. Nevertheless we stress the role of fast-focused sonography assessment of chest and abdomen, mainly of ICV size and inspiratory variation of its diameter, to discern “empty” from “full” patient, choose the correct timing of different therapies (fluids, amines…), avoid adverse effects such tachyarrhythmias induced by amines in hypovolemic, monitor the real efficacy of treatments.

The importance of anaemia in acute heart failure patients

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Background: Anaemia is a common comorbidity in patients (pts) with acute heart failure (AHF), with a prevalence even up to 50%. However, its role is still unclear, as well as its relation to biomarkers.

Study Design: To evaluate the relationship between anaemia, biomarkers and comorbidities in AHF pts.

Materials and Methods: We analyzed 286 pts (mean age 74.91 year; 52.8% men). Anaemic pts (Group I, 46.5%) were significantly elderly (p < 0.001), mostly women (p < 0.001), with significantly worse renal function, according to serum creatinine (p < 0.001) and GFR (p < 0.018) and they had higher prevalence of ischaemic cardiomyopathy (p < 0.047). Otherwise, the prevalence of hypertension, atrial fibrillation, diabetes mellitus, and COPD, did not differ among two groups. Although anemic pts had significantly higher NT-proBNP level on admission (p < 0.019), there was no difference between groups with regard to left ventricle ejection fraction (LVEF, p = 0.774) and length of stay (p = 0.819), but they had lower heart rate on admission (p < 0.016). In the subgroup of pts who had measured BNP level (n = 119), there was no difference between anemic and non anemic pts (p = 0.679). On the other hand, the analysis of the subgroup of pts (n = 167) with measurements of C-reactive protein...
It all started with a toothache – aspecific clinical features in subarachnoid hemorrhage: a case report

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Background: Clinical presentation of subarachnoid hemorrhage (SAH) can be extremely variable ranging from nearly asymptomaticity to sudden death. Secondary headaches include those associated with temporal arteritis, trigeminal neuralgia, sleep apnea, post-herpetic neuralgia, cervical spondylosis, SAH, intracerebral hemorrhage, intracranial neoplasm, and post-concussive syndrome. Here, we present the case of a 53-year-old man with undiagnosed subarachnoid hemorrhage.

Case Presentation: A 53-year-old man from Brescia, Italy, presented to our emergency room with fever, toothache, severe pain on his right cheek and migraine on the right side occurred after a visit to his dentist; indeed, he underwent a tooth-extraction 5 days before. Moreover he complained pain at his right lower limb. The pain was not so responsive to acetaminophen 1g prescribed by his doctor a couple of days before. At his arrival vital signs were normal. No history of disease, no chronic therapies emerged.

Neurological exam resulted negative. The patient appeared worried about the pain and used to answer the questions a little bit hesitantly, but not that much alarming. At the end of clinical examination, he complained loss of memory in the last few days; to deepen this anamnestic feature, the friend who accompanied him was also questioned. She said that the patient had actually had a change in the last days, with loss of memory getting worse. After an analgesic (acetaminophen+codeine), considering the headache and the “change” noticed in the last few days, we decided to request a CT brain, and this was the result: subarachnoid hemorrhage among CSF spaces in right temporoparietal cortex, along the middle cerebral artery and in the right ventricular trigon. The patient was quickly moved to the nearest hospital with a neurosurgery department and treated with chemoembolization; now he’s completing his rehab

Conclusions: Never undervalue an headache! SAH due to associated intracranial aneurysm formation can present subly. Prior knowledge about the possible existence of such life threatening diseases in patients presenting headache and no focal neurological symptoms is mandatory for their survival. Moreover, history taking can be sometimes misleading; in this case the pain the patient kept complaining could be referred to his previous dental disorders? Can loss of memory be considered suggestive of SAH? would you have request a CT brain?

Procalcitonin, presepsin, pro-adrenomedullin, fibrin degradation products, and lactate in early diagnosis and prognosis of septic patient newly admitted to medical ward from ED

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Background: More than 50% of all septic patients admitted to ICU derive from intermediate care units. Biomarkers represent the most promising tool for early diagnosis of sepsis; but their accuracy in intermediate care units has been largely disregarded [1]. Moreover given the complexity of the septic patho-physiology a panel of biomarkers could be more effective than a single one. For this reason we tested acute phase protein, cell surface, vasotonous related, coagulation system, and tissue hypoxia markers in early ruling in/out of sepsis in systemic inflammatory response syndrome (SIRS) patients [2-3].

Study Design: Prospective observational study.

Materials and Methods: This study included all SIRS patients newly admitted to a medical ward from February till May 2012. Cases were diagnosed as sepsis or non-infective SIRS using clinical examination, cultures of the biological fluid, and imaging during a 7 days follow-up. Investigators were blinded to biomarker results. Survivor at 7 and 30 days were also assessed. Samples for procalcitonin (PCT), presepsin (sCD14-ST), pro-adrenomedullin (PRO-ADM), fibrin degradation products (FDP) and lactate (LCT) were collected within 4 hour from admission. Their role in predicting diagnosis and survival, alone or in combination, have been investigated by receiver operating characteristic curve (ROC), Youden index, relative risk and binary logistic regression.

Results: Among the 60 sepsis patients (microbiological and clinical sepsis), the most common sites of infection were lung (67%), urinary tract (17%), abdomen (5%) and skin (8%). In one third of septic patients cultures turned out positive. The sepsis group had significantly higher levels of PCT, sCD14-ST and FDP than non-infective SIRS group. The area under ROC was 0.80, 0.78, and 0.67 for FDP, PCT, and sCD14-ST respectively. The combination of FDP and PCT provided a Positive and Negative Predictive Value of 90 and 81%, respectively.
Conclusions: In intermediate care setting patients, the combination of FDP and PCT could be useful for an early discrimination of sepsis from non-infective SIRS. PRO-ADM, sCD14-ST, and lactate should considered as early indicators of more intensive ward care and precocious ICU admission.

Serial assessment of serum Cystatin C provides no additive value for the diagnosis of AKI in patients admitted from the Emergency Department


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Background: The early diagnosis of AKI at ED presentation is still a challenging issue. RIFLE criteria represent a poor marker of early renal dysfunction since previous creatinine serum concentration and progressive diuresis decrease in patients referring to ED is difficult to properly assess, representing a relevant reason of delay in diagnosis.

Study Design: This was a prospective clinical trial conducted in order to compare the ability of serial assessment of serum Creatinine (SCr) and serum Cystatin C (SCysC) for detecting AKI in patient admitted from the Emergency Department.

Materials and Methods: Serial blood samples for SCys C, SCr and estimated GFR (MDRD) were obtained at 0, 6, 12, 24, 48 and 72 hours from presentation to the ED. RIFLE criteria were used to define AKI.

Results: 203 patients were enrolled from November 2008 to April 2009, but only 198 (M 53%; F 47%) were included in the statistical analysis. According to the RIFLE criteria all patients were split into two groups: AKI or NO AKI. ROC curve analysis for SCysC, SCr and MDRD had a similar AUC for AKI diagnosis at all the considered times. The time course of the three parameters confirmed that serial assessment of SCysC had a greater congestive status at ED admission with a significative loss of fluids at discharge. Hydration Index obtained by BIA proved its prognostic value for death in cardiac patients at admission.

Conclusions: In conclusion, in patients admitted from Emergency Department, serial assessment of SCysC to the currently accepted markers of diagnosis (SCr and MDRD) does not improve the diagnostic performance for AKI.

Comparison of serial assessments of BIVA and Copeptin on efficacy and risk stratification in patients admitted with dyspnoea in Emergency Department


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Background: In patients referring to the Emergency Department (ED) for shortness of breath (SOB), emergency physicians should consider all different causes of dyspnoea, prescribe an adequate treatment without delay, especially in life-threatening conditions, in order to improve outcomes.

Study Design: Aim of this study was to investigate prognostic significance of serial assessments of BIVA and Copeptin, from admission to discharge, in patients hospitalized for acute dyspnoea from cardiac or non cardiac origin. We conducted a multicenter, prospective cohort study in patients presenting to ED for acute dyspnoea.

