



Collaborative research: the access key to the future

MAURO ATTI - Scientific, Sales & Marketing Director Bellco srl

We warmly welcome you to the 2009 WCN and we take this opportunity to express our deep gratitude for the goals achieved thanks to the collaborative research in dialysis and all similar sectors that see in the patients' criticality and the personalization of the treatments the challenges to take up for today and for the future. Dialysis may without any doubt be placed among the points of

excellence of the European health systems, in particular of those of the South-Western area, both for the quality of treatment, probably the best in the world, and for the quality of research.

Most of the innovations in the history of dialysis originated in Italy, France, Spain and Belgium where annual mortality rate is among the lowest in the world.

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On the occasion of the World Congress of Nephrology 2009, Bellco is on line with its website:

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BELCO: BACK TO THE FUTURE

Bellco renews its commitment as leader in the development of 'Right therapies' in Dialysis and Intensive Care

Bellco, a biomedical company always active in the dialysis and intensive care sector, is optimistically looking at the future. Founded in 1972 by Mario Veronesi, the inventor of the Italian biomedical sector, it has always been in the forefront keeping a watchful eye on the needs of patients, doctors and healthcare professionals in renal replacement therapy. The credit for the design and

development of bicarbonate dialysis is due to Bellco and still today is the world reference 'standard'.

In 1989 it was the first company to introduce haemodiafiltration into clinical practice, which was later to be confirmed as the 'golden standard' of dialysis therapies.

Since 2005 the therapeutic excellence typical of Bellco is also applied to the field of *Intensive Care* with advanced and innovative life-saving products.

The historical 'BELLa Compagnia' - 'Good Company' - of Mirandola, led today by a new company team that includes the private equity funds ARGOS SODITIC for 60%, MPS Venture (Gruppo Montepaschi) for 30% and the management for 10%.

These international financial groups, strongly convinced of Bellco's potential and Healthcare markets opportunities, have decided to stay focused on renal care, being closer to customers' needs and fuel the growth.

The Bellco management seizes on this new challenge with a rich series of research projects in collaboration with the largest reference bodies in this sector and is increasingly open to the evolution of advanced therapies on the international scenario. On the European market, that stands out for the high therapeutical standards, Bellco sets itself as the leader in the field of advanced therapies.

Biocompatibility, cardiovascular stability, nutritional state and clearance efficiency are the priority challenges for Bellco's Therapeutic Dialysis: continual research and innovation



Bellco: the machine and the superheroes of HDF. From technological to therapeutic innovation.



Great technological innovation and a continual search for the 'right therapy', typical of the Bellco DNA, have brought forth **Formula® Therapy**. This machine gives nephrologists a vast and exclusive choice of innovative, accurate and flexible instruments for haemodiafiltration therapies. The excellence and extreme precision of Formula® Therapy are guaranteed by the Coriolis differential flow meter, a system that controls hourly ultrafiltration during treatment. The special **Double ultraFiltration System** of the dialysing solution together with the hydraulic circuit features (completely single-pass with a low hydraulic volume) provide the highest possible safeguard for the patient by producing an ultrapure dialysis fluid. Again with a view to supplying the 'right therapy', Formula® Therapy also offers the possibility to measure the dialysis dose through Kt/V, a universally recognised method, using the precise measurement of the dialysance, thanks to innovative and non invasive conductivity probes and the dialysis time. Formula® Therapy is the only machine that allows dialysis therapies totally customised. All this makes Formula® Therapy an excellent, precise, safe and versatile machine: in short, it is the "machine" suited to the Superheroes. Associating the Superheroes with the therapies (on-line HDF, Mid Dilution, PHF®, HFR Aequilibrium) underlines that it is the very therapies that give added value to the patients to guarantee a better quality of life. They are the response to a uremic population in continuous evolution, more and more sensitive because characterized by comorbidities and complications.

