The MEDA pole comprises physicians conducting research in the three acute medicine units of the UCL Cliniques Universitaires Saint-Luc and CHU UCL Namur site Mont-Godinne: anesthesiology, intensive care, and emergency medicine. Our primary research work is devoted to clinical research, from local original studies to international multi-center studies, either academic or industry-sponsored. The MEDA pole does not currently have its own experimental lab, so that some PhD students of the clinical units develop their thesis work in other poles according to a translational research.

The research is primarily focused on the following topics: (1) sepsis and septic shock; (2) pulmonary embolism and new anticoagulant drugs; (3) airway and respiratory management; (4) acute intoxication and poisoning; (5) neuromuscular block during surgery; (6) nutrition; (7) acute pain management; (8) elderly patient management during cardiac surgery; (9) organ donation following cardio-circulatory death.

Most of the researchers of this group belong to international collaborative groups, resulting in national or European leading board coordination and some co-authoring studies published in the highest impact factor journals. One of the challenges of this research sector focused on acutely-ill patients is developing fundamental aspects of clinical studies, participating in preliminary phases of drug developments, and including patients outside working hours (at nights and weekends).
Furthering our understanding of sepsis and septic shock

Pierre-François Laterre, Xavier Wittebolle

- Combatting bacterial resistance in Europe: our intensive care unit is actively participating in a wide European consortium between pharmaceutical companies and universities, aiming to give antibiotic drug development a much-needed boost by pioneering new ways of designing and implementing efficient clinical trials for novel antibiotics. This COMBACTE consortium project is devoted to the performance of clinical trials of new class of antibiotics with a novel mode of action, like an innovative human monoclonal antibody that binds with high affinity Staphylococcus aureus alpha toxin. This multicenter clinical trial will evaluate the efficacy and safety of this specific toxin-neutralizing agent at preventing infections in patients at risk of S. aureus surgical site infections and mechanically-ventilated patients at risk for S. aureus pneumonia.

- Targeting innovative pathways with stem cells for the treatment of severe sepsis: The SEPCELL project is a Phase Ib/IIa randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the safety and efficacy of intravenously-administered suspension of allogeneic expanded adipose-derived stem cells in patients with severe sepsis secondary to severe community-acquired pneumonia. The completion of this study will contribute to the production of fundamental scientific knowledge on stem cells and their mode of action, and presents a wide translational character, assessing the immunomodulatory properties of stem cells to target other therapeutic pathways than the traditional standard of care with antibiotics.

- Investigating a new vasopressor in severe septic shock: PF Laterre is the world principal investigator of an industry-sponsored study devoted to Selepressin, a selective vasopressin type 1a receptor agonist which increases arterial pressure and has the potential to reduce vascular leakage and pulmonary oedema. This trial has started in 2015, is currently conducted at 50-60 sites in Europe and the United States and will enroll 1800 patients. This is a double-blind, randomized, placebo-controlled, phase IIb/III two-part adaptive clinical trial, designed to investigate the efficacy and safety of multiple dosing regimens of selepressin.

- Improving the quality of care for septic patients in the intensive care unit (ICU): A major concern of ICUs worldwide is how to qualitatively assess the standard of care, especially in septic clinical cases. This evaluation requires our center to join forces with a worldwide network of ICU research centers. We participated in two multicenter studies on this topic:
  - A global, prospective, observational, quality improvement study of compliance with international guidelines (Survival Sepsis Campaign) in patients with either severe sepsis or septic shock. Compliance with these guidelines was found to be low (approximately 20%) and patients whose care included compliance with these guidelines exhibited a 40% reduction in their risk of dying in hospital.
  - 730 participating centers in 84 countries prospectively collected data on all adult patients admitted to their ICUs during 10 days. The objective was to assess differences between hospitals and countries in terms of ICU mortality. This large database highlighted that sepsis is still a major health problem worldwide, associated with high mortality rates in all countries.

- Improving the treatment of sepsis and septic shock: We participated in a multicenter, randomized, double-blind, placebo-controlled Phase IIb trial comparing the efficacy/safety of two IV doses of AZD9773, a polyclonal antibody against tumor necrosis factor-α, in adult patients with severe sepsis/septic shock. The results demonstrated that AZD9773 rapidly and efficiently decreased plasma tumor necrosis factor-α concentration in patients with severe sepsis/septic shock, though this effect did not translate into clinical benefit.

