

The background of the entire page is a photograph of a laboratory. Several scientists in white lab coats are working at their stations. In the foreground, a scientist is looking through a microscope. In the background, another scientist is working at a computer workstation. The scene is brightly lit, suggesting a modern and professional research environment.

SCIENTIFIC REPORT
2007

ISTITUTO CLINICO
HUMANITAS
Istituto di Ricovero e Cura
a Carattere Scientifico



SCIENTIFIC
REPORT

2007





SUMMARY

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The year 2007 was an extremely important year for research in Humanitas. Research has enabled, throughout the year, to create new and important links with the national and international scientific community. This has been possible also thanks to the opening of the new Research, Teaching and Rehabilitation Centre, where ample space is dedicated to the laboratories - equipped with the most advanced technology - multimedial library and conference centre. Already accommodated in these new spaces are the basic and translational research laboratories with a layout which favours a wide range of research so as to include



researchers coming from various branches of medicine.

Everyone concerned has been committed to ensuring quality of care, to clinical transference of research in a context aimed at maintaining a high standard of safety for operators, patients and visitors.

Training programmes for nurses, doctors and researchers have carried on throughout the year; in particular those activities of high scientific level already supported in the past regarding diverse subjects and accredited with ECM recognition.

These initiatives have given the opportunity to invite speakers of renowned international fame, experts mainly in the fields of immunity, oncology and gastroenterology.

Involvement of Humanitas researchers has grown in this context, both as coordinators and heads of departments participating in projects financed by third parties from public and private sectors. We believe this important result to be an obvious sign of the fervour of the Institute's scientific life, whose efficacy has been assessed by external referees nominated by the financiers.

In confirmation of this result is the publication of papers in the most important national and international journals, the total Impact Factor of which reached 724 points.

My thanks go to all those people who with their daily commitment have shared the inspirational principles of Humanitas, the results of which are only partly represented in this presentation. Special thanks also to the foundations which accompany us in our activities and to all the individual citizens who have supported the activities of care, assistance and research of our Institute.

Ivan Colombo
Chief Executive Officer

The key element that has characterized scientific life in 2007 of Istituto Clinico Humanitas is represented by opening of the new Research and Teaching Centre in the area of Perseghetto, opposite Humanitas. The new building, which includes in an integrated context experimental research, clinical medicine (rehabilitation) and teaching is an opportunity and a challenge.

The new Centre is a symbol of integration that



we strive to obtain between bench work, bed side patient care and teaching to scientists and physicians. It has provided and will provide an opportunity to recruit new independent scientists as well as to train a new generation of scientists and physician-scientists. Indeed, over the past year, recruitment of new groups and scientists has been pursued. In terms of scientific productivity, as assessed by conventional criteria, (impact factor and level of impact factor of journals where Istituto Clinico Humanitas publishes), the past year has seen a steady increase both in terms of quantity and in terms of quality. In addition, a number of projects have seen the integrated efforts of bench research with clinical investigation. The scientific activity of Istituto Clinico Humanitas has been and will be integrated at an international level in many respects. Seminars and the now prestigious Humanitas Lectures have provided a forum for cultural exchange within our institution and at large with the milanese and northern Italy scientific

community. Scientific life has also been characterized by the recruitment and work with us of a significant number of foreign fellows, at different levels, from PhD students to visiting scientists.

Finally, a substantial amount of the research efforts conducted in our institution are supported by international funding agencies or charities, most notably the European Commission. Diverse institutions ranging from private pharmaceutical companies to charities such as Italian Association for Cancer Research, Telethon, Fondazione Cariplo, Fondazione De Andrè, have supported our research activity. No less important are small donations from individual donors. These represent a trust of confidence in our ability to conduct research for human health which we must live up to.

The scientific activity of 2007 has added a new dimension to our efforts. For the first time, we have reached the community, by engaging in an interaction with High Schools in the Rozzano area. We are strongly committed to fostering understanding and appreciation of science in the community, with a special focus on young generations. I am confident that the work done in 2007 provides a firm basis for growth and improvement in the coming years to meet our mission to foster science and clinical medicine in our locations in Rozzano, Bergamo, Turin, Catania and Castellanza.

Alberto Mantovani
Scientific Director



ACTIVITIES DATA

ADMISSIONS

Year 2007	Elective Inpatient Admissions	Emergency Inpatient Admissions	Total Inpatient Admissions	Access to Day-Hospital	Overall Total
Anaesthesia and Cardiosurgery Intensive Care	13	19	32	-	32
Anaesthesia Intensive Care	24	72	96	-	96
Clinical Cardiology	295	187	482	3	485
Haemodinamics and Invasive Cardiology	791	257	1,048	1	1,049
Cardiology 3	112	198	310	55	365
Cardiosurgery	530	208	738	-	738
General Surgery	743	96	839	189	1,028
General Surgery 3	537	60	597	212	809
General and Minimally Invasive Surgery	930	231	1,161	308	1,469
Neurosurgery	519	249	768	155	923
Plastic Surgery	386	21	407	299	706
Plastic Surgery 2	447	6	453	315	768
Thoracic Surgery	849	118	967	208	1,175
Vascular Surgery	415	97	512	162	674
Vascular Surgery 2	311	88	399	140	539
General Medicine - Dermatology	31	25	56	184	240
Electrophysiology and Electrostimulation	531	221	752	3	755
Endocrinology and Diabetology	51	72	123	270	393
Orthopaedic Physiotherapy	1,587	-	1,587	1	1,588
Neurohabilitation	232	1	233	-	233
Cardiorespiratory Rehabilitation	466	1	467	-	467
Gastroenterology	428	442	870	399	1,269
Gynaecology	395	41	436	276	712
Reproductive Medicine	196	27	223	3,439	3,662
Oncologic Gynaecology	111	14	125	37	162
Epathology	411	303	714	272	986
Pneumology	126	539	665	30	695
Emergency Medicine	4	606	610	6	616
Nephrology	133	478	611	72	683
Neurology 2	52	203	255	28	283
Neurology 3	94	46	140	-	140
Nuclear Medicine	140	-	140	1	141
Ophthalmology	235	36	271	590	861
Medical Oncology and Haematology	1,721	646	2,367	12,661	15,028
Otorhinolaryngology	606	20	626	35	661
Orthopaedics	694	11	705	809	1,514
Orthopaedics Hip and Knee Prothesic Surgery	1,285	26	1,311	234	1,545
Orthopaedics Hand Surgery	69	73	142	751	893
Orthopaedics Artroscoy Surgery	261	1	262	108	370
Pediatric and Neuro Orthopaedics Surgery	179	8	187	127	314
Orthopaedics Shoulder Surgery in Artroscoy	694	8	702	899	1,601
Orthopaedics Foot Surgery	152	-	152	-	152
Rheumatology	73	38	111	549	660
Radiotherapy and Radiosurgery	9	-	9	-	9
Traumatology I	112	2	114	95	209
Traumatology II	137	599	736	117	853
Thrombosis Center	9	-	9	-	9
Coronary Care Unit	3	22	25	-	25
Urology	1,355	344	1,699	335	2,034
Stroke Unit	40	376	416	-	416
Totale	19,524	7,136	26,660	24,375	51,035