Materials and Methods: BIVA measurements, clinical data and blood samples were performed at admission in ED (T0), after 24 hours (T24) and before hospital discharge (TD). A 90-days follow-up, aimed to verify cardiovascular events (death and rehospitalization), was also performed by a phone call.

Results: We enrolled 290 consecutive patients that we divided in two subgroups on the basis of cardiac or non cardiac origin of the dyspnoea: acute heart failure patients (AHF) and acute no heart failure (no AHF). In all patients with shortness of breath, compared with a control group, Copeptin T0 values were significantly (p<0.05) higher: 28 [8.99-54.67] vs 9.3 [5.5-13] pmol/L. Copeptin T0 had a strong predictive value for 90 days post-discharge events in all patients and in cardiac group (acute heart failure). Median value was 20.4 [8.1-49.3] pmol/L in all patients without events, and 42.61 [1176.9] pmol/L in patients with events (p<0.05). The difference between Copeptin values from admission to discharge had prognostic significance in all patients but not if the two subgroups were considered. In patients with cardiac dyspnoea BIVA showed a greater congestive status at ED admission with a significative loss of fluids at discharge. Hydration Index obtained by BIA proved its prognostic value for death in cardiac patients at admission.

Conclusions: This study confirms, in patients coming to ED for SOB, the prognostic role of Copeptin in stratifying for future cardiac events. Copeptin serial assessments during hospitalization seem not to add any utility to this prognostic value. On the other hand, in AHF patients, variations of congestive status monitored by BIVA could provide important information on treatment efficacy and, potentially, in risk stratification.
Ventimask in acute hypercapnic respiratory failure caused by chronic obstructive pulmonary disease exacerbation before starting with bilevel-positive airway pressure

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**Background:** Patients with chronic obstructive pulmonary disease (COPD) during an episode of acute or acute on chronic respiratory failure due to infection present a special problem with regard to the relief of hypoxia. Oxygen therapy to correct the hypoxemia becomes necessary but may sometimes lead to depression of ventilation and may worsen the inequality of ventilation/perfusion ratio by the Haldane mechanism.

**Materials and Methods:** The study involved 40 patients with COPD exacerbation divided in two groups: Group A = 20 patients randomized to Ventimask plus standard therapy and Group B = 20 patients randomised to Ventury mask plus standard therapy. The primary endpoint was to evaluate the efficacy of oxygen therapy with Ventimask compared with Venturi mask in terms of avoiding the need for non-invasive bilevel-PAP during the first hour from an acute episode of COPD exacerbation and mild respiratory acidosis (ph ranged from 7.35 to 7.32).

**Results:** Our results did not show any significant changes of arterial blood gases values between the two groups. In Group A, ph and PaCO2 were respectively 7.32 ± 0.11 and 68.5 ± 13.6 mmHg, at admission, and 7.33±0.05 and 64.8 ± 4.9 mmHg after 1 hour. In group B ph and PaCO2 were respectively 7.32±0.11 and 65.7±13.6 mmHg at admission, and 7.33 ± 0.03 and 64.0 ± 5.5 mmHg after 1 hour. 5 patients (75%) started with bilevel-PAP in group A and 16 (80%) in group B.

**Conclusions:** Our conclusion showed any significant differences between the two oxygen mask delivery in terms of preventing the need of bilevel-PAP and reducing carbon dioxide retention.

Proteomics analysis reveals a promising candidate diagnostic biomarker for heart failure

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**Background:** Heart failure (HF) diagnostic biomarkers such as the natriuretic peptides (NPs) are widely used with great success but have limitations for the screen of acute dyspnea patients. Innovative biomarkers could provide improved diagnostic for acute dyspnea patients admitted to the emergency department.

**Study Design:** prospective case-control proteomic study with ELISA validation.

**Materials and Methods:** We launched a prospective case-control study and investigated for polypeptides specific to HF through a capillary electrophoresis-mass spectrometry (CE-MS) proteomic analysis. The putative biomarker was identified by Orbitrap liquid chromatography-MS and validated both by western blot and ELISA. A rat model of HF was tested for biomarker expression levels by realtime qPCR.

**Results:** We identified ×64 (patent deposited) as a new HF diagnostic biomarker with a high sensitivity and specificity (AUC = 0.933; CI 95%: 0.89-0.96; p<0.0001). ×64 was validated for HF diagnostic in bicentric independent cohorts. Use of ×64 alone or in combination with BNP improved the diagnostic performance for HF. Evaluation of ×64 plasma concentrations in an external cohort led to sensitivity of 80% and specificity of 90% for HF diagnostic. Test of ×64 plasma concentrations in an external cohort led to a sensitivity of 80% and a specificity of 90% for HF diagnostic. Test of ×64 in the poor BNP performance zone led to AUC of 0.643 (CI 95%: 0.479-0.787) for BNP (p=0.034). Heart failure rats revealed increased ×64 mRNA levels specifically in atria.

**Conclusions:** This study identifies ×64 as a new acute heart failure biomarker that could provide information in complement to the natriuretics peptides. Further studies are required before the full validation of this biomarker for future clinical use.

Paroxysmal atrial fibrillation and syncope resulting in fracture of the cranial occipital bone: to treat or non to treat with anticoagulant drugs? This is the problem

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**Background:** Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. AF progresses from short, rare episodes, to longer and more frequent attacks, developing over years sustained forms of AF. Asymptomatic AF is common even in symptomatic patients, irrespective
of whether the initial presentation was persistent or paroxysmal and is manifested with nonspecific symptoms, such as dizziness or syncope. Management of AF patients is aimed at reducing symptoms and at preventing severe complications associated with AF, prevention of whom relies on antithrombotic therapy, control of ventricular rate and adequate therapy of concomitant cardiac diseases. Stroke risk in paroxysmal AF is not different from that in persistent or permanent AF, and is dependent upon the presence of stroke risk factors. Otherwise, an assessment of bleeding risk should be part of the patient assessment before starting anticoagulation.

**Clinical case:** A 50-years-old woman presented herself to Emergency Department (ED) of Melegnano (Italy) for syncope and minor head injury, falling to the ground from a distance of about 150 cm. Her GCS at access was 15. After a first normal ECG performed at her arrival, a new one required during cardiological examination for arrhythmic pulse showed an AF unresponsive to carotid sinus massage. Three hours after the trauma was also performed a brain CT scan with evidence of basal skull fracture at the occipital bone. As indicated by neurosurgeon, the patient had two other brain CT scan respectively at 9 and 18 hours from the injury, showing only at the first (at 9 hour) a small subdural hematoma at the site of trauma, not confirmed by the next. The patient was admitted to the coronary care unit where, after the administration of drugs for rhythm control, sinus rhythm was restored within 24 hours from access and maintained until the time of discharge (5 days after injury). The lady returned to home with the only indication to take antiarrhythmic therapy.

**Conclusions:** In our case, given the limited persistence over time of AF, has been chosen not to start antithrombotic therapy, only monitoring the patient over time. In literature there is no consensus about if or when to start antithrombotic therapy in patients with fracture of the skull and with a recent history of atrial fibrillation. It would be appropriate to conduct a study to determine the time and manner for the management of the AF in this type of patients.

**Hypertension and left ventricular deformation in correlation to functional capacity**

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**Purpose** Our study aimed to evaluate how increased arterial blood pressure (BP) values can impact the parameters of left ventricle (LV) systolic deformation (specifically LV rotation, torsion and twist) in correlation to general functional capacity, measured by oxygen consumption during cardiopulmonary exercise testing (CPET), in subjects with mildly or moderately elevated BP.

**Methods:** Study group included 103 patients (pts) with normal systolic function, divided into 2 groups based on the presence of arterial hypertension (HA) as diagnosed by ambulatory blood pressure monitoring (ABPM): Group 1 (68 pts) with HA (systolic BP >130 mmHg) and Group 2 (35 pts) with normal BP. All pts underwent CPET. We performed standard two-dimensional echocardiography. Analysis was done offline.

