IBD: East Meets West

September 11 – 12, 2015
InterContinental Shenzhen
Shenzhen, P. R. China
Abstracts of Invited Lectures
Poster Abstracts

Falk Symposium 198

IBD: EAST MEETS WEST

Shenzhen, P. R. China
September 11 – 12, 2015

Scientific Organization:
M.A. Kamm, Melbourne (Australia)
S.C. Ng, Hong Kong (Hong Kong)
G. Rogler, Zurich (Switzerland)
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Session I

Genetic risk factors in IBD: Do they play the same role in East and West?
Risk genes in Europe and America: What are the most important pathways affected?

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The genetic exploration of the etiology of IBD has taken a long way from discovery of disease-associated variants in the NOD2 gene some 10 years ago, which in contrast to the strong signal in association statistics only explain a minor fraction of disease inheritance, to the present model that describes IBD as a polygenic disorder. More than 160 disease loci and genes have been described for IBD in the Caucasian ethnicity. Few are resolved to the level of the causative variants, while many of these represent genetic or functional principles that are not yet (fully) identified. In general each disease variant and locus carries only a small risk with odd’s ratios little above 1. Therefore the prevailing disease model is a polygenic susceptibility in which disease associated variants are not exclusive to affected patients but show also a wide distribution in the normal population. Pathways identified include innate immunity (barrier function), autophagy and bacterial clearance mechanisms, T-cell related cytokine regulation (with a particular prominence of IL23R related regulation) and general destructive events.

Interestingly, systematic studies in other ethnicities than Caucasians have not been able to reveal a striking difference in disease phenotypes but have identified different sets of disease genes. Some genes that show multiple disease associated variants in Caucasians (e.g. NOD2) show a completely different background spectrum of variations in other ethnicities which are not of any relevance for IBD. Asian cohorts have been characterized through independent genome wide association studies in a similar fashion to what has been done in Caucasians. TNFSF15, ATG16L1, IL23R, which have also been found in Caucasians, play a leading role in Asian Crohn’s disease. Additional disease genes that are unique have been reported in Korean, Japanese and Chinese cohorts.

With targeted therapies that specifically inhibit single molecules such ethnic differences may become important for therapeutic efficacy, too. In the near future novel therapies may no longer just require bridging studies following the formal proof of efficacy in Caucasians but may have to undergo either an independent clinical development or should be backed by strong translational molecular studies that ensure a similar mechanistic effect across ethnicities.
Risk genes in the Asia/Pacific area: What are the most important pathways affected?

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Genetic factors play important roles in the pathogenesis of inflammatory bowel disease (IBD), and IBD is now recognized as a complex disease resulted from interplay between genetic and environment factors. To date, over 160 IBD susceptibility loci have been identified using genome-wide association studies (GWAS). The risk genes identified in these studies are involved in various pathways in innate and adaptive immune response such as innate bacterial sensing, autophagy and interleukin-23 receptor/T helper cell 17 pathway. It has been noted that the genetic backgrounds of Asian IBD patients differs from other populations. Some major risk loci in Caucasians are not found to be associated with IBD in Asia, e.g, nucleotide oligomerization domain-2 (NOD2), interleukin-23 receptor, autophagy-related 16-like 1 (ATG16L1) and IRGM. Instead, other rare variants of these genes are identified as risk loci. Even for genes shared between Asia and European population, some risk genes such as HLA and TNFSF15 seem to play more important roles in Asia. GWAS and replication studies in Asian population have identified several novel but more shared risk genes in Asian IBD patients. The pervasive sharing of risk genes indicating pathways underlying the etiology of IBD may be common between Asia and other areas. However, the importance of individual pathways may be different. Novel risk genes may indicate novel pathways for IBD in Asia. Identifying the most important pathways affected in Asian IBD patients may provide a better understanding of pathogenesis of IBD in Asia and improve the clinical management of the patients.

Keywords: Inflammatory bowel disease, Risk genes, Genetic Susceptibility
The promise of epigenetics. Has it delivered new insights?

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Genome-wide association studies (GWAS) in IBD have now identified approximately 200 loci (typically defined as 500kb windows around peak signals, or alternatively, by recombination patterns defining inherited blocks), with the vast majority of loci (a) contributing to both Crohn’s disease and ulcerative colitis (UC), (b) demonstrating consistent direction of effects between European and Asian populations, and (c) having association signals driven by non-coding, likely regulatory variation. A seminal advance has been the recognition that in fine-mapping precise disease-associated alleles within loci, marked enrichment of probable alleles has been observed within cell-specific enhancers defined by various chromatin marks, such as H3K27ac and H3K4me1, which identify active and poised enhancers, respectively. Enrichment of cell specific enhancers across various diseases has correlated with present understanding of disease pathogenesis; neurologic, autoimmune and metabolic diseases demonstrate the greatest enrichment of GWAS signals for neural, immune and liver cell-specific enhancer marks, respectively. Within immune cells, the greatest enrichment has been reported in various CD4+ T cells, such as Th17 cells in numerous chronic immune-mediated diseases, including IBD.

Interestingly, although Crohn’s disease and UC share many loci, illustrative differences in cell-specific epigenetic enrichment scores have been observed. For example, UC has demonstrated greater enrichment of active enhancer marks from colonic mucosa compared to Crohn’s disease; conversely, Crohn’s disease, perhaps surprisingly, has demonstrated greater enrichment of B cell enhancer marks compared to UC. Monocyte enrichment has been generally more modest, and may reflect tissue-specific epigenetic mechanisms in macrophage and dendritic cell gene expression and function that have not yet been fully elaborated. The epigenetic studies reported thus far highlight the critical importance of examination of disease-relevant cells and tissues; mechanistically, epigenetic studies provide fundamental insight into cellular proliferation, apoptosis, differentiation and plasticity. Such basic insight provides the key to linking inherited germline variants to developmental factors that drive age-dependent immune function, IBD predisposition and progression and ultimately, patient outcomes.
State-of-the-Art Lecture

Environment and genes: What is the interaction?