ACTIVITIES DATA

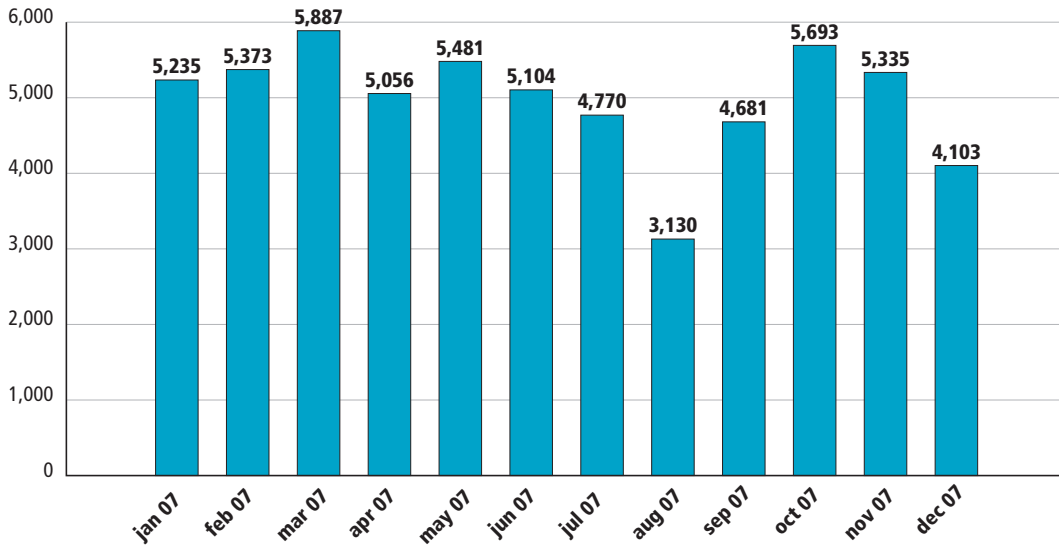
OUTPATIENT SERVICES

Year 2007	Outpatients	Outpatients from Emergency centre	Total Outpatients	Inpatients	Pre-post Admission	Overall total
Anaesthesia Intensive Care	872	82	954	1,515	5,257	7,726
Cardiology 3	3,867	343	4,210	462	106	4,778
Cardiorespiratory Rehabilitation	2,633	-	2,633	23,987	63	26,683
Cardiosurgery	722	14	736	74	21	831
Clinical Cardiology	21,693	1,549	23,242	8,051	29,151	60,444
Coronary Care Unit	343	53	396	286	4	686
DAY HOSPITALSurgery	494	-	494	276	7,543	8,313
Digestive Endoscopy	11,854	127	11,981	5,133	122	17,236
Echocardiography	5,364	69	5,433	6,085	504	12,022
Echography	36,584	1,044	37,628	5,498	709	43,835
Electrophysiology and Electrostimulation	3,657	200	3,857	451	15	4,323
Emergency Department	812	61,652	62,464	12,766	79	75,309
Endocrinology and Diabetology	8,995	4	8,999	1,011	476	10,486
Epathology	1,924	14	1,938	884	85	2,907
Gastroenterology	3,835	1	3,836	282	73	4,191
General and Minimally Invasive Surgery	6,139	172	6,311	452	2,707	9,470
General Medicine - Dermatology	19,249	833	20,082	688	579	21,349
General Surgery	3,490	2	3,492	156	1,629	5,277
General Surgery 3	4,266	-	4,266	65	1,578	5,909
Gynaecology	15,051	395	15,446	279	950	16,675
Haemodynamics and Invasive Cardiology	695	202	897	233	496	1,626
Interventional Radiology	146	7	153	2,221	1	2,375
Laboratory Tests	877,881	263,139	1,141,020	1,208,474	259,273	2,608,767
Medical Oncology and Haematology	22,734	169	22,903	8,726	803	32,432
Nephrology	61,005	44	61,049	5,545	87	66,681
Neurohabilitation	1,967	-	1,967	18,555	111	20,633
Neurology 2	16,639	655	17,294	1,229	97	18,620
Neurology 3	3,367	146	3,513	452	27	3,992
Neurosurgery	4,069	386	4,455	603	167	5,225
Nuclear Medicine	7,667	-	7,667	860	372	8,899
Oncologic Gynaecology	1,915	210	2,125	62	290	2,477
Ophthalmology	42,458	2,038	44,496	687	6,895	52,078
Orthopaedic Physiotherapy	27,705	-	27,705	38,651	2,864	69,220
Orthopaedics	13,933	5	13,938	288	2,555	16,781
Orthopaedics Arthroscopy Surgery	258	-	258	-	-	258
Orthopaedics Foot Surgery	289	-	289	-	36	325
Orthopaedics Hand Surgery	6,996	4,579	11,575	173	3,592	15,340
Orthopaedics Hip and Knee Prothetic Surgery	4,437	13	4,450	50	95	4,595
Orthopaedics Shoulder Surgery in Arthroscopy	5,566	6	5,572	51	2,559	8,182
Otorhinolaryngology	11,289	3,218	14,507	1,348	1,413	17,268
Pathology	22,441	30	22,471	8,745	5,868	37,084
Pediatric and Neuro Orthopaedics Surgery	2,364	1	2,365	3	277	2,645
Plastic Surgery	3,492	258	3,750	206	1,695	5,651
Plastic Surgery 2	1,686	-	1,686	79	1,900	3,665
Pneumology	5,998	7	6,005	1,475	745	8,225
Radiology and Diagnostic Imaging Division	76,308	29,444	105,752	54,611	13,077	173,440
Radiotherapy and Radiosurgery	67,846	-	67,846	5,338	792	73,976
Reproductive Medicine	21,192	324	21,516	193	2,219	23,928
Rheumatology	5,750	18	5,768	219	22	6,009
Stroke Unit	7,120	762	7,882	2,102	59	10,043
Thoracic Surgery	1,282	32	1,314	907	806	3,027
Thrombosis Center	25,463	698	26,161	2,977	1,765	30,903
Traumatology I	358	29	387	4	259	650
Traumatology II	3,091	2,140	5,231	473	937	6,641
Urology	10,085	879	10,964	1,048	1,426	13,438
Vascular Surgery	6,181	93	6,274	2,012	1,191	9,477
Vascular Surgery 2	4,572	82	4,654	1,100	911	6,665
Totale	1,528,089	376,168	1,904,257	1,438,101	367,333	3,709,691