ARGOS SODITIC, founded in 1989, is an independent European Private Equity firm that operates in the risk capital sector (with offices in Paris, Milan, Geneva) focused on MBO/MBI in medium sized companies across Continental Europe. Despite the fact that 2008 was a challenging year for buy-out firms, Bellco represents the fourth acquisition of last year.

MPS Venture SGR deals in closed equity funds within Gruppo Montepaschi, the third largest Italian banking group with market shares in all the reference business areas. With over 30.000 employees, 3.000 branches and an articulated structure of distribution network, the Gruppo Montepaschi offers its services to over 6 millions of customers and stands as the promoter of an innovation strategy as development support. The main aim of the closed funds managed by MPS Venture is to finance the development of Italian companies operating in manufacturing, commerce and services.

for personalised solutions, aiming at ensuring a better quality of life. All this is guaranteed by a complete and integrated range of products and systems necessary for haemodialysis treatments.

In *Intensive Care* the feather in Bellco's cap is **CPFA®**, a life-saving treatment for septic shock, which today is the major cause of death in intensive care.

The data provided by GiViTi (Italian Group for the Assessment of Intervention in Inten-

sive Care) show over 26,000 cases of severe sepsis and over 6,000 cases of septic shock with a mortality rate of 70%. Over 750,000 cases of severe sepsis in the USA per year. Some preliminary results show how **CPFA®** allows a reduction in the mortality rate in the case of septic shock.

Bellco reasserts today its identity and history and distinguishes by its strong calling to innovation and development of advanced therapies ever more suited to Nephrology and Intensive Care.

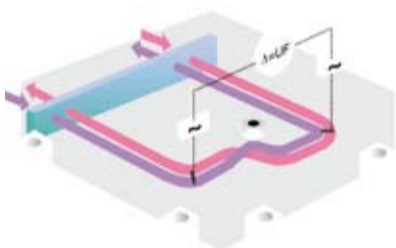
Coriolis: the state-of-the-art technology turns 20. Why a control system allows top performance

The heart of any modern haemodialysis machine is the system that controls hourly ultrafiltration during the replacement treatment. Various design solutions can be implemented to ensure the safety of continuous but especially accurate control of this variable. Bellco was the first company in the world that already way back in the eighties chose from the various possible solutions to utilize and patent a differential flow meter based on the Coriolis principle. Thanks to the continual technological updates its functioning is simple and linear: the flow meter automatically and mechanically reads the difference between the fluid flowing into the dialyser and the fluid flowing out of the dialyser. This measurement is made by positioning two oscillating U-shaped tubes where the IN and OUT flows run in countercurrent. The benefits of this valuable instrument lie in the ease of disinfection and in the possibility

of continuously measuring the hourly weight loss. Unlike other instruments this translates into enhanced therapeutic efficacy since the treatment time set is real. Other instruments, for example balancing chambers, require continuous interruptions of the dialysis fluid flow to the dialyser to allow emptying and filling the chambers. This affects the actual duration of the replacement treatment and hence the clearance of low-molecular-weight molecules in the case of standard dialysis and medium- to high-molecular-weight molecules in the case of haemodiafiltration therapies. Formula® Therapy, on the contrary, does not continuously

interrupt the dialysis fluid flow thus maximising performance of on-line haemodiafiltration therapies, such as **Mid Dilution**, which combines the advantages of pre- and post-dilution using only one specifically designed dialyser. The OLPür™ MD dialyser is made up of a fibre bundle divided into a peripheral ring and a core. The blood flows into the dialyser perfusing only the core fibres and running across them achieves **HDF in post-dilution**, since having reached the head of the dialyser opposite to the inlet it mixes with the ultrapure reinfusion fluid coming from the same dialysing solution; the blood then runs across the peripheral fibres achieving **HDF in pre-dilution**.

The Coriolis differential flow meter is further proof of the avant-garde and innovative solutions Bellco offers for the construction of haemodialysis machines that guarantee high therapeutic standards.