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Inflammatory bowel disease (IBD) results from a continuum of complex interactions between a quartet of host-derived and external elements that involve various aspects of the intestinal microbiota, the immune system which is centered around the intestinal epithelial cell barrier, the genetic composition of the host, and specific environmental factors. Recent studies into the complexity of these arrangements increasingly support the syndromic nature of this disorder and the need to parse out how this microbial-immune-genetic axis is organized along the specific phenotypic distillations of disease in order to go beyond the assigned clinical descriptors currently in practice, namely ulcerative colitis (UC) and Crohn’s disease (CD). Indeed, studies of the microbiota, immune system, and genetics in their totality have revealed more similarities than differences between these two extreme phenotypes (UC and CD), suggesting that IBD is a consequence of dysfunctional modules and an accumulation of their associated phenotypes. These involve a wide range of interacting biologic pathways that affect innate immunity, adaptive immunity, endoplasmic reticulum stress and autophagy as well as metabolic pathways associated with cellular homeostasis. It is further likely that all of the aforementioned host factors including the microbiota, which is as much a part of ourselves as is any organ system, are under the influence of yet to be understood environmental factors that predispose to and precipitate IBD. Notwithstanding the importance of genetic predisposition, these environmental influences are no doubt central to disease pathogenesis in light of the rapid emergence of IBD throughout the world and assumption of disease in migrating populations from low to high risk environments. It can thus be anticipated that environmental factors that modify the risk for development of IBD have the common attribute of affecting the relationship between the commensal microbiota and the immune system in a manner that intersects with the functionally relevant immunogenetic pathways, and potentially modifies them through epigenetic effects, in a manner that are uniquely operative within a particular syndromic context of IBD and occur sequentially and in a reiterative fashion perhaps beginning in early life.
Session II

IBD: Environmental contributions to disease onset in East and West?
What impacts the epithelial barrier?

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The gut represents a unique interface towards our environment. It not only facilitates digestion and resorption, but also battles ingested pathogens, while also controlling an immense community of commensal microorganisms. To aid with the latter, it produces a wide range of innate immune mediators, such as antimicrobial peptides (AMPs), which can combat viruses, bacteria, and fungi. Gut AMPs have differing activity ranges and modes of action, so their expression varies depending on the present conditions and threats. The most famous examples for site specific AMPs are probably the two α-defensins HD5 and HD6. In a homeostatic state, they are exclusive to the Paneth cells of the small intestine. Since the importance of gut microbiota has become more and more evident, research on AMPs has also increased. This is particularly obvious in the case of inflammatory bowel diseases, but also noticeable in other disorders. Defects in the AMP machinery have been linked to increased susceptibility to infections, chronic inflammation, and disturbances in commensal composition. The gut provides a complex and challenging environment for the study of interactions between AMPs and microbes; and while we are now widely aware of their crucial role in keeping us healthy, more research is needed to fully uncover the involved multi-level crosstalks of their actions. Besides environmental factors, which control epithelial host defense, new data which will be presented here, indicate prominent regulation by bone marrow derived cells which can also impact on the expression of defensins. Understanding these mechanisms will aid in developing new anti-infectious, anti-inflammatory and maybe even anti-tumorigenic drugs.
Factors causing cell stress: Do they come from the environment?

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Over the last decades, we have witnessed a profound increase in the incidence of the inflammatory bowel diseases (IBD) Crohn’s disease and ulcerative colitis. While initially confined to Western countries, a profound increase in incidence in China and other Asian countries, and indeed globally, has been observed over the last two decades in particular, which coincides with major lifestyle changes. Genetic studies have unravelled the genetic underpinning of IBD indicating parallels but also important differences between Caucasian and Asian populations, but needless to say, genetics cannot possibly explain the troubling increase in incidence of these diseases around the world. However, they may provide a window into environmentally-affected mechanisms that trigger and drive disease. Cellular stress mechanisms, especially operative in the intestinal epithelium, have been demonstrated to instigate intestinal inflammation of the mucosal surface of the intestine. These stress mechanisms are affected by genetic risk variation, but importantly, are critical integrators of external and internal perturbations. This lecture will discuss the role of these mechanisms in the context of IBD pathogenesis and possible environmental triggers.
What role does a dysfunction of autophagy play for IBD onset?

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The application of state-of-the-art genetic analyses to inflammatory bowel disease (IBD) resulted in the discovery of the link between the cellular stress response autophagy and IBD susceptibility. Autophagy (meaning “self-eating”) is an evolutionarily conserved cell stress response that plays diverse roles in various physiological processes, such as adaptation to starvation, degradation of aberrant proteins or organelles, protein secretion, innate and adaptive immunity, and programmed cell death, making autophagy an integral player in maintaining intestinal homeostasis. Functional studies demonstrate that IBD-associated genetic variants in autophagy-related genes primarily impair their function and suggest several distinct, but related roles for dysfunctional autophagy in disease pathogenesis. These autophagy-dependent processes include: (1) intracellular bacterial killing, (2) anti-microbial peptide secretion by Paneth cells, (3) pro-inflammatory cytokine production by macrophages, (4) antigen presentation by dendritic cells, and (5) endoplasmic reticulum stress responses in enterocytes. The overall effect of dysregulation of these processes is determined by cell type, stimulus, as well as cellular context. Additional studies suggest that impaired autophagy may also exacerbate intestinal inflammation through promoting dysbiosis of the intestinal microbiome, or the expansion of pathobionts, such as adherent-invasive Escherichia coli. Similar to the multi-factorial nature of IBD susceptibility, autophagic function is impaired not only by genetic risk variants, but also environmental and microbial factors associated with IBD. These findings suggest that a dysfunction of autophagy is a critical factor in IBD susceptibility and that increased understanding of the roles of autophagy in the maintenance of intestinal homeostasis could lead to new avenues of IBD therapeutic intervention.
The hygiene hypothesis: Is the evidence the same all over the world?