**Results:** Groups 1 and 2 didn’t differ in age and gender, but significant differences were observed in: body mass index (p<0.001), left atrial dimension (p=0.012), interventricular septum diastolic thickness (p<0.004), posterior wall diastolic thickness (p<0.007), mitral valve (MV) tissue E-wave velocity (MVe) (p=0.001). Groups were similar in the degree of basal and apical systolic rotation and LV torsion and oxygen consumption at peak-exercise (VO2peak), but significant difference was found in oxygen consumption at anaerobic threshold (ATVO2): 18.45 ml/kg/min in hypertensive group (Group 1) vs. 20.69 ml/kg/min in Group 2 (p=0.016). We established positive linear correlation between ATVO2 and LV twist (p<0.023) and also LV enddiastolic volume (EDV) (p<0.002), enddiastolic volume (ESV) (p<0.002), cardiac output (CO) (p<0.006) and stroke volume (SV) (p<0.003). Positive linear correlation was also found between VO2peak and: LV twist (p<0.047), LV torsion (p<0.026) and LV measurements: EDV (p<0.021), ESV (p<0.02) and SV (p<0.025). There was no correlation between ATVO2 and VO2peak and parameters of diastole (MV annular velocities, diastolic recoil ratio, etc.) and LV mass. According to Regression Model, LV twist and LV torsion were chosen, respectively, to be the strongest independent negative predictors of VO2 at AT (β=−0.235, p=0.023) and VO2peak (β=−0.2, p=0.046).

**Conclusions:** Our data indicated that delicate changes in systolic function expressed through alterations in systolic deformation of left ventricle, that occur in hypertension, could lead to decrease of functional capacity, independently of LV diastolic function and mass in mild to moderate hypertension, and, as a compensatory mechanism, an increase of LV deformation could be expected.

**Approach and management of neurological symptomatic meningioma in emergency-department: a clinical case**

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**Background:** the meningioma is an extrinsic, or extra-axial brain’s tumor that originates from cells of the meninges, particularly in the layer of the arachnoid, with relatively slow growth, this is the most common tumour among intracranial neoplasms in our environment, consequently clinical signs or symptoms may therefore occur months or even years before receiving a diagnosis. For this kind of tumor, microsurgical excision is considered the best solution with different approaches depending on the site of the lesion, especially for meningiomas that have reached a size such as to compress the neurovascular structures of the brain stem and therefore represent a potential danger to the life of the patient.
Clinical case: M. F, a 63 years old woman, accede to our E.R. (emergency response) department presenting a left eye palpebral ptosis, a divergent squint in the left eye and headache without other signs and symptoms. Her remote and present pathological anamnesis (H.P.I. history of the present illness) were both silent and she denied drug allergies. The neurologist on duty visited the woman: he confirmed the palpebral ptosis, the third cranial nerve deficit and the headache without other neurological signs and then he required a brain CT without contrast medium in the suspicious of the presence of acute lesions responsible for our patient case history; in the frontal region of the brain she underlined a large dishomogeneous hypodensity with smooth borders, interdigitated aspect, probably of edematous origin. Because of these findings, by common consent with the neurologist and radiologist colleague, the patient was subjected to careful examination through NMR with contrast medium. The NMR confirmed the presence in the left frontal region of a large expansive lesion [frontal meningioma, ø 5cm], with enhancement after the injection of contrast medium (gadoteric acid 0,5mmol), originating from the dural meningeal layer; it displaced contralaterally the cerebral falx and deepened towards the median bony line. This mass caused edema in the left adjacent cerebral parenchyma in the frontal lobe and in the cingulate gyrus. At the end of the examination the patient was brought back in the room, was again monitored and added as therapy endovenous Soldesan 8mg into association with a gastro protective (Ranitidine) for the onset of a new episode of headache. The patient was transferred to the Hospital San Matteo Hospital in Pavia UO Neurosurgery. During hospitalization, the patient was subjected to a surgical removal of the lesion by craniotomy and biopsy findings histologically to ascertain the characteristics of the mass.

Discussion: The meningioma is an extrinsic, or extra-axial brain’s tumor that originates from cells of the meninges, particularly in the layer of the arachnoid, with relatively slow growth, this is the most common tumour among intracranial neoplasms in our environment, consequently clinical signs or symptoms may therefore occur months or even years before receiving a diagnosis. In our case the gradual expansion hemangiomia in the frontal region has led to a compression of the oculomotor nerve sx entailing an initial suffering of somatic motor fibers, deputies innervations of extrinsic muscles of the eye (the superior rectus, the medial rectus, the inferior rectus and inferior oblique and elevator muscle of upper eyelid). The pharmacological treatment involves the use of different categories of drugs: steroids (dexamethasone, methyl-prednisolone), non-osmotic diuretics (furosemide, acid etacrino), osmotic diuretics (glycerol and mannitol), barbiturates. In our case, the patient was treated with Soldesan (dexamethasone) because steroids have excellent activity on edema that develops around the focal tumors and abscesses, reducing intracranial pressure and prolonging the patient’s clinical stability, at least until definitive intervention, surgical removal. For this kind of tumor, microsurgical excision is considered the best solution with different approaches depending on the site of the lesion, especially for meningiomas that have reached a size such as to compress the neurovascular structures of the brain stem and therefore represent a potential danger to the life of the patient. In this case the patient was subjected to a surgical removal of the lesion by craniotomy because it’s difficult to use an endoscopic endonasal approach if the lateral extent of the tumor passes more than 1 cm beyond the lateral limits of our exposure, beyond which even angled scopes and instruments provide limited visualization and reach.

Conclusion: The primary treatment of meningiomas is surgery which can be curative if the tumor is completely removed, especially for meningiomas that have reached a size such as to compress the neurovascular structures of the brain stem and therefore represent a potential danger to the life of the patient. The completeness of the resection is the single most important prognostic factor for recurrence. An approach tailored is stabilized by the tumour size, location, and extension. In the emergency department is important monitoring the patient and prolong the patient’s clinical stability with the use of appropriate drug therapy until it will be transferred into the appropriate department.

Galectine 3 evaluation in patients with acute heart failure (AHF) at ER admission is high predictive of 30 days events (death and rehospitalization)

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Background: In literature there are few knowledge regarding correlates of cardiac structure, function and prognostic value of GAL 3 values. The serum levels of Galectin 3 (GAL 3), a β- galactoside-binding lectin over expressed by macrophages during phagocytosis, are higher in patients with AHF and are independent of and additive to NT-proBNP in predicting short term mortality. The endpoint of the study was to assess the role of GAL 3 in AHF patient at the moment of ED presentation in order to detect 30 days adverse events (death and rehospitalization).

Study Design: In a prospective, blinded international study, 171 emergency department (ED) patients with AHF were evaluated with testing for amino-terminal pro-B type natriuretic peptide (NT-proBNP), BNP, GAL 3. The primary endpoint was death at 30 days and rehospitalization.

Materials and Methods: We enrolled subjects between April 2012 and June 2013 at two tertiary care academic medical center members of the Global Research on Acute Conditions Team: Sant’Andrea Hospital (Rome, Italy) and the Massachusetts General Hospital (Boston, MA). All
study procedures were approved by local institutional review boards. 171 AHF patients were evaluated at the moment of ED arrival with clinical judgement, blood tests for Gal 3. In-hospital and 30 days follow-up events, deaths, or rehospitalization were recorded.

**Results:** GAL 3 level was significant higher in older patients and it was significant higher in patients with estimate higher Glomerular Filtration Rate (eGFR), higher levels of Gal 3 was correlated with a decrease of eGFR. Median [IQR] GAL3 of events (33.76 [24.84-49.76]) vs no events (25.3 [17.79-36.3]) was statistically significant (p<0.001). The AUC of GAL3 for combined end point was 0.72 (p<0.001), with a cut off value of 17 ng/ml (Sensitivity 85%, Specificity 76%). Percentage of patients who reached the combined end points of: in-hospital mortality + death at 30 days follow up + rehospitalization with a value of GAL3 < 17.8 ng/ml was greater (92.8%) compared to the GAL 3< 17.8 ng/ml group (7.2%). The multivariate cox regression analysis demonstrated that only GAL 3 is a independent variable (p<0.005) to predict death and rehospitalization with a value of 32.24 ng/ml. Brain Natriuretic Peptide (BNP) at ED arrival was not able to distinguish within 30 days events.