Coriolis principle applied to measurement of a fluid

For the determination of the flow, an oscillating U-shaped tube is used through which the fluid to be measured flows. This movement is proportional to the fluid mass flow rate and is caused by the Coriolis force acting on the tube. The entity of the Coriolis force depends on the mass moved, its speed in the system and consequently the mass flow rate. The Coriolis forces produced in the measuring tube cause a phase shift in the tube oscillations. The mass flow rate determines a deceleration in oscillation at the tube inlet and an acceleration at the outlet. The phase difference between the inlet and the outlet increases as the mass flow rate increases. Electrodynamical sensors record the tube oscillations at the inlet and the outlet.

Curiosity

In the oil industry an appropriately sized flow meter is used to determine the amount of oil loaded/unloaded to/from the oil tankers to allow easily measuring the fluid mass moved.

Double filtration of the whole dialysis fluid. Safety is not an option!

The main characteristic of on-line haemodiafiltration is the possibility of maximising the convective flows without having to resort to infusion bags, which can be a strength but can also become a weakness if no particular attention is paid to the purity of the infusion fluid. The new Formula® Therapy equipment has a good three different filtration stages, each using membranes with different characteristics and adsorption in order to guarantee absolute purity of both the infusion and the dialysis fluid.

If we observe the formation of the dialysis/infusion fluid we see that the liquid passes through an ultrafilter positioned immediately at the inlet, called Multipure, which holds back dirt residues and even bacteria and endotoxins thanks to its positively charged Posydyne N66® membrane. After the mixing with the concentrate solutions, the dialysing fluid just produced passes through the

Double Filtration System (DFS) composed of two ultrafilters with a Medisulfone® membrane positioned in series and thoroughly tested before each treatment. The two ultrafilters represent an efficient barrier to endotoxins and pyrogens.

DFS acts not only on the infusion fluid but also on the dialysis fluid. This exclusive feature is very useful in case of backfiltration where for various reasons a passage of dialysing solution through the dialyzer membrane towards the blood may occur. As to the infusion fluid, the external connection machine-disposable is a critical point as regards contamination of the extracorporeal circuit and consequently the patient. To solve this potential problem Formula® Therapy has a special connector which is fully disinfected during the disinfection process of the equipment.



Despite all these measures being already a unique solution in terms of safety, the 'safety first' concept is the utilization guideline in on-line **PHF®** therapy. The last ultrafilter for the reinfused solution is directly positioned on the dialyser (double chamber dialyser). Consequently, being sterile, single-use and in direct contact with the blood, it is the fourth and final barrier against possible contamination: in fact, there is not a single unprotected point between the last ultrafilter and the patient. Due to this peculiarity the PHF® therapy is the safest HDF on-line therapy in the world.