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In medicine, the hygiene hypothesis, or more correctly, the ‘microbial deprivation’ hypothesis, is a hypothesis that states, that a lack of early childhood exposure to infectious agents, microorganisms (e.g. gut flora or probiotics) and parasites increases susceptibility to allergic diseases by suppressing the natural development of the immune system. The hypothesis arose when a decline in the incidence of infectious diseases within a community mimicked the inverse increase in immune-mediated diseases, such as asthma, atopy, multiple sclerosis and Crohn’s disease. Inflammatory bowel diseases (IBD) have been increasing in Western countries since the 1950’s. This increase has also been more recently evident in developing countries in Asia and the Middle East in the past decade. The significant increase in IBD in the most populous region of the world may mean equivalent numbers of IBD cases in the West and the East by 2025. Whether the microbial deprivation hypothesis is responsible for the increase in IBD in these geographical regions remains unknown. However, the timing of the increase in IBD with improvement in affluence, decrease in population crowding, improved sanitation and access to clean hot water, increased use of disinfectant and childhood antibiotics, and dietary changes, may support this theory. If so, this supports the importance of environmental risk factors in the etiology of IBD rather than genetics.
Dissecting the contribution of gut microbiome to human disease phenome

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Human phenotypes are dictated by the information contents of and molecular crosstalk between the genome and the microbiome. The harmonious integration between human genome and microbiome is the foundation for maintaining a healthy phenome. Poorly balanced diets can turn the gut microbiome from a partner for health to a “pathogen” in chronic diseases. Accumulating evidence supports the new hypothesis that obesity and related metabolic diseases develop because of low-grade, systemic and chronic inflammation induced by endotoxin released into bloodstream from a diet-disrupted gut microbiota. For example, our study showed that an endotoxin-producing bacterium *Enterobacter cloacae* B29 isolated from the gut of a morbidly obese human volunteer can cause fully developed obesity phenotypes including systemic inflammation, adiposity and insulin resistance when mono-associated with germfree mice. This indicates that specific members of the gut microbiota have the genetic potential to contribute significantly to the development of metabolic disease phenotypes. Thus, the contribution of microbiome to human metabolic phenome must be taken into account when assessing human health. Due to the tight integration of gut microbiota into human global metabolism, molecular profiling of urine metabolites can provide a new window for reflecting physiological functions of gut microbiome. Changes of gut microbiota and urine metabolites can thus be correlated to find out “who does what in the microbiome”. Using this strategy in our recent study on dietary alleviation of human genetic obesity in Prader-Willi syndrome, we assembled more than 100 high quality draft genomes of prevalent gut bacteria directly from a large metagenomic dataset. Correlation analysis between abundance of these genomes and urine concentration of metabolites identified specific bacteria, which carry the genes for enzymes required to ferment choline into TMA, a precursor of TMAO, a metabolic toxin for inducing atherosclerosis, indicating that these bacteria may contribute to metabolic deteriorations in the hosts. Understanding the contribution of gut microbiota to human metabolic phenome can lead to new insights on mechanisms of chronic diseases such as obesity and diabetes and development of new measures for their management.
Session III

The mucosal innate immune system: What does it teach us for the development of new therapy?
Endothelial cell – immune cell interaction

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The presence of different amounts of leukocytes in the various compartments of the body is essential to health and alterations of immune cell subsets in number or type is often associated with disease. Inflammation, like that occurring in the bowel of patients with inflammatory bowel disease (IBD; Crohn’s disease and ulcerative colitis), typically results from an excessive accumulation of T cells, B cells, macrophages and other immunocytes. This excessive accumulation is caused by the disruption of the normally finely tuned mechanisms that regulate leukocyte homing, i.e., the process of transferring leukocytes from the circulation into the interstitial tissue. These regulatory mechanisms involve expression of specific molecules on the surface of immune cells, such as integrins and chemokine receptors, the expression of counter-receptors on endothelial cells, and the secretion of a variety of soluble chemokines by both the leukocytes and the endothelial cells. Immune cells homing to the gut express different types of integrins and chemokine receptors, like integrin α4β7, CCR9, CXCR4 and CXCR2 by CD8+ T cells, α4β7, CCR9 and CXCR6 by Th17 cells, α4β7 and CCR9 by Treg cells, and α4β7, CCR9 and CXCR10 by plasma cells. Addressins are the counter-receptors for these molecules in the intestinal vasculature, and they are differentially expressed along the gastrointestinal tract. MAAdCAM-1 is the prototypical intestinal cell adhesion molecule, and is expressed in the small and large bowel and it is up-regulated during inflammation; CCL20, a ligand for CCR6, is highly expressed in Peyer’s patches and the small bowel, and it is also up-regulated in inflammation; CCL25, a ligand for CCR9, is expressed in the small but not the large bowel; CCL28, a ligand for CCR10, is expressed primarily in the colon and regulates localization of IgA-secreting cells. There are multiple receptor-ligand pairs throughout the intestine (as in other tissues), some of the better characterized being α4β7/MAAdCAM-1 and α4β1/VCAM-1. In IBD the activation state of both immune and endothelial cells is increased, resulting in an inappropriate and continuous accumulation of leukocytes in the affected intestinal segments which promotes and sustains inflammation. In addition to alterations and proliferation of blood endothelial cells, i.e., angiogenesis, abnormalities of the lymphatic system have also been increasingly recognized as contributing to IBD pathogenesis. Particularly in Crohn’s disease, the presence of lymphangitis, lymphangiogenesis and altered immune cell lymphatic trafficking point to an important disruption of lymphatic function and defective lymphatic drainage.

Considering the above, it seems logical that interrupting the accumulation of leukocytes in the gut should alleviate inflammation. This has led to the development of a series of monoclonal antibodies directed at blocking a variety of molecules involved in leukocyte recruitment, including natalizumab (anti-α4 Tysabri®, Antegren®), AJM300 (anti-α4), etrolizumab (anti-β7, rhuMab-Beta7), vedolizumab (anti-α4β7, LDP-02, MLN-02, MLN0002), PF-00547659 (anti-MAAdCAM-1), Alicaforsen (anti-ICAM-1) and CCX282-B (anti-CCR9, GSK-1605786, Traficet-EN™).
Variable degrees of success and failure have been observed in clinical trials, but it is likely that this pathophysiology-based therapeutic approach will become a new tool in the therapeutic armamentarium for IBD.
Bacteria at the barrier interface – causal role for dysbiosis in Crohn’s disease