**Conclusions:** Our findings support the previous hypothesis that GAL-3 assessed in AHF patients at the moment of presentation in ED might provide to detect the occurrence of 30 days adverse events (death and rehospitalization).

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**ED overcrowding: experience of Emergency Observational Care Unit into the Tor Vergata University Hospital (PTV)**

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**Objectives:** To examine how and whether the development of the EOCU has impacted on the ED efficiency and on different indexes of crowding.

**Methods:** We developed a 20-24-bed inpatient-based emergency observational care unit (EOCU) implemented without any significant additional resources amount. The main tasks of EOCU has been to take care of patients after having charged in ED and to look for an hospital admission, both in our University Hospital and in other hospitals in the district of Rome. This was a preintervention and postintervention cohort study that assessed the impact of the new management of patients charged in the ED on the efficiency of the emergency rooms using data comparing 12 months before and 12 months after the EOCU implementation. The study setting is represented by the Emergency Department of the Tor Vergata University Hospital (PTV).

**Results:** From February 20th 2012 and February 17th 2013, 2498 have been charged in EOCU. The activity in the EOCU has been limited over time, in fact patients have been charged in the EOCU for less than 3 days. EOCU induced a significant decrease in the number of patients boarded in Emergency Room from 4843 in the 2011-2012 to 3747 in the 2012-2013 (P<0.0001). Accordingly, the averaged boarded time in the ER has been substantially reduced from 3123.4±53.2 min in 2011-2012 to 1814.2±32.3 min in 2012-2013 (p<0.001). In the year in which EOCU was operating, a significant decrease in the waiting time from triage to the visit was clearly evident. The improved Emergency Room performance is also confirmed by the significant reduction of patients who left the Emergency Room without being seen. This is a key point because the overcrowding mainly due to patients waiting for a hospital charge produce the worse effect when limits the main task of an Emergency Room which is to visit referring patients. Furthermore, EOCU does not seem to affect re-hospitalization: in the 2011-2012 150.8±14.3 patients/months were charged a second time as compared to 158.8±24.6 in 2012-2013 (not significant).

**Conclusion:** This is, to our knowledge, the first study in Europe aimed to evaluate the possible role played by a structural change in the ED in the attempt to improve overcrowding. The attempt has been increasing and improving active patient care capacity through the implementation of a remotely situated acute care unit, which pushes the boundaries of traditional ED management beyond that conceived for emergency room-based observations units. By evaluating our data the improvement of the ED overcrowding seems due to a slight increase of the rate of patients discharge at home and mainly to a substantial increase of patients admitted to other hospitals. The dedicated managing of patients waiting in ED for a hospital admission have a positive effect on the Emergency Room activity.

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**Insidious chest pain: a case report**

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Background: Intramural haematoma (IMH) belongs to "AAS: acute aortic syndrome" followed by penetrating atherosclerotic ulcer (PAU) and the classical acute aortic dissection. AAS has an incidence of around 30 cases per million per year, of which 80% are aortic dissections, 15% intramural hematomas, and 5% penetrating atherosclerotic ulcers.12 It occurs as a bleeding into the aortic wall (media) without initial rupture of the intima and the classic flap formation. Despite IMH of the thoracic aorta being a disease of the aorta, its optimal initial treatment still remains a hot debatable issue. Aortic intramural haematoma can firstly appear to hypertensive and atherosclerotic patients who suffer an impulsive haemorrhage from vasa vasorum rupture into the media either spontaneously, or less commonly, as a result of PAU.

Clinical case: CR man 81 years old arrived in PS on the 22/5/2013 at 18.44 pm asymptomatic but sent to accidental detection of tachycardia, hypotension and oppressive chest pain in the supine position for a few weeks. The patient was suffering from hypertension, moderate internal carotid artery stenosis, chronic renal failure, aortic valve replacement, sensory motor hemisindrome right, hypercholesterolemia, recent hospitalization in vascular surgery for placement of endoprosthesis in a penetrating ulcer of the descending thoracic discharged the day 15/5. Home therapy: atorvastatin, citalopram, olmesartan, omeprazole, lercanidipina, allopurinol, ASA. Vital parameters: BP 100/65 mmhg, HR 90 AR, objectively the patient was alert, cooperative, valid and arrhythmic cardiac tones, chest MV in all lung and mild pretilial succulence. We performed ECG: absolute arrhythmia atrial fibrillation (not dated), EGA: anemia (Hb 10.6 g/dl) compared to the value 10 days before, blood tests with detection of creatinine 1.7 mg/dl (chronic renal failure already known), TNI negative 0.005 ng/dl, blood count with tally hb 11.2 g/dl (other parameters in the standard), coagulation: fibrinogen 806 mg/dl, d-dimer 4103 ug/l (added to the differential diagnosis with pulmonary embolism). Although the patient was completely asymptomatic and in good hemodynamic compensation, given the severity of aortic disease and the recent intervention of placement of endoprosthesis at the descending thoracic aorta, in agreement with the vascular surgeon it was decided to go directly to an examination of the second level to study the patient’s vascular situation in suspicion of descending thoracic aortic endoprosthesis dislodgment in differential diagnosis of pulmonary embolism. We performed TC chest with enhancement: “intramural hematoma of type AI with a maximum thickness greater than 15 mm in the typical anterior right side, extending from the bulb up to 2 cm on the trunk anonymous, without obvious intimal lesion”. The patient at 22.30 was transferred to the ICU on the advice of the cardiac surgeon for MONITORENG in the absence of current indications for emergency cardiac surgery. During the hospitalization, the patient was subjected to pharmacological cardioversion with amiodarone and subsequent restoration of the RS and optimization of blood pressure control with ace-inhibitor and calcium channel blocker, beta-blocker was suspended for the onset of bradycardia. Was performed chest CT control: stability of the hematoma that appears not stocked and slightly reduced in thickness. The patient was transferred to the cardiac surgery department where he remained asymptomatic and in good hemodynamic compensation. After a few days of observation, the patient was transferred to the department of rehabilitation. In this case we have chosen a conservative strategy aiming at an optimization of blood pressure.

Conclusions: The introduction of endovascular treatment has opened up new perspectives on the treatment of acute aortic syndrome affecting the descending aorta; it is an excellent choice in the early treatment of complications and in most cases leads to aortic remodelling which can modify the natural history and improve the prognosis of this disease.

A case of severe hyponatremia: when treatment is threatening

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Background: Central pontine myelinolysis (CPM) is a neurological disease caused by severe damage of the myelin sheath of nerve cells in the brainstem, more precisely in the area termed the pons. Predominately of iatrogenic origin, it pressure, too abrupt to be compensated by the tissue compartment. This difference in osmotic pressures determines myelin cells death. Clinical presentation of CPM is heterogeneous: from seizures, disturbed consciousness, gait changes, quadraparesis, dysphagia, dysarthria, diplopia, loss of consciousness to life threatening locked-in syndrome. Diagnosis is based on imaging: MRI demonstrates an area of high signal return on T2 weighted images.