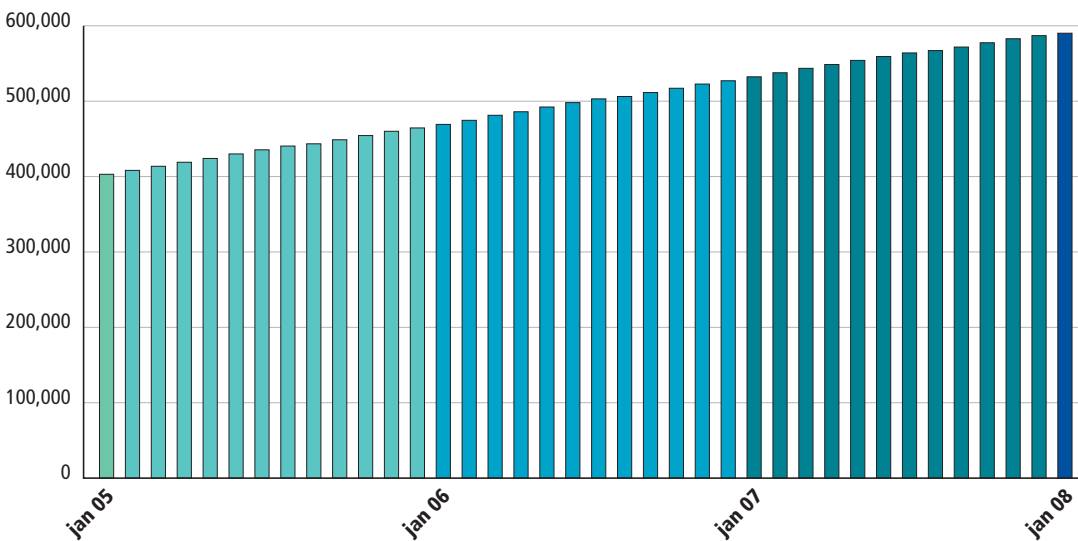
SECTION 1

ISTITUTO CLINICO HUMANITAS ESTIMATE OF PATIENTS

Monthly data



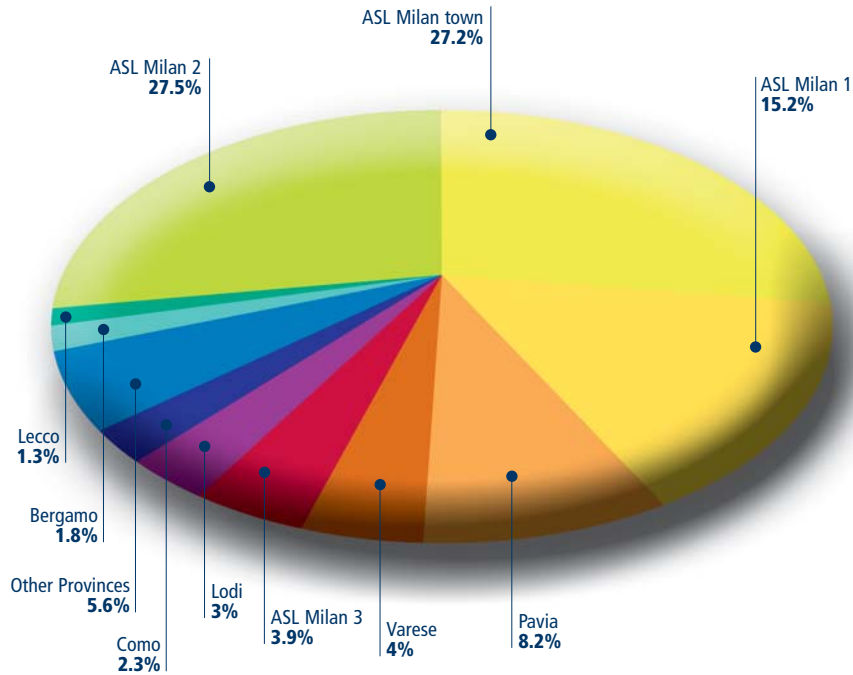
Cumulative



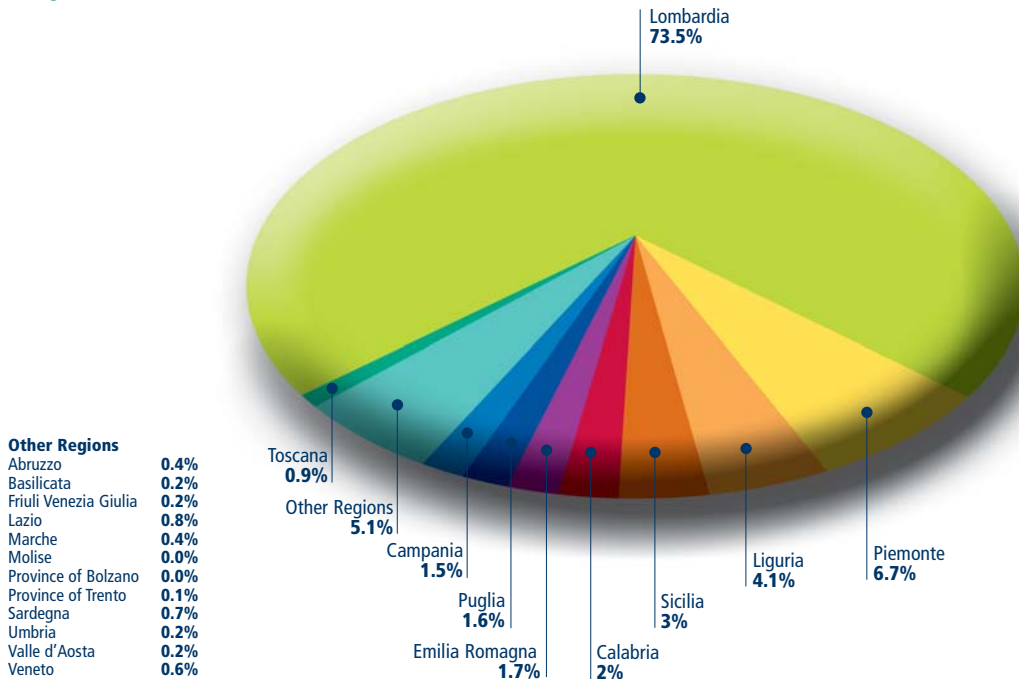
SECTION 2

PATIENTS' ORIGIN

Lombardia



Italy

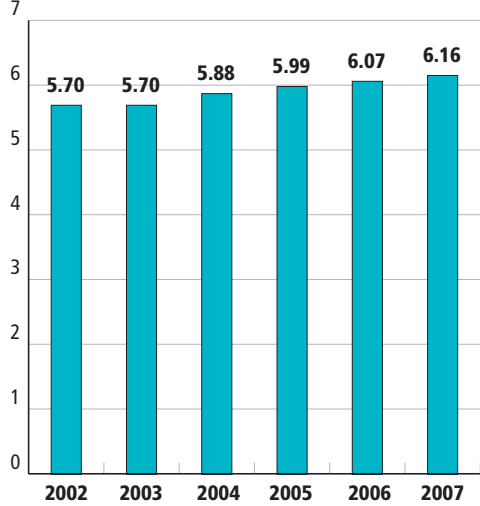


Other Regions	
Abruzzo	0.4%
Basilicata	0.2%
Friuli Venezia Giulia	0.2%
Lazio	0.8%
Marche	0.4%
Molise	0.0%
Province of Bolzano	0.0%
Province of Trento	0.1%
Sardegna	0.7%
Umbria	0.2%
Valle d'Aosta	0.2%
Veneto	0.6%