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Genome-wide association studies identified 163 susceptibility loci in IBD with substantial overlap between other immune disorders or infections providing clear evidence for a central role of intestinal bacteria and innate barrier mechanisms in the pathogenesis of Crohn’s disease (CD). Targeted deletion of ER stress, autophagy and necroptosis-related pathways in the epithelium supported the role of Paneth cell dysfunction and antimicrobial defense in the pathogenesis of small intestinal inflammation. Due to the lack of germfree models for ileal CD, proof for causality of microbes or dysbiosis in the onset of ileitis is lacking. We showed in TNF-delta-ARE mice that ileal inflammation is associated with the development of dysbiosis and, most importantly, microbiota transfer experiments confirmed a causal relationship between microbial dysbiosis and disease initiation in CD-like ileitis. Transmissive pathology was induced by a compositionally and functionally diverse microbiota, while single associations with a CD-derived pathobiont was not successful to transfer disease. Paneth cell dysfunction and loss of antimicrobial defense followed the induction of inflammation but did not precede tissue pathology. Despite the identification of barrier-related bacterial components in colitis-inducing enterococci, so far all our results point towards a community effect of the complex microbiota, rather than the selection of aggressive phylotypes as single agents causing CD. Interestingly, CD microbiota is most susceptible to iron-induced alterations independent of disease activity, suggesting that changes in community structure might not necessarily reflect dysbiotic causality in the disease pathogenesis. Thus, understanding the true nature of a dysbiotic and disease-conditioning microbiota seems of essential importance to judge the risk of relapse in IBD patients after therapeutic intervention or to achieve efficacy in fecal microbiota transplantation.

References:


Macrophages, lymphocytes or dendritic cells: Which are the important players?

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Therapies being introduced for inflammatory bowel disease involve antibodies to gut-homing molecules such as α4β7 (Vedolizumab) used ostensibly to remove gut-homing lymphocytes. However, dendritic, antigen-presenting cells (DC) in blood have potential to home to different tissues including gut (α4β7) and skin (CLA), whilst monocytes and monocyte-derived DC lack these markers. On reaching gut, DC become gut-specific expressing α4β7 and CCR9 (ileal homing marker) in the absence of skin-homing CLA. They spread veiled extensions, sample their environment, phagocytose/process antigens, produce cytokines and initiate innate immunity; myeloid DC also traffic via afferent lymph to draining lymph nodes. There they determine whether primary adaptive immune responses occur and their nature and also tissue-homing properties of lymphocytes stimulated; gut-specific DC generally stimulate T cells homing to gut. The removal of gut-homing DC as well as T cells by agents such as Vedolizumab is likely to be critical in prevention of gut-focussed immunity.

An alternative approach is to modulate homing capacity of DC and T cells they stimulate. We have identified two new routes by which gut-focussed immunity is modified. Firstly, some probiotic bacteria or their products can modify homing of DC. We have identified a serine and threonine rich peptide (STp) of Lactobacillus plantarum that is resistant to degradation by gut enzymes. This peptide induces a ‘tolerogenic’ phenotype in DC and T cells they stimulate, reduces expression of gut homing markers and induces skin homing potential. Stimulated T cells will therefore not only lack homing to gut but also be diverted to skin; gut bacteria will evade elimination with gut inflammation prevented. This peptide may represent a new class of ‘postbiotic’ therapies.

Secondly studies of activity of blood DC in childhood Crohn’s disease (CD) before and after treatment with enteral nutrition (EN) or infliximab (INX) included analysis of DC homing markers. Children with ileal disease (4/18 patients) expressed CCR9 on blood DC. All but these 4 patients showed recovery from CD on EN accompanied by normalisation of DC – reduction in activation markers and TLRs. Patients not responding to EN were successfully treated with INX and their CCR9 positive DC reduced to normal levels (Vora et al. 2015) Homing marker expression on blood DC could thus have diagnostic potential and provide information on mechanisms involved in different treatment protocols.

In conclusion peptides from probiotic bacteria and current biological IBD therapies may involve the distribution and activity of DC and their effects on effector T cell populations.
Innate lymphoid cells: Future therapy targets in IBD?

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Innate lymphoid cells (ILCs) are a recently discovered family of innate lymphocytes that are substantially represented at mucosal surfaces and have been implicated in the protection of epithelial barriers. Various types of ILCs can be discriminated based on the expression of distinct transcription factors controlling the expression of a distinct set of cytokine genes endowing the various ILC subsets with a specific range of effector functions. Currently, three groups of ILCs are being recognized. Group 1 ILCs (ILC1s) are a diverse group of ILCs comprised of natural killer (NK) cells and other, poorly defined subsets of ILCs. It is believed that the ILC1 fate decision is controlled by the T-box transcription factor T-bet endowing ILC1s with the capability to produce large amounts of IFN-γ. ILC2s express high levels of GATA-3, produce IL-5 and IL-13 and have been involved in immunity to helminth infections and in the pathogenesis of allergic diseases. Group 3 ILCs developmentally depend on the transcription factor RORγt and produce the cytokines IL-22, IL-17A and IL-17F. ILC3s are believed to be involved in the protection against intestinal bacterial infections and, if inappropriately stimulated, can be important drivers of inflammatory disorders. Current concepts support the view that ILCs produce cytokines that support epithelial regeneration and repair. However, ILCs can also aggravate inflammatory bowel diseases. I will discuss how ILC plasticity may explain these seemingly disparate functions and how a better understanding of the underlying molecular cues may be harnessed for the treatment of IBD.

Research in my lab is supported by grants from the European Research Council (ERC) and Deutsche Forschungsgemeinschaft.
Session IV

Environmental triggers for disease onset: Can we avoid them?
Psychological stress and depression: Risk factors for IBD?

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While it is widely accepted that chronic diseases such as inflammatory bowel disease (IBD) may trigger negative psychological emotions such as distress and even depression it is unknown if this response to a chronic illness like IBD is solely a psychological response to an adverse situation or whether it also represents a biological response; that is the active inflammatory state of IBD intersecting with the pathobiology of what mediates mood and anxiety disorders. Our group has shown that persons with active IBD were more likely to report distress, avoidant coping and lower well-being compared to healthy controls but persons with inactive IBD were no different than controls on those parameters. Hence, it is not IBD per se that is associated with negative psychological attributes but rather disease activity is pivotal. Our group has also shown that persons with IBD are significantly more likely to have a lifetime history of mood and panic disorders compared to controls. That is, long before their diagnosis of IBD they were diagnosed with a psychiatric disorder which suggests that the pathobiology of psychiatric disease may predispose to the development of IBD. In studies assessing the prevalence of mood and anxiety disorders in IBD the rates are always higher than community controls. Clinicians caring for persons with IBD will have to be mindful of this important comorbidity and its treatment may be as important in improving patient quality of life as treating the underlying inflammatory disease.