Clinical case: A 57 year-old man was brought to the emergency department because of inability to stand after a fall. At the clinical examination, he presented a hematoma on his right eyelid, jaundice and ataxia. His past medical history was significant for art erial hypertension, mitral valve insufficiency, dilated cardiomyopathy, dyslipidemia, smoking, alcoholism (with a daily alcohol consumption of four beers and 4 bottles of wine). At the admission, a complete blood test was performed and it pointed out: Hb 13 g/dl, PTL 150000/mm3, WBC 12200/mm3, GG T 277 UI/l, bilirubin 61 mmol/l, CPK 369 UI/l, Na+ 110 mmol/l, K+ 2.8 mmol/l. Considering these results, the patient was given 2L of saline solution + 4g of KCl in order to correct its electrolyte disorders (after 5 hours of IV fluids: Na+ 113 mmol/l and K+ 4.1 mmol/l). He was then admitted to the gastroenterology ward where further biological tests had been run: at 18h Na+ 128 mmol/l and K+ 3.1 mmol/l, at 36h Na+ 133 mmol/l and K+ 2.9 mmol/l. In the meanwhile, the patient presented an episode of delirium tremens caused by withdrawal of alcohol, treated with benzodiazepine, and a CT-scan was performed, to evaluate the neurological condition at the onset of this new symptomatology, and showed an absence of any neurological abnormalities other than a diffuse cerebral atrophy. Due to a general improvement of his medical state, the patient was discharged after 48h of hospitalization with Na+ and K+ values equal to 140 mmol/l and 3.1 mmol/l, respectively. One week later, he went back to the ER because of a severe alteration of his general conditions: disturbed consciousness, gait changes, tremors, dysarthria and a focal motor deficit of his left arm. The axial T2 weighted MR scan revealed a symmetric area of abnormal high signal intensity within the basis pontis, characteristic of central pontine myelinolysis. Thanks to the physical therapy, the patient partially recovered: mobility problems improved even though a few cognitive disorders persisted after rehabilitation.
Discussion: CPM is a certain consequence of a too much rapid correction of hyponatremia. This disorder typically presents in a devastating fashion, but the prognosis is less dramatic than it was thought in the past. Predisposing factors include severe underlying medical illness, nutritional deficiency or, as in this clinical case, a history of chronic alcoholism. According to former case reports, it has been highlighted that these individuals are more likely to develop CPM, despite the right approach to the hyponatremic issue, demonstrating an innate inclination of their nervous cells to a greater osmotic damage.

Conclusions: Considering what has been brought into light by these studies, it appears to be fundamental the slow adjustment of severe hyponatremia, especially in patients with predisposing factors to CPM. Recent therapeutic guidelines for the restoration of normal Na values should aim for gradual correction, i.e. by $\leq 10$ mmol/L within 24h following in a more strict way the guide lines in such kind of patients.

A strange awakening from a particular coma

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Background: The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the main cause of hyponatremia in elderly. This alteration plays an important role in the clinical situation of the patient. In geriatric patient the pharmacological analysis is often underestimated but in several studies it has been demonstrated to be involved in SIADH diagnosis. SIADH is characterized by hyponatremia as a consequence of interference with urinary dilution. The etiopathogenetic mechanism sertraline-mediated is unclear but the clinical consequences may be damaging in patients with comorbidity, especially in geriatric patients where the decrease of plasma sodium level represents an urgency. This report describes the case of a great elderly female in treatment with sertraline that has developed hyponatremia associated to inappropriate hormone secretion.

Case Presentation: We report a case of an 89-year-old hypertensive female with clinical history of diabetes mellitus type 2 treated with oral hypoglycemic therapy. The patient was admitted to our geriatric ward with right femoral endoprosthesis pertrochanteric post-traumatic, sarcopenia, obesity. The examination revealed tachypnea with a normal-capillary saturinemia, regular tachycardia, breath sounds not much evoked for the low collaboration of the patient, abdomen treatable with no pain on palpation of all quadrants. The neurological examination did not found focal deficit. The electrocardiogram showed sinus tachycardia and chest x-ray was normal. Before the hospitalization the patient was living at her home in a mild-moderate family-dependent condition. In admission in our department she showed a neglected clothing, depressive and unsociable state(statements), and a negative attitude toward the possibility to recover. Despite the incitement of relatives and the many efforts of the physiotherapist, the patient defeatist attitude assumed with opposition to medical practices not being able to fast kernel tracing (FKT) cycle. Considering the clinical history, with no factors of risk or controindications and the anxiety, we introduced in the therapy sertraline, a selective serotonin reuptake inhibitors (SSRI), indicated for the treatment of Post-Traumatic Stress Disorder (PTSD) in women, in particular we selected an antidepressive, sedative not much activating molecule. The therapy started with 25mg/day and one week later the dosis was increased to 50mg a day. Meanwhile the patient refused to eat and didn't accept the mobilization. Was continued the therapy in act supplemented with multivitamin and energizing compounds. One week later the patient showed a new acute event characterized by diarrheal bowel, nausea, lack of appetite, oliguria, mild succulence declivous by chemical blood discrepancy likely, although the blood volume was normal (without indicative signs of cardiovascular failure). We tought to intestinal dismicrobism or to an intollerance concomitant to metformin. After three weeks of that treatment we evidenced a cognitive worsening, the patient become unconscious and the many efforts of the physiotherapist, the patient defeatist attitude assumed with opposition to medical practices not being able to fast kernel tracing (FKT) cycle. Considering the clinical history, with no factors of risk or controindications and the anxiety, we introduced in the therapy sertraline, a selective serotonin reuptake inhibitors (SSRI), indicated for the treatment of Post-Traumatic Stress Disorder (PTSD) in women, in particular we selected an antidepressive, sedative not much activating molecule. The therapy started with 25mg/day and one week later the dosis was increased to 50mg a day. Meanwhile the patient refused to eat and didn't accept the mobilization. Was continued the therapy in act supplemented with multivitamin and energizing compounds. One week later the patient showed a new acute event characterized by diarrheal bowel, nausea, lack of appetite, oliguria, mild succulence declivous by chemical blood discrepancy likely, although the blood volume was normal (without indicative signs of cardiovascular failure).}

Clinical and demographic predictors of hyponatremia in a geriatric population admitted to a rehabilitation institute

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Conclusions: Considering what has been brought into light by these studies, it appears to be fundamental the slow adjustment of severe hyponatremia, especially in patients with predisposing factors to CPM. Recent therapeutic guidelines for the restoration of normal Na values should aim for gradual correction, i.e. by $\leq 10$ mmol/L within 24h following in a more strict way the guide lines in such kind of patients.
Background: Age-related changes make older adults more vulnerable to shifts in water balance and more vulnerable to the development of an electrolyte imbalance. Electrolyte imbalances are not uncommon and they are also potentially deadly. Hyponatremia is the most common electrolyte disorder in hospitalised patients. Mild, or even asymptomatic, hyponatremia may be associated with increased morbidity and the risk of mortality. While the symptoms of hyponatremia are not always severe, the danger may be real. Its development could be conditioned by the presence of very common clinical conditions; however hyponatremia could also be a consequence of drug use. Geriatric patients are known to be characterised by polypathology and polypharmacotherapy, both risk factors for the development of hyponatremia.

Study Design: We evaluate a geriatric population whose subjects are particularly at risk of developing hyponatremia because of their comorbidity and polypharmacotherapy. The population consists of elderly patients hospitalized during the course of 2012 and continuously related to a rehabilitation institution. We performed a cross-sectional study to determine which and how many patients developed hyponatremia during hospitalization, and to identify any correlation with demographic, clinical, functional and outcome characteristics in our geriatric population.

Materials and Methods: The study population consists of patients who were hospitalized in 2012 with complete parameters required by the study. We collected the following parameters: age, sex, length of hospital stay, outcome, admission diagnosis, pharmacological therapy, blood tests, Barthel Index, Cumulative Illness Rating Scale (CIRS-C and CIRS-S) and Mini Mental State Examination (MMSE).

Results: 56 out of 276 patients had at least one episode of hyponatremia during the hospitalization. The results showed a statistically significant association between hyponatremia and hyperglycemia ($r = 0.144^*, P = 0.031$), hypochloraemia ($r = -0.375^{**,} \ P < 0.001$), length of hospital stay ($r = 0.125^*, P = 0.039$), diagnosis of polypathology ($r = -0.171^{**}, P = 0.004$), therapeutic combination of 3 or more drugs ($r = 0.254^{**}, p < 0.001$), decrease in the value of the Barthel index ($r = -0.138^* , P = 0.034$), increase in the value of CIRS-C ($r = 0.295^*, P = 0.015$) and CIRS-S ($r = 0.191, P = 0.068$). Evaluating the multivariate analysis, the only variable that showed an independent association, from a statistical viewpoint, with the presence of hyponatremia is the length of hospitalization.