Formula® The

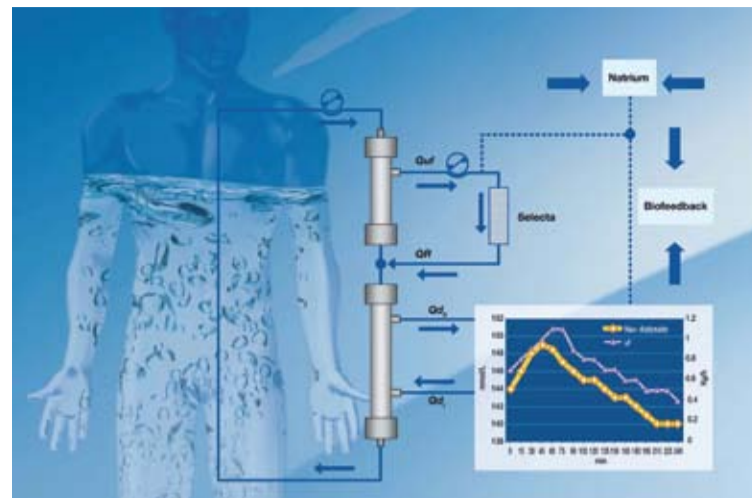


rapy and HDF

Selective clearance and feedback: HFR Aequilibrium

Bellco offers the right therapies in response to the needs of uremic patients with constant age increase, suffering from clinical complications and comorbidities and more sensitive to intradialytic cardiovascular problems. **HFR Evolution®** is an integrated haemodiafiltration system: its dual-chamber filter with the adsorbent cartridge **Selecta** regenerates the patient's ultrafiltrate, which is used as the reinfusion liquid, thus avoiding problems of sterility and apyrogenicity of the reinfusion liquid. In substitution treatments of patients suffering from chronic uraemia, **Selecta** offers numerous clinical advantages, especially with regard to the removal of specific toxins. **Selecta** offers an 'active' type of removal through selective adsorption, unlike the simple 'passive' removal that exclusively depends on hydraulic permeability and on the diffusive permeability of the membrane.

HFR Aequilibrium is the Bellco haemodiafiltration therapy that allows to treat patients suffering from MIA syndrome, as per HFR indications, as well as patients with intradialytic hypotension and high sensitivity to the unbalance syndrome. This is a biofeedback therapy automatically controlled by the **Formula® Therapy** machine. The heart of the system is the bicompartimental mathematical model **Aequilibrium** which allows modula-



ting the hourly ultrafiltration and the sodium concentration in the dialysis fluid during the dialysis session in order to ensure greater intradialytic pressure stability in relation to the patient's response. The patient is controlled instant by instant by the **Natrium** biosensor fitted in **Formula® Therapy**, which continuously checks the conductivity of the ultrafiltrate - about 95% due to the concentration of sodium - by means of a disposable probe integrated in the endogenous infusion circuit. The information received from the **Natrium** sensor allows the **Aequilibrium** mathematical model to more accurately control the weight and sodium removal during the treatment. The main advantage of this technique is precisely that only the sodium the patient has taken in the interdialytic period is removed resulting in a balanced condition. **Aequilibrium**

controls weight removal and sodium extraction, focusing in particular on weight removal in the first half and on sodium removal in the second half of the dialysis session, achieved by means of conductivity modulations and hourly ultrafiltration. **Natrium** and the **Aequilibrium** mathematical model start to dialogue from the 15th minute of treatment guaranteeing that the patient reaches the natriemia end point at the end of the dialysis set. More in-depth tests demonstrated that, compared to bicarbonate dialysis, the stability of the circulating volume significantly increased with a substantial decrease of intradialytic hypotensive phenomena. **Formula® Therapy** is confirmed as a new-generation machine able to continually monitor the patient and appropriately modify the clinical recipe in order to guarantee the end points the nephrologist establishes.

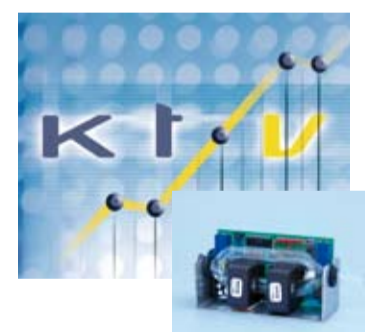
Adequacy: not only (but also) Kt/V. The perfection of non invasive- technology

Clinical evaluation of the adequacy of the dialytic treatment is a fundamental objective. An evaluation criterion was established many years ago, which, despite its limits, still today represents a simple and effective index: **Kt/V**. This index expresses the dialysis dose administered evaluating the volume of body water cleared of urea with respect to the total body water of the patient.

There are various mathematical approaches to calculate this index. A valid alternative is direct measurement by the monitor during the treatment. Many machines are capable of making this measurement and practically all of them apply the same method whereby the ionic dialysance is measured by means of conductivity probes. The fundamental difference between the various monitors is the nature and accuracy of the probes used. **Formula® Therapy** utilizes inductive probes

that offer unquestionable advantages as regards reliability and non-invasiveness.