Life is full of common stressors and persons with IBD rate typical life stresses such as finances, family and work stresses in their top three. Chronic high perceived stress may be a precursor to mood and anxiety disorders. Often persons with IBD will report that life stress has been associated with a flare of their disease. Our group has reported that high perceived stress is associated with a symptomatic flare of IBD. In a subsequent study where high perceived stress was once again associated with increased symptoms, it did not correlate with fecal calprotectin levels. In Crohn’s disease symptoms did not correlate with fecal calprotectin and in ulcerative colitis the correlation was weakly positive. So while high perceived stress and symptoms are associated, high perceived stress is not associated with active inflammation. Stress may enhance symptoms but not necessarily active disease. When a patient with IBD reports increased symptoms it is incumbent on the clinician to inquire as to the state of the patient’s mental health and stress levels and not reflexively consider that the patient will require an increase in immunomodulating therapy.

Hence, there is a complex relationship between mental health disorders and IBD. How the basic biology of these two conditions is shared remains to be explored. Whether psychiatric comorbidity is a true risk factor for development of IBD is still unknown. Clinically, they are highly likely to coexist and it behooves clinicians to be regularly inquiring of their patients with IBD as to their mental health status and pursuing adequate treatment when required. Further, when patients are highly
stressed and have increased symptoms, the stress will need to be managed, as the 
increased symptoms may not reflect active inflammatory disease.

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An (anti)inflammatory microbiota: Defining the role in IBD?

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The incidence and prevalence rates of inflammatory bowel diseases (IBD) in Australia are considered to be among the highest in the world. Disease recurrence remains the major source of morbidity and impaired quality of life for IBD patients, and new therapeutic and/or preventative interventions are urgently needed, if the health and economic burdens of IBD are to be restrained. It is now accepted that the gut microbiota contribute to the genotype-environment-lifestyle interactions triggering IBD episodes, but efforts to identify “pathogen(s)” causing disease has historically met with limited success. The advent of culture-independent techniques for characterizing the structure and/or function of microbial communities (hereafter referred to as metagenomics), used largely in observational and/or case-control studies of IBD, have confirmed substantive changes in gut microbiota profiles (dysbiosis) associated with IBD. However, several recent longitudinal studies of Crohn’s disease patients have produced additional insights, including the identification of candidate microorganisms that may contribute to an “inflammatory microbiota” triggering disease. Concomitantly, these studies have also provided evidence for the role of “anti-inflammatory” microbiota in providing a protective effect and/or promoting remission via immunomodulation. In that context, *Faecalibacterium prausnitzii* is a gut bacterium that produces anti-inflammatory factors, and can improve gut barrier function in chemically-induced colitic mice. Although this bacterium is abundant in healthy individuals, it is depleted in many IBD patients. Furthermore, longitudinal studies of Crohn’s Disease and ulcerative colitis patients have shown the poor restoration of *F. prausnitzii* populations is predictive of recurrent disease. In summation, the functional bases and implications of dysbiosis in IBD are still largely undefined, but the evidence suggests that specific members of the gut microbiota can contribute either pro- or anti-inflammatory effects, and their ecological fitness in the large bowel affects the onset and recurrence of IBD. Metagenomics and related approaches offer the potential to provide novel and important insights into these microbiota and thereby the pathophysiology of IBD, and likely will provide a rationale for new targeted strategies to improve the risk stratification, clinical management and treatment of IBD patients.
Smoking and diet: Impact on disease course?

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**Background:** Smoking increases the risk of developing Crohn’s disease (CD) and decreases that of ulcerative colitis. The western diet, possibly through an increased consumption of linoleic acid, may be associated with an increased risk of IBD. The impact of smoking and diet on disease course is less clear.

**Key Messages:** Current smoking worsens the course of CD, increasing the incidence of flares, the need for steroids, immunosuppressants, and re-operations. Conversely, smoking cessation has a rapid beneficial effect on disease course, decreasing the risk of flares and of post-operative recurrences. From three months after the quit date, quitters have a disease course similar to that of never smokers. Achieving smoking cessation in CD is thus an important goal of therapy. On the contrary, smoking improves the course of ulcerative colitis and in particular, is associated with a decreased need for colectomy. Smoking cessation increases the risk of flare and the need for steroids or immunosuppressants. However patients with ulcerative colitis should not be discouraged to quit, because the beneficial effect of smoking for their disease is counterbalanced by the deleterious systemic effects of tobacco. Among dietary interventions, only exclusive enteral nutrition was shown to induce remission and achieve mucosal healing in some patients with CD. The beneficial effect of liquid defined diet is observed whatever the type of administration (orally or by tube), the type of diet regarding protein and fat content, and resulting alterations in the gut microbiota. In ulcerative colitis, enteral nutrition has no effect. Finally, popularized restrictive diets in IBD as the specific-carbohydrate diet and the gluten-free diet have not been rigorously tested. In a small trial, a semi-vegetarian diet was shown to be effective in maintaining remission over two years in CD.

**Conclusion:** Patients with IBD should not smoke and avoid passive smoking. Aside from defined liquid diets, there is no rationale for advising particular diets.
High altitude journey, flights and hypoxia: Any role for disease flares?

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Several studies have demonstrated over the last few years that hypoxia and inflammation are closely related. While hypoxia may lead to inflammation, inflammation can also lead to hypoxia in the tissue via different mechanisms, such as edema and vasoconstriction. Both, inflammation and hypoxia seem also to play an important role in IBD. Several studies on surgical specimens taken from IBD patients showed an elevated level of hypoxia-inducible factors (HIF)-1α and HIF-2α. These two factors trigger the expression of genes that are responsible for the maintenance of intestinal epithelial barrier function and are involved in inflammation. Based on these findings, we hypothesized that IBD patients might be prone to develop flares while travelling to high altitudes or travelling by aircraft. We therefore conducted a questionnaire-based survey. IBD patients from in- and outpatient clinics of three Swiss tertiary hospitals (Triemli Zurich, University Hospital Zurich, and Centre Hospitalier Universitaire Vaudois) were recruited. We found that IBD patients with recent flare-up episodes more frequently travelled by aircraft or journeyed to high altitude regions within four weeks of experiencing these episode(s) when compared to the group that remained in remission. We conclude that flights and stays at an altitude of > 2000 m above the sea level are a risk factor for IBD flare-up episodes.