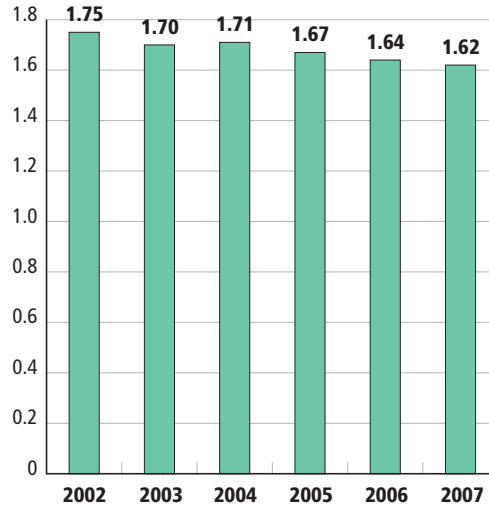
SECTION 3

CASE MIX ANALYSIS

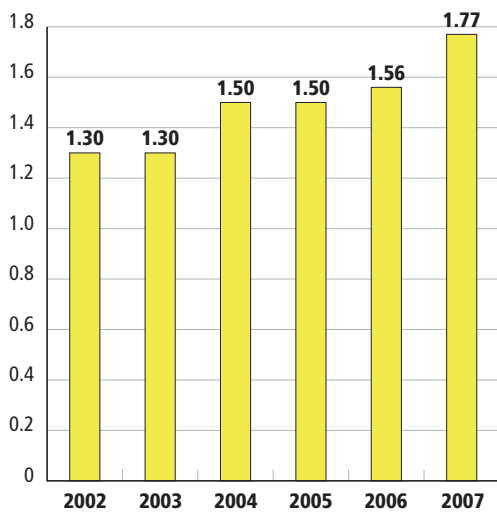
Average length of stay



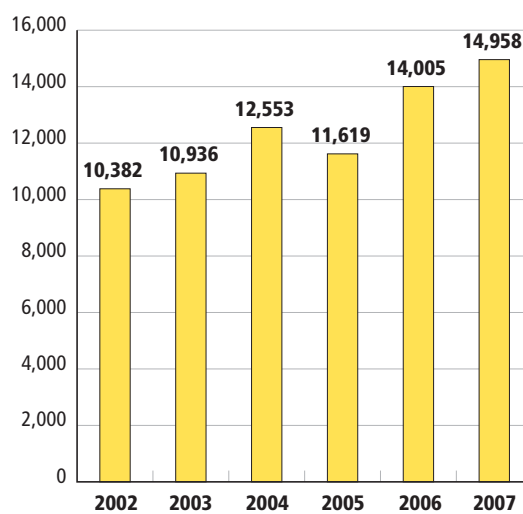
Relative weight



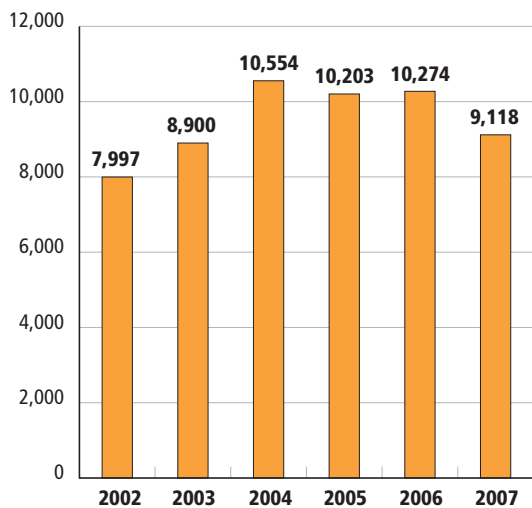
Mortality in-Hospital



Medical Day Hospital



Surgical Day Hospital

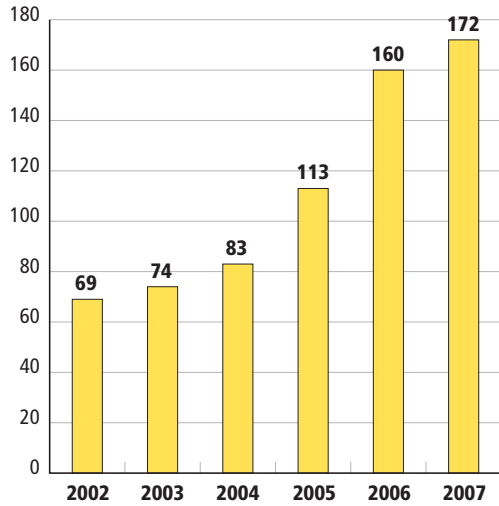


SECTION 4

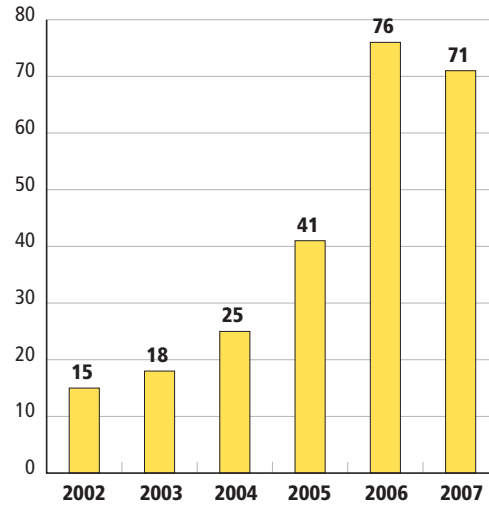
SCIENTIFIC PRODUCTION INDICES

GENERAL

Total papers reviewed

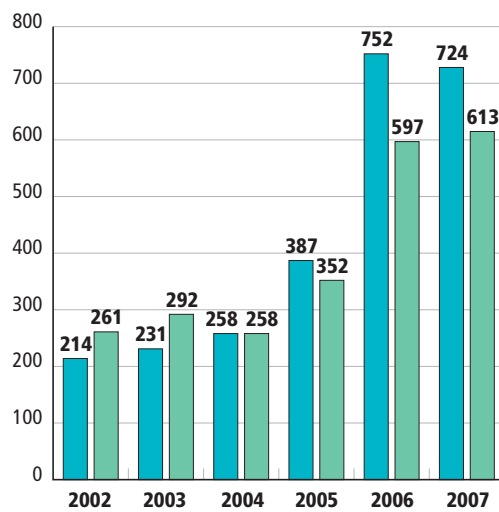


GASTROENTEROLOGY

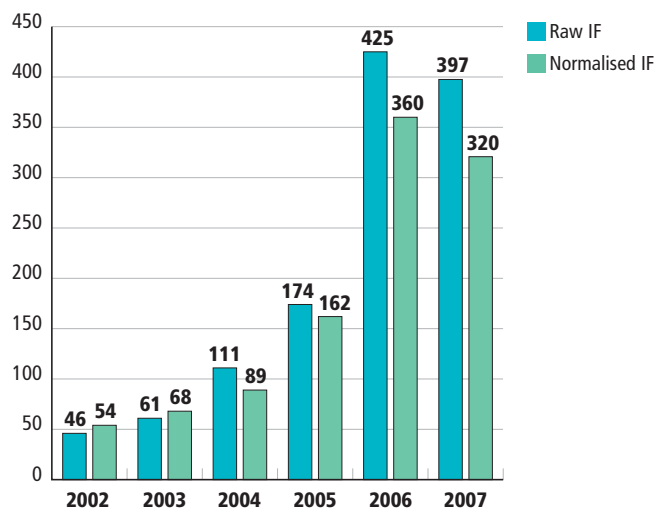


GENERAL

Total Impact Factor

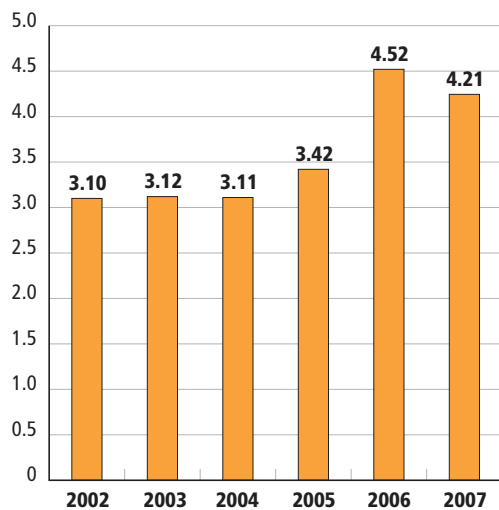


GASTROENTEROLOGY

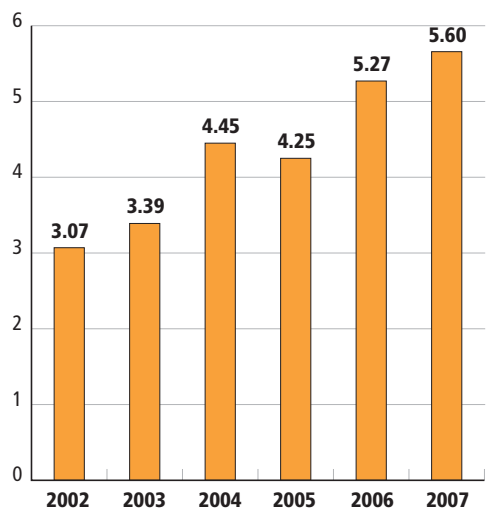


GENERAL

Average Impact Factor



GASTROENTEROLOGY

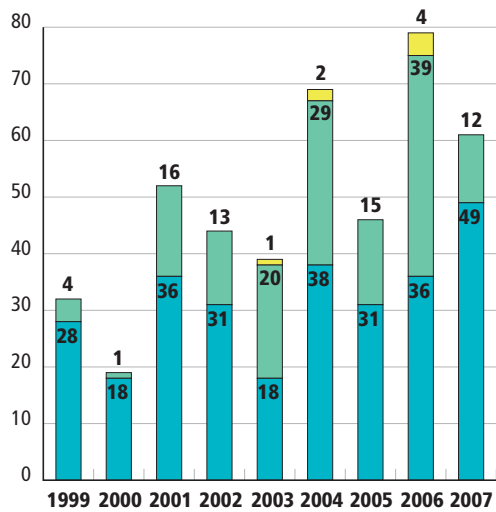


SECTION 5

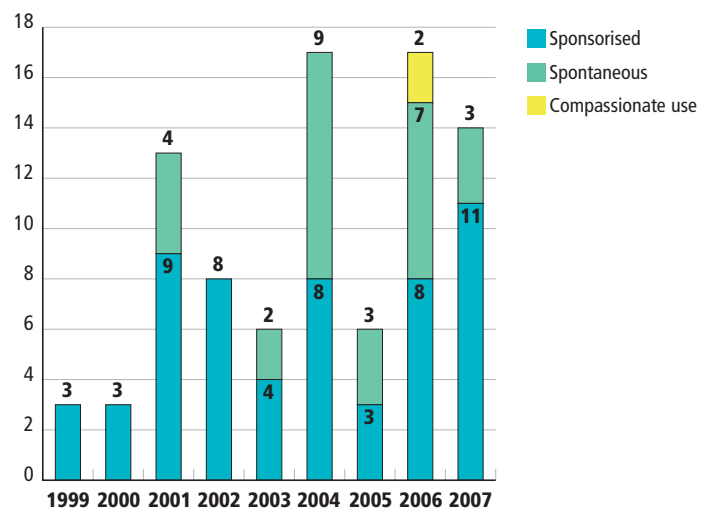
RESEARCH AND CLINICAL INNOVATION INDICES

GENERAL

Total number of studies

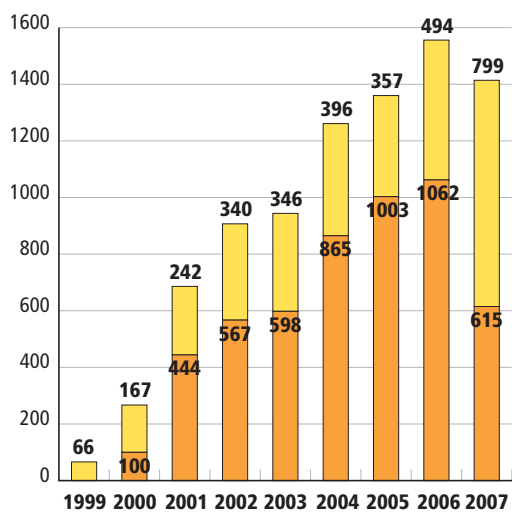


GASTROENTEROLOGY

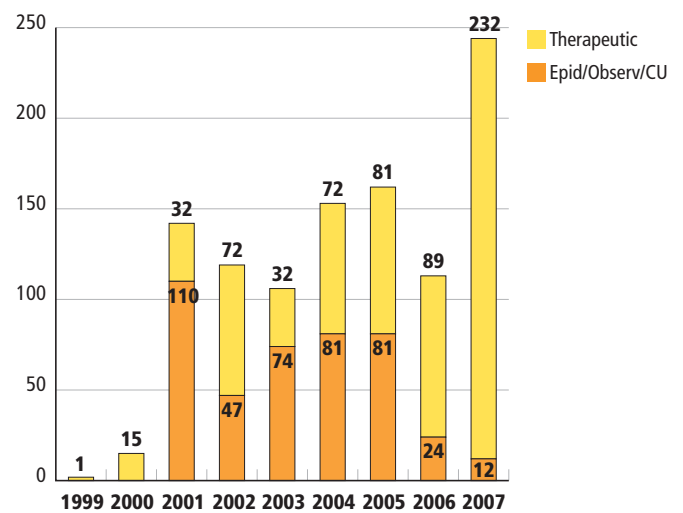


GENERAL

Number Patients Enrolled



GASTROENTEROLOGY





RESEARCH ACTIVITIES

This part of the Scientific Report contains:

- a list of the Heads of Divisions and staff that participated in research projects in the areas of:
gastroenterology, oncology, cardiology, surgery, medicine and neuro-rehabilitation
- the abstracts of main papers published during 2007.