- We performed a prospective, randomized, controlled study in patients with intra-abdominal or lower respiratory tract infections caused by Enterobacteriaceae. This study sought to assess the pharmacokinetics and target attainment rates of 6g of temocillin daily over three administrations, each delivered once every 8 h (three times daily)
or via continuous infusion in critically-ill patients. The conclusion was that administering 6g daily of temocillin via continuous infusion led to a larger proportion of critically-ill patients exhibiting free drug serum concentrations covering Enterobacteriaceae infections.

- We reviewed “bacteriophage therapy” in its capacity as alternative to antibiotics for treating invasive bacterial infection and found it to be a novel alternative to antimicrobial chemotherapy. We demonstrated that bacteriophage therapy displayed several advantages and few adverse events were reported, though underreporting cannot be ruled out. However, further well-conducted studies are required to define the role and safety of phage therapy in daily clinical practice for treating patients with various infections.

- Furthering understanding of septic shock and its risk stratification: We performed a local prospective observational study on 102 patients in septic shock, the primary objective being to determine if those who died or required sustained vaspressors at Day 7 exhibited arginine vasopressin (AVP) deficiency compared to vasopressor-free patients. No such a relative deficiency was found. This study further confirmed previous data on the ability of the CT-proAVP (C-terminal of preprovasopressin) to predict patient severity in severe sepsis and septic shock.

- Improving our understanding of Streptococcus pneumoniae in community-acquired pneumonia (CAP) in the ICU: Myeloid-related protein (MRP) 8/14 is a major component of neutrophils that is released upon infection or injury. MRP8/14 is essential for protective immunity in cases of infection involving a variety of micro-organisms through its capacity to chelate manganese and zinc. Here, we sought to determine the role of MRP8/14 in pneumococcal pneumonia. The results revealed that, in a model of CAP, MRP8/14 is misused by S. pneumoniae, facilitating bacterial growth by attenuating zinc toxicity toward the pathogen.

Cheryl Hickmann, Pierre-François Laterre

- Impact of early exercise on signaling pathways in muscle metabolism in patients with sepsis: Neuromuscular impairment in patients hospitalized in intensive care unit is an important risk factor for morbidity and mortality. Characterized by an increased catabolism of the muscle, it generates a significant negative impact on quality of life after discharge from intensive care. The objective of this project is to demonstrate that maintaining muscle activity at an early stage in patients with severe sepsis, restores the balance of skeletal muscle protein. By achieving muscle micro-biopsies, we analyze the signaling pathways of catabolism and protein synthesis in skeletal muscle. In parallel, the morphological analysis attempts to objectify a limitation of the loss of muscle fibers, and to detect an impact on the appearance of myopathic and/or neuropathic lesions which characterize this patient population.

Management of pulmonary embolism in outpatients and monitoring the new oral anticoagulants (DOAC)

Franck Verschuren

- Pulmonary embolism has long been a subject of clinical research in our center, this potentially life-threatening condition representing a significant diagnostic, therapeutic, and prognostic challenge for physicians. All aspects of pulmonary embolism have already been explored through the efforts of original local or international clinical studies, including its suspicion (potential significance of expired CO2 measurement for improving diagnostic efficacy), its diagnosis (validation of multidetector spiral CT), its ambulatory therapy (validation of the PESI score for outpatient treatment), and its risk stratification (the prognostic value of pro-B-Type natriuretic peptide; the PREP study for the evaluation of the prognostic factors). We recently participated in two major studies validating a new cut-off value for D-dimer measurement in suspected cases of pulmonary embolism (JAMA publication) as well as confirming the conditions governing use of thrombolysis as treatment of sub-massive pulmonary embolism (New England Journal of Medicine publication).
- Monitoring and managing anticoagulation induced by direct thrombin inhibitors (DOAC) in the perioperative period: This clinical research area has borne results in several prospective local and national studies, as well as in international studies on the perioperative management of patients on direct oral anticoagulants (DOACs):
  - to monitor hemorrhagic and thromboembolic events;
  - to validate biological tests in cases involving low DOAC concentrations;
  - to validate interruption of DOAC prior to commencing loco-regional anesthesia;
  - to validate bedside guidelines for help during the anesthesiology consultation for the perioperative management of DOACs.