To further evaluate the potential influence of hypoxia on the course of IBD on a biomolecular level and to test the effects of hypoxia under standardized conditions, we initiated a prospective and controlled investigation in both healthy controls and IBD patients in stable remission. Ten healthy volunteers, 10 Crohn’s disease (CD) patients and 10 ulcerative colitis (UC) patients will underwent a 3 hours exposure to hypoxic conditions simulating an altitude of 4000 m.a.s.l. in a hyperbaric pressure chamber situated at the Swiss aeromedical centers Dubendorf, Switzerland. Stool samples analyzing calprotectin and microbiotal composition, biopsy samples from the rectosigmoid region and blood samples were repetitively collected and analyzed in conjunction with detailed records of clinical symptoms. First results will be presented in the talk.
IBD and environment: Are there differences between East and West?

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**Background:** The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis occur worldwide with differences in epidemiology, etiology and phenotype between regions. Breakthroughs have occurred in IBD genetics, although the genes that predispose to IBD differ between racial groups. What do we know about the “envirotype” of those who develop IBD and are there differences between East and West?

**Key Messages:** The strongest IBD risk factor identified to date is a family history of IBD. Whilst likely representing an underlying genetic predisposition, it may also reflect shared environmental factors amongst family members. Cigarette smoking increases the risk of developing CD, whilst smoking is less common in those who develop UC. Having ceased smoking increases the risk of developing UC subsequently. Unlike the West, cigarette smoking appears to play a lesser role in the East. Other environmental risk factors are inconsistent. Studies of migrant populations moving from regions of low to high IBD incidence point to early life as a key time for environmental triggers. In these populations, it is the second generation (those born in the high incidence region) with higher IBD incidence rates than their parents. Early life environmental exposures have been studied exhaustively but, except for having been breastfed, few putative early childhood environmental risk factors have been shown consistently to alter the risk of developing IBD.

**Conclusions:** The identification of IBD environmental risk factors remains elusive in both the East and West. In the West, case-control studies are unlikely to move the field forward without multi-level (phenotype, genotype, diet history, “envirotype”, microbiome) data, ideally collected prospectively. Cohort studies (such as the GEM project) may address some of these issues. However, in the East where IBD incidence is still increasing, well-designed comprehensive case-control studies may identify differences that give an insight into the “envirotype” driving IBD incidence.
Session V

Treatment decisions: Common markers in East and West?
Inflammatory bowel disease (IBD) is thought to be the result of abnormal immune responses to commensal microbiota in genetically susceptible individuals. Routine laboratory parameters including CRP, leukocyte count, ESR are highly unspecific and do not correlate with colonic inflammation. Recent work has demonstrated that serum antibodies against microbes or self-antigens have been used as markers in predicting disease course, complications, and response to medications and surgery, and demonstrated to be useful in differentiating subjects with IBD from non-IBD. The first discovered serologic marker associated with IBD is anti-Saccharomyces cerevisiae (ASCA), which has the best combined sensitivity (31–45%) and specificity (90–100%) for diagnosing IBD. ASCA has been the focus of extensive investigation for the diagnosis of Crohn’s disease (CD) and for disease stratification. It is more associated with CD and present in 50–70% of CD patients. Moreover, ASCA shows a quantitative and qualitative association with fibrostenotic and internal penetrating disease courses as well as the need for CD-related surgery. A case-control study in an adult population has shown a higher risk for surgery in ASCA-positive patients, indicating that ASCA functions as a serum biomarker in CD diagnosis and predicts the disease prognosis. Anti-neutrophil cytoplasmic antibodies (ANCAs) are autoantibodies directed against a constituent of neutrophil granules. Perinuclear-ANCA (pANCA) has a specificity of approximately 90% for both CD and ulcerative colitis (UC) patients. pANCA is detected in 50–85% of UC patients and 10–20% of CD patients. Therefore, pANCA is more associated with UC. Recent reports have shown that combined testing for pANCA and ASCA, which is relatively specific for CD, may be a sensitive and specific way to distinguish UC from CD. Recently, anti-glycan antibodies have been found including anti-laminaribioside carbohydrate IgG (ALCA), anti-mannobioside carbohydrate IgG (AMCA), anti-chitobioside carbohydrate IgA (ACCA), anti-laminarin (anti-L), and anti-chitin (anti-C) carbohydrate antibodies. Elevated levels of these serological biomarkers have been found to be associated with IBD-susceptible gene variants. These biomarkers serve as valuable complementary tools in IBD diagnosis and treatment for its non-invasive, easily accessible and repetitive, economical, highly specific and sensitive characteristics. However, their actual clinical value needs to be further investigated and validated.
Although the etiopathogenesis of inflammatory bowel diseases (IBD) is still unclear, enormous progress has been made in recent years to improve the diagnosis and treatment of IBD. However, the term IBD summarizes various inflammatory disorders of the bowel that show some major similarities but also distinctive features that allow the categorisation into Crohn’s disease (CD) and ulcerative colitis (UC) and indeterminate colitis (IC). The disease course of the IBDs may vary substantially, e.g. penetrating or stenosing CD or proctitis and pancolitis in UC. Especially after the initial diagnosis, but also during the course of an IBD it would be very helpful, if the disease course of an IBD could be predicted in order to select the most beneficial diagnostic and therapeutic approaches. Even today, the majority of patients with CD require resectional surgery during the course of their disease. A significant number of them will suffer symptomatic recurrence in the years after their operation, leading to new complications and frequently to repeated surgery and the need for specific medical treatment. But also in UC patients, a significant number of patients will undergo surgical treatment due to fulminant disease, insufficient response to medical treatment or complications due to medical treatment or disease, e.g. development of precancerous or neoplastic lesions, refractory bleeding and other.

Although the spectrum of IBDs is broad, the course of disease in different IBDs may vary significantly and post-operative recurrence is common in CD and also following proctocolectomy and ileo-anal pouch anastomosis, the predictors for the future course of an IBD and especially a complicated disease course have not been well identified and remain speculative.