For further information and physicians' CV: www.humanitas.it

MEDICAL ONCOLOGY AND HAEMATOLOGY DEPARTMENT



Unit Director: **Dr. Armando Santoro**

STAFF

Dr. Antonella Anastasia	Dr. Monica Demarco	Dr. Barbara Sarina
Dr. Monica Balzarotti	Dr. Barbara Ercoli	Dr. Licia Vanessa Siracusano
Dr. Alexia Bertuzzi	Dr. Isabella Garassino	Dr. Inna Timofeeva
Dr. Giuseppe Biancofiore	Dr. Giuseppe Gullo	Dr. Luca Tondulli
Dr. Stefania Bramanti	Dr. Natalia Locopo	Dr. Maria Chiara Tronconi
Dr. Federico Cappuzzo	Dr. Massimo Magagnoli	Dr. Elisabetta Todisco
Dr. Carlo Carnaghi	Dr. Giovanna Masci	Dr. Paolo Andrea Zucali
Dr. Luca Castagna	Dr. Rita Mazza	Dr. Monica Zuradelli
Dr. Raffaele Cavina	Dr. Manuela Mencaglia	Costantina Buonerba
Dr. Giovanni Luca Ceresoli	Dr. Andrea Nozza	Rita Finotto
Dr. Claudia D'Alessandro	Dr. Valentina Nucca	
Dr. Fabio De Vincenzo	Dr. Lorenza Rimassa	

PET AND NUCLEAR MEDICINE



Unit Director: **Dr. Arturo Chiti**

STAFF

Dr. Gianluigi Ciocia	Dr. Sara Tadayyon
Dr. Marcello Rodari	Dr. Giovanni Tosi

RADIOTHERAPY AND RADIOSURGERY



Unit Director: **Dr. Marta Scorsetti**

STAFF

Dr. Stefania Agostino Ninone	Dr. Paola Lattuada	Dr. Gaetano Urso
Dr. Mario Bignardi	Dr. Pierina Navarra	Dr. Sabrina Vigorito
Dr. Simona Castiglioni	Dr. Sara Pentimalli	

GENERAL AND MINIMALLY INVASIVE SURGERY



Unit Director: **Prof. Riccardo Rosati**

STAFF

Dr. Francesco Battafarano	Dr. Diego Mariani	Dr. Maria Grazia Turconi
Dr. Ugo Elmore	Prof. Alberto Peracchia	Dr. Mauro Pietro Zago
Dr. Hayato Kurihara	Dr. Uberto Fumagalli Romario	

GENERAL AND ONCOLOGIC SURGERY

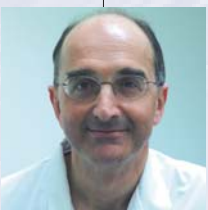


Unit Director: **Dr. Roberto Doci**

STAFF

Dr. Pietro Francesco Bagnoli	Prof. Leandro Gennari	Dr. Arianna Rubino
Dr. Andrea Brocchi	Dr. Sergio Orefice	Dr. Carlo Marco Rossetti
Dr. Luca Cozzaglio	Dr. Vittorio Lorenzo	
Dr. Marco Eboli	Quagliuolo	

GENERAL SURGERY III



Unit Director: **Prof. Marco Montorsi**

STAFF

Dr. Paolo Pietro Bianchi	Dr. Daniele Del Fabbro
Dr. Stefano Bona	Prof. Guido Torzilli

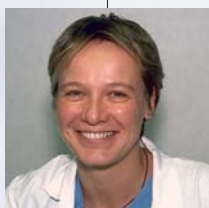
GENERAL ANAESTHESIA AND INTENSIVE CARE DEPARTMENT

Unit Director: **Dr. Giovanni Bordone**

STAFF

Dr. Alessandra Alfano	Dr. Paola Matilde De Pietri	Dr. Gian Luca Marinelli
Dr. Enrico Arosio	Dr. Orazio Difrancesco	Dr. Juan Carlos Pastore
Dr. Jana Balazova	Dr. Cristina Dominoni	Dr. Laura Rocchi
Dr. Gian Michele Battistini	Dr. Nadia Fusilli	Dr. Giorgio Signoroni
Dr. Valentina Bellato	Dr. Vittorio Gavazzeni	Dr. Debora Sportiello
Dr. Gabriella Brancato	Dr. Alessandro Gaggianese	Dr. M. Rosaria Spoto
Dr. Stefania Brusa	Dr. Donatella Girardello	Dr. Guido Turio
Dr. Franco Cancellieri	Dr. Enrico Giustiniano	Dr. Luis Enrique Velarde
Dr. Cristina Carlino	Dr. Sabrina Malara	Carrera
Dr. Vincenzo Cesina	Dr. Silvia Eleonora Malossini	

SURGICAL DAY HOSPITAL

Unit Director: **Dr. Roberta Monzani**

STAFF

Dr. Marco Babbini	Dr. Stefania Gherardi	Dr. Beatrice Rossi
Dr. Francesco Carrera	Dr. Annarita La Rocca	Dr. Claudio Sacchi
Dr. Laura Crozzoli	Dr. Oreste Davide Montino	Dr. Alessandro Scafella
Dr. Chiara Ferrari	Dr. Maria Del Carmen Rodriguez	

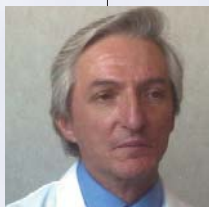
ECHOGRAPHY

Unit Director: **Dr. Giovanni Morandi**

STAFF

Dr. Marina Canevini	Dr. Paola Magnoni	Dr. Ana Lucia Ramos
Dr. Pasquale De Nittis	Dr. Paolo Malerba	Dr. Cristiana Magnaghi

LABORATORY TESTS

Unit Director: **Dr. Alessandro Montanelli**

STAFF

Dr. Barbara Barbieri	Dr. Erminia Casari	Dr. Margherita Longo
Dr. Daniela Bettio	Dr. Elisabetta Corsi	Dr. Rossana Mineri
Dr. Simona Brambilla	Dr. Antonella Ferrario	Dr. Francesca Morabito
Dr. Elena Bredi	Dr. Paola Ferrazzi	Dr. Serenella Valaperta

PATHOLOGY

Unit Director: **Prof. Massimo Roncalli**

STAFF

Dr. Paola Bossi	Dr. Luca Di Tommaso	Dr. Paola Spaggiari
Dr. Piergiuseppe Colombo	Dr. Barbara Fiamengo	
Dr. Maria Grazia Di Rocco	Dr. Daoud Rahal	

RADIOLOGY AND DIAGNOSTIC IMAGING DEPARTMENT

Unit Directors: **Dr. Giorgio Brambilla - Dr. Luca Balzarini**

STAFF

Dr. Cristiana Bonifacio	Dr. Alessandra Pestalozza
Dr. Sara Galli	Dr. Dario Poretti
Dr. Sara Imperato	Dr. Manuel Profili
Dr. Romano Lutman	Dr. Elisa Rognone
Dr. Paolo Malerba	Dr. Felice Rognone
Dr. Lorenzo Monti	Dr. Federica Mrakic Sposta
Dr. Vittorio Pedicini	

► Head: **Prof. Alberto Malesci**

Identification of hereditary juvenile colorectal cancers: prevalence of cases with diverse defects of repair systems of DNA in germinale line (mismatch and base excision repair). Systemic identification of colorectal cancers with instability of microsatellites between tumours submitted to surgical resection: demographic, clinical and genotypic characteristics.

Mutation study of colorectal cancer with instability of microsatellites: search for variables with prognostic value

Mutation K-RAS and B-RAF in colorectal cancers: clinical correlations with hereditary and sporadic defects of DNA repairment system. Functional characterization of gastrin receptor (CCKB) with frameshift mutation of the exon 5 in gastrointestinal tumors with microsatellite instability.

Hypermethylation and epigenetic inactivation of repair genes and cellular cycle reveal sex and age differences in sporadic colorectal cancers with microsatellite instability.

Clinico-pathologic characteristics of pancreatic tumors in respect to phenotype MSI and K-RAS and B-RAF mutations. Determining serum levels of pentraxin 3 (PTX3)

in acute pancreatitis. Prospective, multicentric randomized study comparing pneumatic cardiac dilatation via endoscopic route and laparoscopic myotomy in the treatment of the achalasic patient. Prevalence of CARD15 genotypes associated with Crohn's disease and study of the enteron with video-capsule in patients with irritable bowel syndrome. Assessment study into fibrin glue injection techniques in endoscopy. Primary carcinoma of the liver: research into prognostic biologic factors of tumoral growth. Autologous transplantation of staminal hematopoietic cells preceded by immunoablative conditioning with ampath-h1 for the treatment of severe Crohn's, perforated and refractory of traditional medical treatments. Identification of new antigenic specificities in the serum of patients with primari biliary cirrhosis, sclerodermia and automimmune cholangitis.

Quantification and characterisation of hepatic steatosis with spectroscopic MR in patients with HCV hepatopathy correlated in relation to level of insulin resistance and to the metabolic syndrome.

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Acute small-bowel perforation secondary to capsule endoscopy.
 Gastrointest Endosc. 2008 Jan;67(1):180-183. Epub 2007 Nov 5.
Raw IF(2006): 4.825 Normalized IF: 6

► CONIGLIARO R, BATTAGLIA G, REPICI A, DE PRETIS G, GHEZZO L, BITTINGER M, MESSMANN H, DEMARQUAY JF, TOGNI M, BLANCHI S, FILIBERTI R, CONIO M.
Polyflex stents for malignant oesophageal and oesophagogastric stricture: a prospective, multicentric study.
 Eur J Gastroenterol Hepatol. 2007 Mar;19(3):195-203.
Raw IF (2006): 1.895 Normalized IF: 1

OBJECTIVE: Dysphagia is the most distressing symptom in patients with cancer-related oesophageal obstruction. Endoscopic palliation aims to restore swallowing, avoid reintervention and to reduce hospitalization. This study reports an experience with a new self-expandable plastic stent (Polyflex) in patients with unresectable oesophageal and oesophagogastric junction cancer. METHODS: Sixty patients were prospectively collected. The cause of obstruction was oesophageal squamous cell carcinoma

(44) and adenocarcinoma (eight), lung cancer (seven) and thyroid tumour (one). RESULTS: The stent was successfully placed in 59 patients. Early minor complications occurred in 19 patients (32%), and major complications in 13 (22%). Death occurred in three patients owing to pulmonary embolism (one) and massive haemorrhage (two). Recurrent dysphagia for early stent migration was observed in seven patients. Delayed stent migration occurred in five patients and tumour overgrowth in eight patients. The mean dysphagia score of 2.8 improved to a mean score of 1.0 after stenting (P<0.001). Overall median survival time was 4.6 months.