Kt/V represents an immediate index on clearance of small molecules, an essential goal to be met, but clearly dialytic adequacy also demands excellence in order to achieve other objectives. That is why Bellco's online HDF guarantees not only excellent clearance of small molecules, but also excellent removal of medium-sized molecules thanks to the high performance of the **Phylther®** dialysers. The polyphenylene membrane with which **Phylther®** dialysers are equipped offers extremely regular pore distribution so that there is a high cut-off yet minimal protein loss. In addition, the 'active centres' on its internal surface significantly reduce protein cake effect and guarantee excellent performance throughout the treatment. Another fundamental element is the composition of the rein-



fusion fluid, which must have high levels of tolerability and purity. The **Lympha®** acid concentrates offer real and exclusive online HDF without acetate whose benefits have a strong clinical impact.

For all practical purposes, the replacement solution is to be considered a drug that must be dosed appropriately; that is why **Formula® Therapy** is equipped with an automatic reinfusion flow control system which allows optimising the total exchange volume taking into account the actual conditions of each single session.

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The therapeutic excellence is the child of many factors and the quality of research is undoubtedly one of the parents. The Research, the critical look at every aspect of the treatment and the desire to understand have led to new discoveries but also to more effectively tackling the clinical problems to ensure a better quality of life. What are the reasons of these goals? On the one hand, because of the active propositional nephrology at top international

the universities should be underlined. The degree courses in bioengineering, in particular in Bologna and Milan, have produced specialised engineers who have fed the research facilities and the industries around the town of Mirandola. Among these is Bellco, whose track record includes some of the key innovations in dialysis: bicarbonate dialysis, the first company to introduce it on its machines and today represen-

benchmark therapy for patient well-being and a higher life expectancy (about 30%), Bellco is continuing on the road of innovation with three new haemodiafiltration therapies for which at least 30 clinical trials are in progress on international level, involving universities and hospitals all over Europe.

We in fact think that there are still big challenges ahead against standardisation and for personalisation in dialysis, for example, bringing down the albumin wall. In dialysis, uremic toxins are cleared through semipermeable membranes. Today we cannot clear molecules with a molecular weight of more than 60,000 D as there would be a massive loss of albumin which would have a negative impact on patient survival. Thanks to an exclusive therapy which allows albumin recovery and restitution, we are studying the use of new membranes to overcome this historical barrier. Another major problem is hypotensive collapse during dialysis.

During dialysis 3-5 litres of water and salts are eliminated in a few hours while in normal conditions they are eliminated in 3

days. The consequence is high stress to an already compromised cardiovascular system. We are conducting two clinical studies: one is aimed at predicting a hypotensive phenomenon before it occurs by means of in-line sensors and the other at applying a patient-machine feedback system.

develops into more and more serious states and finally leads to septic shock, fatal in 70% of cases.

We have developed a therapy whereby the sepsis mediators are removed from the plasma and it seems to drastically reduce the mortality rate.

The Italian Group for the Asses-

“There are still big challenges ahead against standardisation and for personalisation in dialysis”

levels, on the other hand, the growth of a network of dialysis-related industries since the sixties.

Thanks to the productive osmosis between clinics, engineers and researchers many fruitful results were obtained.

The invaluable contribution of

ting 100% of worldwide dialysis; one of the first machines 'dedicated' to a single patient; the introduction of haemodiafiltration into clinical practice and the first dedicated congress in 1989.

Now that this dialytic method has been established as the

1989 PUGNOCHIUSO
1991 VELDEN
2004 MONASTIER
2007 PUGNOCHIUSO
2009

SOME OF THE LATEST TESTIMONIAL EVENTS OF THE COLLABORATIVE RESEARCH WAY

Encouraging results have already led to some publications. Our ambition is to extend the use of our technology to other fields, such as heart failure, myeloma, respiratory syndromes and especially sepsis. Sepsis, the primary cause of death in intensive care, starts with a simple infection which

segment of Operations in Intensive Care together with the Mario Negri Institute has decided to promote an independent study to validate the results. 'The connective issue' between industry, universities and health facilities may permit developing new ideas and doing so as a matter of urgency.

bellco
The right therapy way

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Bellco wishes you the very best of WCN 2009!
We're pleased to invite you to the Italian Style Happy Hour starting from 4 p.m. on May 23rd and 24th at Bellco stand no. E04-D07

CREDITS

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