Conclusions: It is recommended that, in the clinical management of the elderly patient, electrolyte monitoring is practiced often and early in the event of a history of disease at risk of hyponatremia and in case of treatment with diuretics, SSRIs or SNRIs, anticonvulsants, ACE inhibitors and other drug classes in all their associations. Hyponatremia also impacts hospital economics as it has been shown to induce longer, more costly hospital stays.

The predictive prognostic role of QTc prolongation in an elderly population: correlation with sudden events

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Background: QTc interval prolongation on the surface electrocardiogram is associated with the development of torsade de pointes (TdP), a polymorphic ventricular tachycardia that may cause sudden cardiac death. Acquired Long QT Syndrome can be caused by different environmental stressors whose removal restores the physiologic condition. The most common environmental stressor involved in acquired long QT syndrome is drug therapy whose adverse effects, combined with other risk factors, such as sex, age, cardiovascular diseases leads to the development of QTc interval elongation.

Study Design: The purpose of this study was to assess the effect of the QTc interval prolongation in an elderly subjects cohort according to the number of comorbidities that characterize this category of patients.

Materials and Methods: There was a sequential series of patients admitted to a rehabilitation ward for a period covering the first half of 2012. We collected the following parameters: age, sex, admission diagnosis, ECG QT interval values corrected according to the Bazett’s formula, electrolytes values and drug therapy.

Results: Out of a total of 415 patients were recorded 132 patients with LQT at the entrance, 24 of which remained unchanged. In the total sample were recorded 23 patients with normal ECG at admission and who have developed a pathological lengthening of the QTc interval during the hospital stay. In total 92 deaths were recorded, 37 of which showed a lengthening of the QTc interval. The results showed a statistically significant association between QT prolongation, sex male ($p < 0.01$), drug therapy ($p < 0.01$) and death ($p < 0.05$). Multivariate analysis showed an OR between QT prolongation and death equal to: OR = 1.735.

Conclusions: The results showed that patients with a lengthening of the QTc at hospital admission appeared to have a risk of sudden death about 73%. This study confirms the important role of the electrocardiographical QT interval values monitoring in function of the polypharmacy and age of the patient with several comorbidities in order to reduce the risk of death related to QTc elongation.

Experience of Emergency Departement of Lodi, Italy about Acute Metformin Intoxication

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Background: Metformin is a biguanide antihyperglycemic agent that decreases insulin resistance, decreases hepatic gluconeogenesis and enhances peripheral glucose uptake by muscle and adipose cells. Metformin is removed through renal mechanisms and its clearance is reduced in renal failure. Metformin ingestion should always be considered in the differential diagnosis of any patient with metabolic acidosis and increased lactate level. Hemodialysis is an efficient method to treat metformin intoxication and correct the metabolic abnormalities; Continuous Veno-Venous Hemofiltration (CVVH) should only be considered in patients who are too hemodynamically unstable to tolerate hemodialysis.

Clinical case: Pt.1 > A 63-years-old man with type 2 diabetes mellitus presented to Emergency Department (ED) of Lodi (Italy) for tachycardia and dyspnea. He also reported diarrhea since 10 days. Initial investigations revealed a wide anion gap metabolic acidosis with hyperlactatemia and hypoglycemia (54 mg/dl). Sodium bicarbonate was administered intravenously, as well as dextrose for hypoglycemia, and the patient was transferred to the Intensive Care Unit (ICU) for further management. His hemodynamic condition became rapidly unstable, up to necessitate an endotracheal intubation. Blood tests showed a serum creatinine of 8.3 mg/dl and a metformin concentration of 41 mcg/ml (normal value < 4 mcg/ml). CVVH was performed with partial improvement of blood gas analysis parameters. Despite this hypotension worsened, becoming unresponsive to norepinephrine until death occurred in 24 hours. Pt.2 > A 76-years-old man with type 2 diabetes mellitus presented to ED of Lodi for dyspnea. He referred a recent surgery amputation of the left foot’s fifth phalanx for osteomyelitis, in levofloxacin therapy. On examination he was lethargic and disoriented. Initial investigations revealed a wide anion gap metabolic acidosis with hyperlactatemia and severe hypoglycemia (20 mg/dl). Blood tests showed a serum creatinine of 10,46 mg/dl and a metformin concentration of 15,7 mcg/ml (normal value < 4 mcg/ml). Sodium bicarbonate was administered intravenously, as well as dextrose for hypoglycemia, and urgent 4 hours hemodialysis session was performed. After a new hemodialysis session the following day a complete normalization of the serum concentration of metformin was obtained. On day 36 the patient was discharged with a normal renal function (comparison data in Table 1).

Conclusions: In our two cases, beyond the different severity and different therapeutic approach, it was clear the genesis of intoxication from metformin (powered by acute renal failure), less obvious was the etiology of acute renal damage responsible of metformin accumulation. A damage for renal hypoperfusion or a direct toxic effect of metformin should be considered. Additionally, for the first patient, we can also hypothesize interstitial nephritis exacerbated by levofloxacin.

Table 1 Comparison between Patient 1 and Patient 2 through highlight laboratory data.

<table>
<thead>
<tr>
<th></th>
<th>Units</th>
<th>Normal value</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>year</td>
<td>63</td>
<td>76</td>
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</tr>
<tr>
<td>Sex</td>
<td></td>
<td>male</td>
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</tr>
<tr>
<td>Presenting symptoms</td>
<td></td>
<td>tachycardia and dyspnea</td>
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</tr>
<tr>
<td>Medical History</td>
<td></td>
<td>- high blood pressure in therapy with ACE-I and diuretic</td>
<td>- recent surgery for amputation of the fifth phalanx of the left foot following osteomyelitis</td>
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</tr>
<tr>
<td>HR ED access</td>
<td>b/min</td>
<td>100</td>
<td>87</td>
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<tr>
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<td>mmHg</td>
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<td>155</td>
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<td>DBP ED access</td>
<td>mmHg</td>
<td>80</td>
<td>80</td>
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<td>Sat O2 ED access</td>
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<td>0,99</td>
<td>0,99</td>
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<tr>
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<td>&lt; 4</td>
<td>ne</td>
<td>2,1</td>
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<tr>
<td>Creatinine baseline</td>
<td>mg/dl</td>
<td>0.64 - 1.27</td>
<td>0.95</td>
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<td>10,46</td>
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<td>Creatinine discharge</td>
<td>mg/dl</td>
<td>0.64 - 1.27</td>
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<tr>
<td>Glucose ED access</td>
<td>mg/dl</td>
<td>70 - 100</td>
<td>54</td>
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<td>Uricemia</td>
<td>mg/dl</td>
<td>17 - 43</td>
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<td>180</td>
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<tr>
<td>AST</td>
<td>U/L</td>
<td>0 - 40</td>
<td>29</td>
<td>36</td>
</tr>
<tr>
<td>ALT</td>
<td>U/L</td>
<td>0 - 40</td>
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<td>30</td>
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<tr>
<td>Na ED access</td>
<td>mmol/L</td>
<td>136 - 146</td>
<td>143</td>
<td>135</td>
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<tr>
<td>Na after therapy</td>
<td>mmol/L</td>
<td>136 - 146</td>
<td>150</td>
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<td>K ED access</td>
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<td>6,1</td>
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<td>K after therapy</td>
<td>mmol/L</td>
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<td>mmol/L</td>
<td>98 - 106</td>
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<td>pCO2 ED access</td>
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<td>20,9</td>
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MMP-1 genetic polymorphism (rs1799750) and sepsis patients: preliminary results


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Background: Diffusion of microorganisms during an infection leads to sepsis, thus reducing survival and, in general, worsening the patient’s prognosis. A positive blood culture shows spreading of microorganisms from the site of infection to the bloodstream. Some microorganisms exploit host’s matrix metalloproteinase (MMP) production to make possible this process. In particular, MMP-1 is a well-known enzyme required for the degradation of tubercular granuloma. The expression of MMP-1 is partially under genetic control, and a functional genetic polymorphism (G+/- at -1607, rs1799750) accounts for differential expression. There is no information on the relationship between genetic variants of these protein and susceptibility or resistance to the spreading of microorganisms during sepsis.