Franck Verschuren

The Cliniques Universitaires Saint-Luc is one of the only hospitals in the world currently involved in the prospective evaluation of two reversal agents for cases of severe hemorrhage or when urgent surgery is required for patients under DOACs. The development of antidotes to DOACs is a major area of clinical research. One potential antidote is called Praxbind and is a humanized antibody fragment (Fab) which binds with a high affinity to the Factor IIa inhibitor Dabigatran. We have participated in an international multicenter study validating its efficacy and safety, with the preliminary data published in the New England Journal of Medicine in 2015.

Our center has been chosen by the European Medical Agency for an audit in order to speed up the development of this reversal agent. Another antidote, Andexanet alfa, is a recombinant engineered version of Human Factor Xa designed to reverse the activity of Factor Xa inhibitors Rivaroxaban and Apixaban. We are involved in a large sponsored international study to validate the efficacy and safety of this reversal agent.

Management of lung and respiratory parameters by improving oxygenation, intubation, and ventilation in patients

Dr L Putz, Dr L Bairy, Dr MA Nisolle, Dr AS Dincq, and Pr A Mayne

- Towards better teaching and thus improved understanding of airway management:

  Anesthesiology is an experienced unit for teaching and improving airway management. Several topics are currently being developed:
  - Managing respiratory tract function: (1) developing “simulation medicine” teaching techniques using simulation dummies for training doctors and nurses; (2) validating technical and material aids for tracheal intubation.
  - Understanding the impact of technical intubation on the voice by implementing and developing treatment techniques for pathologies of the tracheobronchial tree: (1) transbronchial thermoplasty in refractory asthma (with the pneumology unit), and (2) bronchial and tracheal prosthesis implantation following rigid bronchoscopy (with the pneumology unit).

Xavier Wittebolle, Jean Roeseler, Gregory Reychler, and Pierre-François Laterre

Investigating whether noninvasive ventilation should be administered in patients with acute hypoxemic respiratory failure before considering intubation. High-flow oxygen therapy applied through a nasal cannula may offer an alternative in patients with hypoxemia, preventing or delaying the need for intubation. We have participated in a large multicenter study, recently published in the New England Journal of Medicine, that demonstrated that treatment with high-flow oxygen, standard oxygen, or noninvasive ventilation did not result in significantly different intubation rates, yet administering high-flow oxygen significantly improved 90-day mortality rates.
ACUTE MEDICINE

Effect of mechanical ventilation on the quality of sleep in intensive care patients.

The patients at the ICU suffer deterioration of the architecture of their sleep, associated with an extensive fragmentation. This is especially true in patients on mechanical ventilation. Both mode and settings of the ventilation will affect sleep, causing apnea and asynchrony. The objective of this study is to evaluate the impact of ventilation in closed loop (whose settings are automatically adjusted to the patient’s needs: Intellivent-ASV) on sleep fragmentation (fragmentation index = number of awakenings per hour of sleep) of ICU patients compared to conventional ventilation (Pressure Support ventilation).

Managing acute intoxication and the role of genetic polymorphisms in poisoning

Philippe Hantson

- The intensive care unit is responsible for treating individual intoxications and evaluating potential new treatments in cases of rare and life-threatening poisonings. Albumin dialysis performed with the molecular adsorbent recirculating system (MARS™) offers a theoretical ability to effectively remove protein-bound drugs like amlodipine from the circulation, and was thus chosen for treating a severe poisoning with calcium channel blockers. The result revealed amlodipine to have a relatively short elimination half-life. We also observed insulin resistance, leading us to then study the potential interest of high-dose insulin for this calcium-inhibitor intoxication context.

- A recent review focused on the genetic polymorphisms of cytochrome CYP2D6 and their relevance in amphetamine, opioid analgesic, and antidepressant poisoning cases in humans. In particular, we demonstrated that CYP2D6 poor metabolizers of particular antidepressants were generally more prone to adverse effects.