Smoking significantly increases the risk of a complicated disease course in CD with a higher incidence of fistulizing and fibrostenosing disease and earlier recurrence following surgery. Quitting smoking reduces the post-operative recurrence rate significantly. Several studies have shown a more complicated disease course in patients with perforating disease than in those with non-perforating disease. In addition, CD patients with extensive involvement of the small bowel, involvement of the upper GI tract, deep colonic ulcerations and rectal involvement, significant weight loss after onset of disease have a more complicated disease. Also in UC the presence of extensive colitis suggests a more complicated disease course compared to limited disease extension. High CRP levels, the need for early systemic steroids due to disease activity, the lack of response to systemic steroid treatment and the lack of mucosal healing following initial treatment are also predictors for a more complicated disease course both in CD and UC. Several studies suggest that mucosal cytokine profiles may be helpful to predict the recurrence of IBD. Elevated mucosal concentrations of TNF-α, IL-1 and IL-6 in the ileocolonic mucosa have been described as independent predictors for future relapse of IBD. However, the measurement of mucosal cytokine levels is not used in standard clinical care. Postprandial flow measurements in the superior mesenteric artery are closely related to clinical disease activity in patients with CD and repeated measurement of the
postprandial pulsatility index has been reported to be a predictor for the risk of recurrence in CD.

In summary, the prediction of the future disease course of an IBD is based on clinical judgement. Currently, no sophisticated genetic or serological predictors have been identified to allow a scientific prediction of the disease course in IBD and to select and identify those patients earlier that would benefit from more aggressive treatment approaches and more intensive monitoring.
Calprotectin or lactoferrin: Do they help?

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The diagnosis and monitoring of inflammatory bowel disease has traditionally relied on clinical assessment, serum markers of inflammation and endoscopic examination. Fecal biomarkers such as calprotectin (FC) and lactoferrin (FL) are predominantly derived from neutrophils, are easily detectable in the feces, and are emerging as valuable markers of intestinal inflammation.

FC and FL have sufficient discriminating value to assist in differentiating both adult and pediatric patients with gastrointestinal symptoms into those who may have an inflammatory condition versus those with a functional disorder.

In Crohn’s disease (CD), fecal biomarkers reflect the presence of active disease and correlate with the severity of endoscopic lesions. FC has been the most extensively studied biomarker in patients on therapy for CD, and in this context reflects the response to therapy and the achievement of mucosal healing. Increasing FC concentrations after withdrawal of therapy appear to correlate with the risk of clinical relapse. FC is also sufficiently sensitive to monitor for endoscopic CD recurrence in the post-operative setting.

In ulcerative colitis (UC), fecal biomarkers reflect active disease and endoscopic severity. FC reflects response to therapy and the achievement of mucosal healing and can be used to predict relapse in UC. In acute severe ulcerative colitis FC may be able to predict the clinical course including steroid responsiveness and likelihood of colectomy. The role of fecal biomarkers in the monitoring of proctitis however have not yet been established.

Inexpensive, non-invasive and reproducible, fecal biomarkers appear to have a wide utility in the diagnosis and monitoring of inflammatory bowel disease. Further studies are required to accurately describe cut-offs in a variety of clinical settings and to establish firm targets as inflammatory bowel disease management moves towards a treat-to-target approach, with increased monitoring and tighter control of inflammation.
Iron deficiency, zinc, magnesium, vitamin deficiencies: Substitute or not substitute?

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Inflammatory bowel disease (IBD) is characterized by inflammatory reactions, complications, extraintestinal manifestations and a loss of intestinal functions, e.g. failures of absorption and secretion.

Iron deficiency is the most frequent cause of anemia in IBD. Although anemia may have significant impact on the quality of life of IBD patients it is often underdiagnosed and undertreated. Iron deficiency in IBD is caused by multiple factors including iron loss from intestinal bleeding and inflammation-driven blockage of intestinal iron acquisition and macrophage iron reutilization. Basic laboratory screening for anemia in IBD should comprise Hb, full blood counts (including reticulocytes), assessments of total store of body iron with serum-ferritin, transferrin saturation and of the level of inflammation by means of C-reactive protein. Iron supplementation can be achieved by mouth or intravenously. Oral iron supplements are available as either divalent Fe²⁺ (ferrous) salts or trivalent Fe³⁺ (ferric) forms coupled with sugar complexes. Oral iron supplementation is frequently associated with gastrointestinal side effects such as nausea, vomiting, diarrhea, abdominal pain, and constipation. Results from animal studies have created contradictory evidence regarding exacerbation and/or improvement of inflammation. In humans results are even more controversial and interventional studies are lacking. Compared with oral iron, intravenous iron seems to increase Hb and iron storage and improves quality of life more rapidly. In contrast to earlier formulations with high molecular weight dextrans, which comprised relevant risks of severe adverse reactions, modern formulations such as ferric carboxymaltose, iron isomaltoside 1000 and ferumoxytol show much lower side effects.

Zinc is an essential mineral for human health. It is relatively abundant in nature, yet at the same time, overwhelming data suggest that zinc deficiency is one of the most prevalent micronutrient deficiencies worldwide. Nowadays, it is recognized that zinc is important for many basic metabolic processes, and hence essential for optimal growth, immunocompetence and even visual acuity. Low serum zinc concentrations have been reported in Crohn’s disease (CD) and overt zinc deficiency has been described. In CD zinc deficiency can cause characteristic manifestations such as acrodermatitis enteropathica. Apart from inadequate dietary intake of bioavailable zinc, other significant contributors to zinc deficiency may include the excessive intestinal loss of endogenously secreted zinc or impairment in small intestinal absorptive function. Zinc gets absorbed throughout the whole small intestines but most intensive in the jejunum. For assessments of zinc deficiency a clear indicator is lacking as there is no specific biomarker. While determination of plasma zinc concentration is often used, zinc can also be measured in urine and hairs. Zinc supplementation has various therapeutic effects in IBD.

Magnesium deficiency is a frequent complication of IBD demonstrated in 13–88% of patients. Magnesium is absorbed from all parts of the bowels but mainly from jejunum and ileum. Hypomagnesemia is a common complication of short bowel
syndrome. Signs and symptoms of Mg deficiency include: cramps, bone pain, delirium, acute crises of tetany, fatigue, depression, cardiac abnormalities, urolithiasis, impaired healing and colonic motility disorders. Though often measured serum magnesium is not a good marker of magnesium deficiency. Twenty-four-hour urinary excretion of Mg is a sensitive index and should be used. Magnesium can be supplemented both routes orally as well as intravenously.