Aims: To investigate the relationship between MMP-1 genetic polymorphisms rs1799750 and site of infection, culture result and prognosis of a group of patients admitted in a medical ward and diagnosed with sepsis, either microbiologically proven or clinically diagnosed.

Methods: In this pilot study 55 patients with sepsis have been compared. MMP-1 polymorphism has been carried out by intron polymerase chain reaction and capillary electrophoresis. Clinical and laboratory workout has been carried out independent of the results of the test and diagnosis, respectively. Comparison has been carried out with \( \chi^2 \) test and Kaplan Maier curve where indicated.

Results: One third (18 out of 55 patients) of the patients had positive culture test (blood, urine, soft tissues, etc). During the hospital stay 6 patients died. Genotype frequency of rs1799750 was 11, 31 and 13 for G-/G-, G-/G+, G+/G+, respectively. The genotype was not correlated to age, gender and comorbidities of the patients. There was a trend towards an association between positive culture and G+ allele (\( P = 0.062, \text{O.R} = 6.3, 95\% \text{CI} 0.7 - 53.7 \)). All in-hospital deaths occurred in carriers of G allele (Kaplan Maier curve \( P = 0.227 \)).

Discussion: These preliminary results are the first suggestion about a link between microbiological test and indexes of matrix remodeling of the host. This is a consistency between predicted, in vitro, and actual results. Based on the present figures, a final number of 127 samples would provide an 80% beta power with a significance of 0.05 (Alpha value), with continuity correction.

Perspectives: Control of microorganism diffusion during infection could prevent many fatal complications. The results should allow developing a model to individualize therapy in patients with infection, stratify the risk of patients undergoing surgical procedures and, in the long term, suggest a strategy to reduce bacterial invasion within tissues.

References

(Table 1 Continued)

<table>
<thead>
<tr>
<th>Units</th>
<th>Normal value</th>
<th>Patient 1</th>
<th>Patient 2</th>
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</thead>
<tbody>
<tr>
<td>Anion gap ED access</td>
<td>mmol/L</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>Anion gap K+ ED access</td>
<td>mmol/L</td>
<td>10 - 20</td>
<td>37</td>
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<td>Anion gap after therapy</td>
<td>mmol/L</td>
<td>10</td>
<td>10</td>
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<td>Lactic acid ED access</td>
<td>mmol/L</td>
<td>5 - 1.6</td>
<td>17</td>
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<td>Lactic acid after therapy</td>
<td>mmol/L</td>
<td>5 - 1.6</td>
<td>3,6</td>
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<td>pH ED access</td>
<td>mmol/L</td>
<td>7,35 - 7,45</td>
<td>6,85</td>
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<td>mmol/L</td>
<td>7,35 - 7,45</td>
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<tr>
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<td>CVVH</td>
<td>hemodialysis</td>
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<tr>
<td>Hospital stay</td>
<td>day</td>
<td>1 (†)</td>
<td>36</td>
</tr>
</tbody>
</table>

ne = not executed.
*All analyses were performed from plasma of lithium heparin–treated blood samples, except for glucose (plasma treated with fluoride and EDTA) and lactate (whole blood).
ALT, alanine aminotransferase, AST, aspartate aminotransferase.
†death.
Physical training in elderly patients after acute heart failure: a new path from Emergency Room to Cardiac Rehabilitation Division

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Background: Acute heart failure is defined as the appearance of a complex multifactorial syndrome, characterized by an inability of the heart to pump blood adequately as compared to the peripheral tissue demands. Currently heart failure affects 0.4-2% of the adult population in the European Union with a 4 years-mortality of 50%. One of the most significant disability, is represented by the reduced tolerance to physical activity (“bed-rest syndrome”). A further issue strictly linked to the managing of acute heart failure in the Emergency setting is represented by the continuously rising age of patients (≥75 years). Most studies on the role of cardiac rehabilitation in heart failure patient were carried out on a sample of patients definitely younger.

Study Design: We realized an observational study to analyze the effect of an adapted program of physical training in elderly patients charged in ED for acute decompensated heart failure.

Materials and Methods: 28 (mean age 75,4±2,2; range 46-89) patients (15 males and 13 females) were evaluated in the cardiac rehabilitation Division after an acute charge in the ED for decompensated heart failure. Clinical data were collected for each patient. Patients underwent a physical training program adapted for the age and consisting of sessions of calisthenics and physical exercises aimed to improve aerobic performance and coordination functions. We tested 6 min walking test and BORG scale at the end of the walking test at the beginning and at the end of the Cardiac rehabilitation program which had a mean duration of 23.7 days (range 19-30 days). Data are expressed as mean±SEM.

Results: All patients performed the physical activity as prescribed in their Cardiac Rehabilitation Program. Patients showed a significant improvement in their exercise performance as demonstrated by the positive results to 6 min walking test. Infact at the arrival in the cardiac rehabilitation division patients walked during 6 min 129,3±15 m whereas at the end of the Cardiac Rehabilitation Program they walked during 6 min 222,1±21,1 m (p<0.001). In line with this results patients showed also a significant improvement in fatigue perception as demonstrated by the significant decrease of the borg scale at the end of the physical training (3,4±0,4 vs 6,0±6 min 222,1<0,001). In line with this results patients showed also a significant improvement in fatigue perception as demonstrated by the significant decrease of the borg scale at the end of the physical training (3,4±0,4 vs 6,0±6 min 222,1<0,001).

Conclusions: The results of our study suggest that adapted programs of physical training within structured programs of Cardiac Rehabilitation are effective in elderly patients referring to the Emergency Department after acute decompensated heart failure.

Reliability of WBC count and PCT as diagnostic and prognostic biomarkers of infection and sepsis in patients in an Emergency Setting

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Background: Sepsis is a difficult-to-diagnose condition in an emergency setting, highly life-threatening. Procalcitonin (PCT) is currently the most studied infection and sepsis biomarker and its blood levels seem to mirror the severity of illness and outcome. In clinical practice PCT is widely used together with other biomarkers, included white blood cells (WBC) count, to diagnose infections, and to guide antibiotic therapy.

Study design: This study aims to verify in a population of infected patients presenting to our Emergency Department (ED) the diagnostic and prognostic power of WCB and PCT together.

Materials and Methods: 500 patients (M247/F269 mean age: 72±16 years) presenting to our ED with signs/symptoms of local infection or sepsis were enrolled. Each patient underwent laboratory and instrumental diagnostic tests to assess diagnosis. Sepsis diagnosis was made on the basis of current guidelines. APACHEII score was determined for each patients. In-hospital death was recorded. Entire population was subdivided into quartiles by age (I: 19-69, II: 70-77, III: 78-83, IV: 84-102) and PCT and WBC were measured at baseline. We calculated the correlations between PCT and WBC for each quartile. ROC Curves for evaluating diagnostic and prognostic role of PCT and WBC were calculated for each variable alone, and for PCT+WBC combined.

Results: There was no statistical difference between the four subgroups when compared each other, either for PCT, and for WBC. On the contrary, for the APACHEII score there was a statistical difference between I quartile when compared with the III, and the IV (p<0.001). All
the three variables studied were higher in the last quartile (probably for the multiple comorbidities frequent in the elderly, and for the more severity of infection). A direct correlation between PCT and WBC was found in the II, III and IV quartiles (the highest correlation, \( r = 0.34, p<0.0003 \)), but not in the first. ROC curve analysis showed a significant diagnostic and prognostic role of WBC and of PCT either if considered separately (for diagnosis: PCT AUC 0.79, p<0.0001 - WBC AUC 0.71, p<0.0001; for prognosis PCT AUC 0.71, p<0.0001 - WBC AUC 0.63, p<0.001), and in combination (for diagnosis: PCT+WBC AUC 0.75, p<0.0001; for prognosis: PCT+WBC AUC 0.66, p<0.0001).