CONCLUSIONS: Our study suggests that Polyflex stents are competitive with metal stents, with similar efficacy but lower cost. Technical improvements, however, are required to make these stents more user friendly. Large randomized clinical studies are needed to guide in the choice among the different available stents.

- ▶ NENCI A, BECKER C, WULLAERT A, GAREUS R, VAN LOO G, DANESE S, HUTH M, NIKOLAEV A, NEUFERT C, MADISON B, GUMUCIO D, NEURATH MF, PASPARAKIS M.

Epithelial NEMO links innate immunity to chronic intestinal inflammation.

Nature. 2007 Mar 29;446(7135):557-61. Epub 2007 Mar 14.

Raw IF (2006): 26.681 Normalized IF: 7.5

Deregulation of intestinal immune responses seems to have a principal function in the pathogenesis of inflammatory bowel disease. The gut epithelium is critically involved in the maintenance of intestinal immune homeostasis-acting as a physical barrier separating luminal bacteria and immune cells, and also expressing antimicrobial peptides. However, the molecular mechanisms that control this function of gut epithelial cells are poorly understood. Here we show that the transcription factor NF-kappaB, a master regulator of pro-inflammatory responses, functions in gut epithelial cells to control epithelial integrity and the interaction between the mucosal immune system and gut microflora. Intestinal epithelial-cell-specific inhibition of NF-kappaB through conditional ablation of NEMO (also called IkappaB kinase-gamma (IKKgamma)) or both IKK1 (IKKalpha) and IKK2 (IKKbeta)-IKK subunits essential for NF-kappaB activation-spontaneously caused severe chronic intestinal inflammation in mice. NF-kappaB deficiency led to apoptosis of colonic epithelial cells, impaired expression of antimicrobial peptides and translocation of bacteria into the mucosa. Concurrently, this epithelial defect triggered a chronic inflammatory response in the colon, initially dominated by innate immune cells but later also involving T lymphocytes. Deficiency of the gene encoding the adaptor protein MyD88 prevented the development of intestinal inflammation, demonstrating that Toll-like receptor activation by intestinal bacteria is essential for disease pathogenesis in this mouse model. Furthermore, NEMO deficiency sensitized epithelial cells to tumour-necrosis factor (TNF)-induced apoptosis, whereas TNF receptor-1 inactivation inhibited intestinal inflammation, demonstrating that TNF receptor-1 signalling is crucial for disease induction. These findings demonstrate that a primary NF-kappaB signalling defect in intestinal epithelial cells disrupts immune homeostasis in the gastrointestinal

tract, causing an inflammatory-bowel-disease-like phenotype. Our results identify NF-kappaB signalling in the gut epithelium as a critical regulator of epithelial integrity and intestinal immune homeostasis, and have important implications for understanding the mechanisms controlling the pathogenesis of human inflammatory bowel disease.

- ▶ CONIO M, BLANCHI S, FILIBERTI R, REPICI A, BARBIERI M, BILARDI C, SIERSEMA PD.

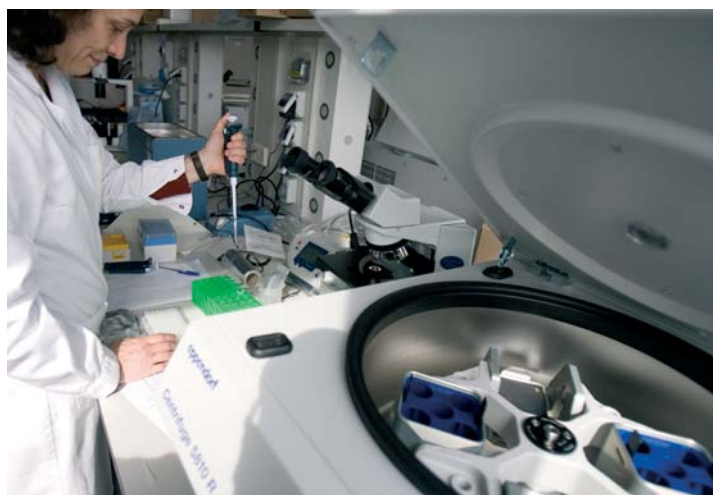
A modified self-expanding Niti-S stent for the management of benign hypopharyngeal strictures.

Gastrointest Endosc. 2007 Apr;65(4):714-720.

Raw IF (2006): 4.825 Normalized IF: 3

BACKGROUND: The management of patients with refractory hypopharyngeal strictures after surgery in combination with radiation therapy is disappointing, and nutrition through feeding tubes is often required. **OBJECTIVE:** To evaluate the efficacy and safety of a modified self-expanding Niti-S metal stent in the treatment of hypopharyngeal strictures after combined therapy for laryngeal cancer. **DESIGN:** Case series. **SETTING:** A general hospital and a university hospital. **PATIENTS:** Seven consecutive patients were included. One of them did not have laryngectomy. **INTERVENTIONS:** All patients received a modified Niti-S stent. **MAIN OUTCOME MEASUREMENTS:** Improvement of dysphagia, avoiding periodic bougienage, and enteral nutrition through feeding tubes. **RESULTS:** After placement of the first stent, dysphagia improved in all patients. Six of 7 patients developed stent migration and/or granulomatous tissue ingrowth or overgrowth. Additional stents were placed in all patients after a median of 3 months after the previous stent





placement. One patient developed an esophagorespiratory fistula caused by a Polyflex stent. Two patients died of causes unrelated to the stent. The remaining 5 patients remained alive and asymptomatic after a median follow-up of 10 months. LIMITATIONS: Periodic stent exchange. Stent placement did not resolve the stricture definitively. We had a limited number of patients and have no long-term outcome data yet. CONCLUSIONS: The use of this modified Niti-S stent avoids both enteral nutrition through feeding tubes and the need for periodic bougienage in patients with difficult-to-treat benign hypopharyngeal strictures.

▶ DANESE S, DEJANA E, FIOCCHI C.

Immune regulation by microvascular endothelial cells: directing innate and adaptive immunity, coagulation, and inflammation.

J Immunol. 2007 May 15;178(10):6017-22.

Raw IF (2006): 6.293 Normalized IF: 6

An effective immune response depends not only on the proper activation, regulation, and function of immune cells, but also on their distribution and retention in diverse tissue microenvironments where they encounter a number of stimuli and other cell types. These activities are mediated by endothelial cells, which form specialized microcirculatory networks used by immune cells under both physiological and pathological circumstances. Endothelial cells represent a highly heterogeneous population of cells with the ability to interact with and modulate the function of immune cells. This review is focused on the role of microvascular endothelial cells in innate and adaptive immunity, inflammation, coagulation, angiogenesis, and the therapeutic implications of targeting endothelial cells in selected autoimmune and chronic inflammatory disorders.

▶ REPICI A, PELLICANO R.

A 2007 panorama on gastro-esophageal reflux disease.

Minerva Gastroenterol Dietol. 2007 Jun;53(2):125-6. No abstract available.

Raw IF (2006): 0 Normalized IF: 0.1

▶ DANESE S.

Inflammation and the mucosal microcirculation in inflammatory bowel disease: the ebb and flow.

Curr Opin Gastroenterol. 2007 Jul;23(4):384-9.

Raw IF (2006): 3.045 Normalized IF: 4

PURPOSE OF REVIEW: Inflammatory bowel disease pathogenesis involves the interplay of multiple biological factors, among which nonimmune cells, including the endothelium, represent a crucial component of disease pathogenesis. RECENT FINDINGS: Endothelial cells play a key role in chronic inflammation through multiple and disparate activities. The mucosal microvasculature in inflammatory bowel disease is dysfunctional, overexpresses inflammatory molecules and undergoes intense angiogenesis, failing to exert its physiological antiinflammatory and anticoagulant activities. SUMMARY: The mucosal microcirculation is abnormal in inflammatory bowel disease and represents a novel component of disease pathogenesis; targeting the various abnormalities of the inflammatory bowel disease microcirculation may lead to new forms of therapeutic intervention.

▶ SCALDAFERRI F, SANS M, VETRANO S, GRAZIANI C, DE CRISTOFARO R, GERLITZ B, REPICI A, ARENA V, MALESCI A, PANES J, GRINNELL BW, DANESE S*.