Managing deep neuromuscular block during surgery

Pr Ph Dubois and Dr L Putz

- The induction and maintenance of profound neuromuscular block improves conditions for tracheal intubation and for operating during intra-abdominal laparoscopic surgery. The potential benefit in other types of surgery (orthopedics, throat, bronchial endoscopies, ...) remains unconfirmed.

- Spontaneous recovery from neuromuscular block may last longer than the surgery. Before recovering a clear threshold to ensure safety (TOF ratio: 0.9), the extubated patient risks experiencing breathing difficulties and pulmonary complications (residual paralysis state). Pharmacological reversal of the neuromuscular block using neostigmine only partially improves the situation.

- Sugammadex, a new reversal agent of rocuronium-induced block, has been proven able to interrupt deeper blocks more quickly at the end of surgery. This opens the door to many clinical opportunities that can benefit patients, anesthesiologists, and surgeons. Much further investigation must be undertaken to pinpoint and demonstrate these benefits, as well as their value in terms of cost.

- Objectively monitoring the neuromuscular transmission is key to intraoperative management of the block and preventing residual paralysis. Technical adjustments improve the function, and new devices are currently being developed.

Nutrition

Philippe Hantson

- Growing evidences show that the nutritional status of patient affects the perioperative mortality and morbidity. For oncologic patients, the weight loss may be an independent variable of the patient outcome. Thus, the level of malnutrition is correlated with a decrease in life expectancy, increased morbidity, including infection, and to a lesser response to carcinolytic treatment and the loss of independence. Our research team focuses the impact of malnutrition, this detection and this correction before surgery in ENT oncologic surgery and in lung transplantation surgery.
We have participated in a large multicenter study assessing the effect of body mass index on intensive care outcomes, demonstrating that being underweight was independently associated with a higher risk of 60-day in-hospital death, in comparison with being overweight.

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**Improving pain management in cases of pain-inducing procedures**

Charles Grégoire and Franck Verschuren

Pain is the most significant symptom that causes patients to require emergency care. Despite this, only 60% of these patients receive analgesic medication, and often late and inefficiently at that. Pain induced by a diagnostic or therapeutic medical procedure is typically short-lived, predictable, and may require intravenous sedation. Dexmedetomidine is an agonist of alpha 2 adrenergic receptors used to induce analgesia, anxiolysis, and mild to moderate sedation, associated with low risks of respiratory depression. Little information exists concerning dexmedetomidine in the current medical literature. We investigated whether the combination of dexmedetomidine and ketamine can achieve a level of conscious sedation within maximum safety conditions in emergency care, for which 40 patients with either wrist fracture or dislocation, pneumothorax requiring acute drainage or abscess requiring drainage were included.

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**Assessing the fragility of older patients during cardiac surgery**

Pr M Gourdin, Pr M de Saint-Hubert, Pr I Michaux, and Dr L Gabriel

The literature suggests to evaluate scales of risk stratification for surgical and perioperative morbidity in elderly patients undergoing cardiac surgery. A study team comprising an anesthesiologist, geriatrician, intensive care physician, and cardiologist is currently evaluating the clinical, biological, and sociological parameters of a cohort of geriatric patients in the cardiac surgery context.

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**Organ donation after a cardio-circulatory death: a valuable source for increasing the organ donation pool in Belgium**

Patrick Evrard, Philippe Hantson, and Franck Verschuren

Belgium is considered a leader and pioneer in organ donation and transplantation. Our center was the first in Belgium to implement a standard protocol for organ donation after cardio-circulatory death (DCD) in the early 2000s. These DCDs presently account for 80 of the 282 annual donors in Belgium. These donations may result from "expected cardiac arrests" of patients with incurable diseases in the ICU or from "unsuccessful resuscitation" of patients following out-of-hospital cardiac arrest. The intensive care, emergency, and anesthesiology units of our institution together play an important role in optimizing organ procurement from DCD donors. Prof. Patrick Evrard (UCL Mont-Godinne) has been in charge of implementing a national protocol for this category of donors. Future developments should now be undertaken to improve the technical approach by implementing the use of extracorporeal membrane oxygenation for multi-organ procurement, as well as a more structured policy for increasing the potential pool of donors in the Brussels area, and finally in helping other Belgian centers locally develop the same procedure.
**SELECTED PUBLICATIONS**


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