**Conclusions:** Our data demonstrate that WBC and PCT are reliable diagnostic and prognostic biomarkers of infection, also when considered in combination, and with the aid of severity clinical scores. PCT confirms its stronger usefulness as a diagnostic marker of infection, in fact its AUC is higher than that of WBC; this indicates the better specificity of this biomarker as diagnostic tool in infections and in sepsis. A multi-diagnostic tools approach is fundamental to perform a correct and rapid diagnosis of infection, and of sepsis in the ED.

**Biomarkers for organ damage in hypertensive crisis**

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**Background:** Background: Hypertensive crises (76% urgencies, 24% emergencies) represented more than one fourth of all medical urgencies/emergencies. Little is known about the elevation of plasmatic levels of BNP, NGAL, HS-TnT, Copeptin and Galectin 3 during an hypertensive emergency. The role of these biomarkers has never widely examined during the organ failure consequent to an hypertensive crisis.

**Hypothesis:** The early identification of cardiovascular, neurological, renal, or systemic injury, through the determination of plasmatic levels of different biomarkers, could be useful to identify and prevent the possible consequences of an acute hypertensive crisis.

**Primary objective:** Detect the plasmatic levels of BNP, NGAL, HS-TnT, Copeptin, Galectin 1 and S-100 in all patients admitted to ED for an hypertensive crisis. Determine if differences are present between patients who develop an organ failure or not. Establish the diagnostic value of single biomarker or their combined use to early identify patients with organ damage.

**Secondary objectives:** Determine the prognostic value of BNP, NGAL, HS-TnT, Copeptin and Galectin 1 to identify those patients with a worse prognosis.

**Materials and Methods:** Design: Prospective, observational, international and multi-centric study.

- **Inclusion criteria:**
  - systolic blood pressure values > 180 mmHg and diastolic values > 120 mmHg
  - age >18
- **Assessments required:**
  - Medical history
  - Concomitant medications (prior 7 days)
  - Physical Examination
  - Vital parameters
  - 12-lead ECG
  - Chest X-Ray
  - Labs: hemochrome, general clinical chemistry.
  - Collection of blood samples to determine plasmatic levels of BNP, NGAL, HS-TnT, Copeptin, Galectin 3 and S-100.
  - Echocardiography
  - 30 day phone call follow-up to evaluate events (re-hospitalization or death) and Global patients' assessment
  - 180 day phone call follow-up to evaluate events (re-hospitalization or death) and Global patients' assessment

**Patients**
100 patients each centre.

**Duration**
One year to enroll 100 patients and six month to complete the follow-up.

**Additional Costs**
Our study will not require additional costs. The main centre will provide to analyze all blood samples to determine the plasmatic levels of biomarkers.

**Antithrombotic therapy and short-term outcome in mild head injury: a retrospective analysis in the Venice Area second level Emergency Department (ED)**

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Background: Traumatic brain injury (TBI) carries a heavy burden on the society because of permanent consequences and death toll. Many studies have identified a causal relationship between anticoagulant therapy and poor outcome of mild TBI. In the last decade, because of the increased use of antiplatelet therapy in patients at risk of cardiovascular diseases, many studies have sought a causal relationship between antiplatelet medications and TBI poor outcome with conflicting results. For this reason and because of the lack of specific guidelines on mild TBI in patients taking antiplatelet therapies, our study has compared the outcome of patients taking antiplatelet or anticoagulant medications with that of the untreated population after mild TBI.

Study Design: Single centre, retrospective, observational.

Materials and Methods: We evaluated all patients with TBI who came to the Emergency Room of the Venetian second level Emergency Department between Jan 1st, 2011 and Dec 31st, 2012. We enrolled 1100 patients with mild TBI (Glasgow Coma Scale, GCS, 14-15), aged 18 or older and with Glasgow Outcome Scale (GOS) 1 to 5, excluding those with GOS 6 (lost at follow up).

Results: The gender distribution was similar (50% males and 50% females). Falls were the most frequent cause of mild TBI (45%), with a mean age significantly higher than that of the patients with mild TBI from other causes (76 ± 17 years vs. 48 ± 19 years). The mean age of the patients on antithrombotic medications was significantly higher than that of patients not taking antithrombotic drugs (80 ± 10 years vs. 55 ± 23 years). Falls were the most frequent cause of mild TBI in patients taking antithrombotic medications (75%) than in those not taking antithrombotic drugs (37%). Elderly patients underwent cerebral Computerized Tomography (CT) scanning more often (60%) than the rest of the population (47%). Patients taking antithrombotic medications underwent CT scan more often (77%) than those not on antithrombotic therapy (45%). A second CT scan revealed worsening haemorrhagic lesions in 7% of patients, more often in patients 75 years or older (13%) than in younger patients (3%). Outcome was similar in patients taking antiplatelet drugs and in the remaining cohort, but it showed a fourfold higher risk of negative outcome in patients taking antiplatelet medications and a twenty fold higher risk of negative outcome in patients aged 75 years or older. Older patients were those having the highest rate of mild TBI from falls and those most often on antithrombotic therapy.

Conclusions: Advanced age is the most important risk factor for poor outcome after mild TBI. We recommend to include this diagnostic criteria in mild TBI guidelines to appropriately evaluate the elderly population affected by mild TBI with CT scan. We ruled out any effect of the antiplatelet therapy on the outcome of mild TBI patients while we confirm the high risk in those taking anticoagulant medications. Prospective studies should be undertaken to thoroughly verify the relationship between pre-injury antiplatelet therapy and TBI, taking into account confounding factors such as age, TBI severity and mechanism of trauma.

The future of atrial fibrillation approach in the Emergency Room: between new antiarrhythmic and anticoagulant drugs

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Atrial fibrillation (AF) is the most common cardiac dysrhythmia and occurs in 3-10% of emergency admissions; significant morbidity and mortality result from AF and the emergency physician has to evaluate the initial step towards the therapeutic decisions. There are two main strategies for the management of AF: rate and rhythm control. Current guidelines recommend rhythm control as a first line strategy for patients presenting to the ED within 48 hours of the onset of AF or if transesophageal echocardiography (TEE) has excluded left atrial thrombus. Heart rate control strategy aims to maintain a ventricular rate that protects the patient from consequences of tachycardia. Rhythm control strategy targets sinus rhythm restoration by pharmacological cardioversion (CV) antiarrhythmic drugs ± electrical cardioversion and maintenance by antiarrhythmic drugs.

Recent interest has focused on newer agents for rapid CV of acute AF, including Vernakalant which has achieved almost 90% CV rates in routine clinical practice. The effectiveness and safety profile make Vernakalant an ideal ED drug: it acts preferentially in the atria by blocking several ion channels, resulting in prolongation of atrial refractoriness and rate-dependent slowing of atrial conduction, but has little impact on currents involved in ventricular repolarization. It is effective in cardioversion of patients with AF ≤ 7 days and provides a rapid antiarrhythmic effect with approximately 50% of patients converting within 90 minutes after the start of treatment and a median time to conversion of 8-14 minutes. Vernakalant has a satisfactory safety profile in patients with minimal-to-moderate heart disease, including ischemic heart disease and it was significantly superior to intravenous amiodarone in restoration of sinus rhythm within 90 min and within 4 hours after infusion.

Antithrombotic treatment is pivotal in AF to prevent cardioembolic stroke and is considered a primary objective of treatment in this condition. In patients with risk factors for stroke or AF recurrence, oral anticoagulant therapy should then be continued lifelong, irrespective of the apparent maintenance of sinus rhythm following CV. The peri-CV period is always considered a delicate time: the advent of novel oral anticoagulants for stroke prevention in AF, including the oral direct thrombin inhibitor dabigatran etexilate (DE) and the Factor Xa inhibitors rivaroxaban, apixaban and edoxaban is posing new problems and questions for the peri-CV time in the limited condition of non-valvular AF. As the RE-LY study demonstrated, efficacy and safety of DE in a large cohort of patients undergoing CV was comparable to that of warfarin regardless of the use of TEE: one may conclude that DE is a reasonable alternative to warfarin in patients requiring CV. Recently, in Italy Dabigatran has been acknowledged as anticoagulant drug for stroke prevention in non-valvular AF in patients with specific risk factors.