Crucial role of the protein C pathway in governing microvascular inflammation in inflammatory bowel disease.

J Clin Invest. 2007 Jul;117(7):1951-60.

Raw IF (2006): 15.754 Normalized IF: 15

Endothelial protein C receptor (EPCR) and thrombomodulin (TM) are expressed at high levels in the resting microvasculature and convert protein C (PC) into its activated form, which is a potent anticoagulant and antiinflammatory molecule. Here we provide evidence that in Crohn disease (CD) and ulcerative colitis (UC), the 2 major forms of inflammatory bowel disease (IBD), there was loss of expression of endothelial EPCR and TM, which in turns caused impairment of PC activation by the inflamed mucosal microvasculature. In isolated human intestinal endothelial cells, administration of recombinant activated PC had a potent antiinflammatory effect, as demonstrated by downregulated cytokine-dependent cell adhesion molecule expression and chemokine production

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as well as inhibited leukocyte adhesion. In vivo, administration of activated PC was therapeutically effective in ameliorating experimental colitis as evidenced by reduced weight loss, disease activity index, and histological colitis scores as well as inhibited leukocyte adhesion to the inflamed intestinal vessels. The results suggest that the PC pathway represents a new system crucially involved in governing intestinal homeostasis mediated by the mucosal microvasculature. Restoring the PC pathway may represent a new therapeutic approach to suppress intestinal inflammation in IBD.

- ▶ BERNDT U, BARTSCH S, PHILIPSEN L, DANESE S, WIEDENMANN B, DIGNASS AU, HAMMERLE M, STURM A.

Proteomic analysis of the inflamed intestinal mucosa reveals distinctive immune response profiles in Crohn's disease and ulcerative colitis.

J Immunol. 2007 Jul 1;179(1):295-304.

Raw IF (2006): 6.293 Normalized IF: 3

Although Crohn's disease (CrD) and ulcerative colitis (UC) share several clinical features, the mechanisms of tissue injury differ. Because the global cellular function depends upon the protein network environment as a whole, we explored changes in the distribution and association of mucosal proteins to define key events involved in disease pathogenesis. Endoscopic biopsies were taken from CrD, UC, and control colonic mucosa, and Multi-Epitope-Ligand-Cartographie immunofluorescence microscopy with 32 different Abs was performed. Multi-Epitope-Ligand-Cartographie is a novel, highly multiplexed robotic imaging technology which allows integrating cell biology and biomathematical tools to visualize dozens of proteins simultaneously in a structurally intact cell or tissue. In CrD, the number of CD3+CD45RA+ naive T cells was markedly increased, but only activated memory, but not naive, T cells expressed decreased levels of Bax, active caspase-3 or

-8. In UC, only CD4+ T cells coexpressing NF-kappaB were caspase-8 and poly(ADP-ribose)-polymerase positive. Furthermore, the number of CD4+CD25+ T cells was elevated only in UC, whereas in CrD and controls, the number of these cells was similar. By using hub analysis, we also identified that the colocalization pattern with NF-kappaB+ and poly(ADP-ribose)-polymerase+ as base motifs distinguished CrD from UC. High-content proteomic analysis of the intestinal mucosa demonstrated for the first time that different T cell populations within the intestinal mucosa express proteins translating distinct biological functions in each form of inflammatory bowel disease. Thus, topological proteomic analysis may help to unravel the pathogenesis of inflammatory bowel disease by defining distinct immunopathogenic profiles in CrD and UC.

- ▶ MALESCI A, LAGHI L, BIANCHI P, DELCONTE G, RANDOLPH A, TORRI V, CARNAGHI C, DOCI R, ROSATI R, MONTORSI M, RONCALLI M, GENNARI L, SANTORO A.

Reduced likelihood of metastases in patients with microsatellite-unstable colorectal cancer.

Clin Cancer Res. 2007 Jul 1;13(13):3831-9.

Raw IF (2006): 6.177 Normalized IF: 6

PURPOSE: The outcome of patients with colorectal cancer is more favorable when the tumor exhibits high-frequency microsatellite instability (MSI). Although associated with earlier-stage tumors, MSI has been proposed as an independent predictor of survival. We tested the prognostic value of MSI in a large series of patients diagnosed with colorectal cancer in the last decade. **EXPERIMENTAL DESIGN:** The survival of 893 consecutive patients with colorectal cancer characterized by microsatellite status was analyzed. The 89 (10%) patients with MSI cancer were classified according to tumor mismatch repair (MMR) defect, MMR germ-line mutation, hMLH1 and p16 promoter methylation, BRAF and K-ras mutations, and frameshifts of target genes. **RESULTS:** The colorectal cancer-specific survival was significantly ($P = 0.02$) better in patients with MSI cancer than in those with stable tumor (MSS). MSI did not predict a significantly lower risk of cancer-related death if tumor stage was included in the multivariate analysis [hazard ratio, 0.72; 95% confidence interval (95% CI), 0.40-1.29; $P = 0.27$]. Instead, MSI was strongly associated with a decreased likelihood of lymph node (odds ratio, 0.31; 95% CI, 0.17-0.56; $P < 0.001$) and distant organ (odds ratio, 0.13; 95% CI, 0.05-0.33; $P < 0.001$) metastases at diagnosis, independently of tumor pathologic features. Molecular predictors of reduced

metastatic risk, and then of more favorable prognosis, included TGFbetaRII mutation for all MSI tumors, hMSH2 deficiency for hereditary non-polyposis colorectal cancer, and absence of p16 methylation for sporadic hMLH1-deficient cancers. CONCLUSIONS: Tumor MSI is a stage-dependent predictor of survival in patients with colorectal cancer. The decreased likelihood of metastases in patients with MSI cancer is associated with specific genetic and epigenetic changes of the primary tumor.

► REPICI A*, CONIO M, DE ANGELIS C, SAPINO A, MALESCI A, AREZZO A, HERVOSO C, PELLICANO R, COMUNALE S, RIZZETTO M.

Insulated-Tip Knife Endoscopic Mucosal Resection of Large Colorectal Polyps Unsuitable for Standard Polypectomy.

Am J Gastroenterol. 2007 Aug;102(8):1617-23. Epub 2007 Mar 31.

Raw IF (2006): 5.608 Normalized IF: 6

OBJECTIVES: Endoscopic mucosal resection (EMR) has been shown to be safe and effective. En bloc resection is often not achieved using conventional EMR. Insulated-tip knife (It-knife) EMR has been recently proposed for early gastric cancer dissection and removal. This study was conducted to evaluate the safety and efficacy in obtaining en bloc resection with It-knife EMR of large colonic lesions not resectable with standard endoscopic techniques. METHODS: A total of 29 patients (19 men, 10 women, mean age 67.5 yr, range 44-88) were included in the study. Lesions were considered not suitable for standard polypectomy because of large diameter (>3 cm), morphology, and/or position. Lesions were located in the rectum (N = 11), sigmoid: (N = 10), descending: (N = 4), transverse: (N = 2), and hepatic flexure (N = 2). After saline injection, circumferential incision and dissection of the lesions were attempted with the aim of achieving en bloc resection. RESULTS: En bloc resection was achieved in only 55.1% of the lesions (16 out of 29 patients). In the remaining cases, resection was completed with a piecemeal technique. The median size of the en bloc resected specimen was 3 x 3.4 cm. Complications occurred in four patients (13.7%). At histopathology, 13 patients had low-grade dysplasia, 15 high-grade dysplasia. One patient had a tumor invading the submucosa and was submitted to surgery. CONCLUSIONS: It-knife EMR is a promising technique for attempting en bloc resection of large colonic polyps. Adequate training and caution are required because it can be associated with a higher complication rate than with other EMR modalities.

► REPICI A, PAGANO N*.

Endoscopic mucosal resection-endoscopic submucosal dissection: do we really need endoscopic ultrasonography assistance?

Minerva Med. 2007 Aug;98(4):417-421.

Raw IF (2006): 0 Normalized IF: 0.1

Endoscopic mucosal resection has become the standard of care for early gastrointestinal cancer. The application of this new treatment requires an accurate stadiation of the neoplasia. The exclusion of nodal involvement and the evaluation of the depth of tumor penetration within the gastrointestinal wall is essential to select patients who can benefit from this approach. Echoendoscopy allows endoscopists to evaluate subtle changes in the layers of the gastrointestinal wall giving an important aid to local tumor staging and planning the adequate treatment.

► DANESE S*, SCALDAFERRI F, VETRANO S, STEFANELLI T, GRAZIANI C, REPICI A, RICCI R, SGAMBATO A, STRAFACE G, MALESCI A, FIOCCHI C, RUTELLA S.

Critical role of the CD40-CD40 ligand pathway in governing mucosal inflammation-driven angiogenesis in inflammatory bowel disease.

Gut. 2007 Sep;56(9):1248-56. Epub 2007 Feb 22

Raw IF (2006): 9.002

Normalized IF: 8

BACKGROUND AND AIMS:

Angiogenesis is a novel component in inflammatory bowel disease (IBD) pathogenesis. We have previously shown that immune-nonimmune interactions through the CD40-CD40-ligand (CD40L) pathway might sustain gut inflammation, although their effect on regulating inflammation-driven angiogenesis is unknown. The present study evaluated the role of the CD40-CD40L interaction in the promotion of immune-mediated angiogenesis in IBD. METHODS: Human nonimmune cells of colonic origin-namely, human intestinal fibroblasts (HIFs) and human intestinal microvascular endothelial cells (HIMECs)-were activated with either soluble CD40L (sCD40L), or CD40(+) D1.1 cells or CD40L-activated lamina propria T (LPT) cells before measuring pro-angiogenic cytokine release. Blocking antibodies to either CD40 or CD40L were used to disrupt the CD40-CD40L interaction. The dextran sodium sulphate (DSS) model of experimental colitis in CD40 and CD40L knockout mice was established to assess whether the CD40-CD40L pathway was implicated in controlling inflammation-driven angiogenesis in vivo. RESULTS: Engagement of CD40 on



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HIFs promoted the release of vascular endothelial growth factor (VEGF), interleukin-8 (IL-8) and hepatocyte growth factor (HGF). LPT cells were potent inducers of pro-angiogenic cytokine secretion by HIFs. Supernatants from SCD40L-activated HIFs induced migration of HIMECs and tubule formation, both of which were inhibited by blocking antibodies to either VEGF, IL-8 or HGF. Both CD40- and CD40L-deficient mice were protected from DSS-induced colitis and displayed a significant impairment of gut inflammation-driven angiogenesis, as assessed by



microvascular density. **CONCLUSIONS:** The CD40-CD40L pathway appears to be crucially involved in regulating inflammation-driven angiogenesis, suggesting that strategies aimed at blocking CD40-CD40L interactions might be beneficial in acute and chronic intestinal injury.

- DANESE S, STEFANELLI T, OMODEI P, ZATELLI S, BONIFACIO C, BALZARINI L, REPICI A, MALESCI A.

Successful treatment of fistulizing Crohn's disease with certolizumab pegol.

Inflamm Bowel Dis. 2008 Feb;14(2):292-3. Epub 2007 Oct 11. No abstract available.

Letter To The Editor

Raw IF (2006): 3.912 Normalized IF: 1.2

- DANESE S, PAGANO N, ANGELUCCI E, STEFANELLI T, REPICI A, OMODEI P, DAPERNO M, MALESCI A.

Tumor necrosis factor-alpha monoclonal antibodies for Crohn's disease: tipping the balance.

Curr Med Chem. 2007;14(14):1489-97.

Raw IF (2006): 5.207 Normalized IF: 6

Crohn's disease (CD) is a chronic inflammatory disorder which may involve any part of gastrointestinal tract. Chronic inflammation is primarily due to an immunological imbalance between pro- and anti-inflammatory cytokines, and with a defective apoptosis of lamina propria T cells. Amongst the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-alpha) seems

to play a central role in pathogenesis of CD. Over the last years, increasing knowledge on the pathogenesis of CD together with progresses in bio-technology have led to the development of a number of biological agents targeting specific molecules involved in gut inflammation, most importantly TNF-alpha and its receptors. The aim of this paper is to critically review the rationale and state-of-the art for the use TNF- alpha inhibitors in the treatment of CD.

- REPICI A, FREGONESE D, COSTAMAGNA G, DUMAS R, KAHLER G, MEISNER S, GIOVANNINI M, FREEMAN J, PETRUZZIELLO L, HERVOSO C, COMUNALE S, FAROUX R.

Ultraflex precision colonic stent placement for palliation of malignant colonic obstruction: a prospective multicenter study.

Gastrointest. Endosc. 2007 Nov;66 (5):920-7. Epub Sep 26

Raw IF (2006): 4.825 Normalized IF: 6

BACKGROUND: Many patients who develop obstructive colonic symptoms secondary to inoperable colorectal cancer will require palliative treatment. A minimally invasive and potentially long-lasting approach is placement of nitinol self-expanding metal stents (SEMS). **OBJECTIVE:** To determine the effectiveness and safety of a nitinol SEMS designed for colorectal use in the palliative treatment of malignant colonic obstruction. **DESIGN:** Prospective multicenter clinical study. **SETTING:** Nine European study centers. **PATIENTS:** Forty-four patients with malignant colonic obstruction. **INTERVENTIONS:** Placement of nitinol SEMS designed for colorectal use. **MAIN OUTCOME MEASURES:** Technical success, defined as accurate SEMS deployment with adequate stricture coverage, and clinical success, defined as decompression and relief of obstructive colonic symptoms maintained without intervention or serious device-related complications. **RESULTS:** Technical success was attained in 95% of patients, with 95% CI 85%-99%. After 6 months, the rate of clinical success was 81%, 95% CI 69%-96%. Survival at 6 months was 67%, 95% CI 54%-84%. Clinical success was maintained until death in 86% of the nonsurvivors. No perforations or SEMS-related deaths occurred. **LIMITATION:** This investigation was nonrandomized and did not include a control group. **CONCLUSIONS:** In a large prospective investigation, palliative placement of a nitinol SEMS designed for colorectal use was accomplished with a high rate of technical success. Durable clinical success was achieved in a high proportion of patients with low morbidity.

► REPICI A, ADLER DG, GIBBS CM, MALESCI A, PREATONI P, BARON TH.

Stenting of the proximal colon in patients with malignant large bowel obstruction: techniques and outcomes.

Gastrointest Endosc. 2007 Nov;66(5):940-944.

Raw IF (2006): 4.825 Normalized IF: 6

BACKGROUND: Self-expandable metal stents are used throughout the GI tract to relieve malignant obstructions. OBJECTIVE: Our purpose was to determine the outcome after colonic stent placement into the proximal colon. DESIGN: Medical records of patients from 3 institutions who underwent attempts at placement of self-expandable metal stents for malignant obstructions of the proximal colon were retrospectively reviewed. Extracted data included patient characteristics, obstruction location, and goal of procedure (palliation vs bridge to surgery). SETTING: Academic medical centers. PATIENTS: Those with right-sided malignant colonic obstruction. INTERVENTIONS: Placement of colonic stent. MAIN OUTCOME MEASUREMENTS: Initial technical success, relief of obstruction, and early and long-term complications. RESULTS: Twenty-one patients (15 men, 6 women; mean age 67 years) were included. Tumor type was colonic adenocarcinoma in 19 patients. Obstruction was complete in 8 patients and subtotal in 13 patients. Stenting was attempted as a bridge to surgery in 8 patients and as palliation in 13 patients. Initial technical success was achieved in 20 of 21 patients (95%). Complete relief of obstruction was achieved in 17 of 20 patients who had technical success (85%), unachieved in 2 patients (No. 14 and 17), and unknown in 1 patient (No. 6). There were no procedure-related complications (bleeding, perforation, etc). The only long-term complication



was stent reocclusion from tumor ingrowth.

LIMITATIONS: Retrospective, single-arm analysis.

CONCLUSIONS: Self-expandable metal stents appear to be safe and effective in the treatment of malignant obstruction of the proximal colon.

Technical and clinical success rates are comparable to those seen with distal colonic stenting.

► PACLIK D, BERNDT U, GUZY C, DANKOF A, DANESE S, HOLZLOEHNER P, ROSEWICZ S, WIEDENMANN B, WITTIG BM, DIGNASS AU, STURM A.

Galectin-2 induces apoptosis of lamina propria T lymphocytes and ameliorates acute and chronic experimental colitis in mice.

J Mol Med. 2007 Dec 7 [Epub ahead of print].

Raw IF (2006): 5.157 Normalized IF: 3

Galectins have recently emerged as central regulators of the immune system. We have previously demonstrated that carbohydrate-dependent binding of galectin-2 induces apoptosis in activated T cells. Here, we investigate the potential therapeutic effect of galectin-2 in experimental colitis. Galectin-2 expression and its binding profile were determined by immunohistochemistry. Acute and chronic colitis was induced by dextran sodium sulfate administration and in a T-cell transfer colitis model. Apoptosis was assessed by TdT-mediated dUTP-biotin nick-end labeling, and cytokine secretion was determined by cytometric bead array. We show that galectin-2 was constitutively expressed mainly in the epithelial compartment of the mouse intestine and bind to lamina propria mononuclear cells. During colitis, galectin-2 expression was reduced, but could be restored to normal levels by immunosuppressive treatment. Galectin-2 treatment induced apoptosis of mucosal T cells and thus ameliorated acute and chronic dextran-sodium-sulfate-induced colitis and in a T-helper-cell 1-driven model of antigen-specific transfer colitis. Furthermore, the pro-inflammatory cytokine release was inhibited by galectin-2 treatment. In preliminary toxicity studies, galectin-2 was well tolerated. Our study provides evidence that galectin-2 induces apoptosis in vivo and ameliorates acute and chronic murine colitis. Furthermore, galectin-2 has no significant toxicity over a broad dose range, suggesting that it may serve as a new therapeutic agent in the treatment of inflammatory bowel disease.