**Vitamins** are often deficient in IBD. Deficiencies are variable and depend on the disease status. Because of its specific site of absorption, the terminal ileum is particularly predisposed to vitamin B12 (cobalamin) metabolism. In patients with active ileitis and especially in patients with a resected terminal ileum vitamin B12 is often lacking. The most important clinical manifestations of vitamin B12 deficiency include dysfunction of the peripheral and central nervous systems and megaloblastic anemia. Determination of serum vitamin B12 has poor diagnostic accuracy for isolated biochemical deficiency. Measurement of the serum concentration should be combined with additional functional biomarkers such as homocysteine. Most time vitamin B12 deficiency is treated with parenteral supplementation, but, though poorly studied oral supplementation may be also effective in some instances.

Bile acids are required for proper absorption of dietary fat-soluble vitamins A, D, E, and K. Enterohepatic circulation of bile acid is often disturbed by inflamed or resected terminal ileum in CD thus causing bile acid malabsorption and subsequent fat-soluble vitamins deficiency. The role of vitamin D is of particular interest. Its epidemiology, the genetic association of vitamin D receptor polymorphisms, and results in animal models suggest that vitamin D plays an important role in the pathogenesis of IBD. As yet, some trial data of vitamin D supplementation on disease activity in patients with CD suggest promising results.

**In conclusion** iron, zinc, magnesium and vitamin deficiencies have significant impact on complications and quality of life in IBD. It may even influence the course of the disease. Those deficiencies should be thoroughly supplemented.
Session VI

The basics of IBD therapy
Antibiotics for IBD therapy

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The dysbiosis that occurs in inflammatory bowel disease (IBD) suggests that an alteration in the gut microbiome has associations to the disease etiology. Nevertheless, it remains unclear as to whether the dysbiosis is directly linked to the cause of IBD or if it simply reflects a consequence of another process. Ongoing studies using the science of genomics and metagenomics are striving to unravel this exact relationship between the microbiome and IBD. Nevertheless, both circumstantial and direct evidence suggests that administering agents that impact the composition and balance of the microbes in the gut could be therapeutic and impact the course of IBD. As such, significant efforts have gone into the development and testing of therapeutic agents to modulate the gut microbiome. Anitbiotics, probiotics, prebiotics, and more recently fecal microbial transplantation have been utilized to both induce and maintain remission in a host of clinical IBD scenarios. The single best randomized studies for antibiotics in the treatment of IBD comes from the use of nitroimadoles postoperatively in Crohn’s disease to prevent disease recurrence and the best clinical evidence comes from their use in perianal fistulas disease and chronic pouchitis. Although a recent meta-analysis concluded that antibiotics are superior to placebo at inducing remission in both Crohn’s disease and UC, the studies the meta-analysis drew from were heterogenous, of small size and with significant viability in the spectra of antibiotic activity. In contrast the data are limited with the regard to maintaining remission in either Crohn’s disease or ulcerative colitis (UC). Despite the absence of robust clinical trial data, antibiotics continue to be widely used as therapeutic agents in the treatment of IBD, especially post-operatively and with perianal disease and chronic pouchitis.

While antibiotics may have therapeutic effect it is important to also consider the role they may play in directly exacerbating IBD or the risk they impose with regard to infections like Clostridium difficile-associated disease. Thus, while the rationale for devising microbial-based therapeutic interventions in IBD appears sound there are challenges to realizing the potential for therapeutic manipulation of the microbiota in IBD. Not only is there striking disparity in results in animal models vs. the human condition there is also a heterogeneity of IBD in humans that is paralleled by a heterogeneity of therapeutic responses to microbial manipulation. Nevertheless, with encouraging results from fecal microbial transplantation and the science of metagenomics new developments will maximize therapeutic efficacy and minimize safety concerns.
References:

Aminosalicylates have remained foundational therapies for inflammatory bowel disease since the development of sulfasalazine (salazopyrine, SASP) over 50 years ago. While identification of an exact mechanism of action has been elusive, identification of 5-aminosalicylic acid (5-ASA) as the active ingredient has allowed further pharmacological technologies to target 5-ASA to sites along the digestive tract to optimize dosing, delivery and to improve patient compliance.

5-ASA has become the standard inductive and maintenance therapy for patients presenting with mild-moderate ulcerative colitis. While controlled clinical trials demonstrated a dose-response for SASP in the setting of mild-moderate UC, it has been more difficult to distinguish a dose-response for induction or maintenance with 5-ASA beyond 2.4–3 g daily. However, recognition of the spectrum between mild-moderate UC and the heterogeneity of patients extent and severity has elucidated subsets of patients who are more likely to respond to oral dosing up to 4.8 g daily. Similarly, topical (rectal) formulations of 5-ASA administered as retention enemas, foams or suppositories have been highly effective inductive and maintenance agents for the treatment of ulcerative proctitis and left-sided colitis as long as the formulation reaches the proximal extent of colonic inflammation.

Of interest, while oral formulations of 5-ASA have been similarly efficacious for patients with extensive or distal colitis, comparative trials have demonstrated that topical administration for patients with distal disease is more effective than oral formulations. In addition, and somewhat unexpected, the combination of oral and topical 5-ASA has been more efficacious than oral administration for patients with mild-moderately active distal and extensive colitis.

A major attribute of 5-ASA therapies has been the safety and tolerability profiles for both inductive and maintenance treatment. Patients should be “monitored” for rare instances of idiosyncratic nephrotoxicity (interstitial cystitis) and prescribers should be aware of rare allergic/sensitivity reactions including pericarditis, pneumonitis, hepatitis, pancreatitis and colitis.
When should immunosuppression be started?

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Immunomodulators, such as thiopurines and methotrexate, are an important class of drugs in the treatment of inflammatory bowel disease. While thiopurines have proven steroid-sparing effect and established efficacy in the maintenance of remission in ulcerative colitis (UC), the role of methotrexate in UC is unclear although preliminary results from a recent randomized controlled trial suggest no benefit over placebo. In patients with Crohn’s disease (CD), methotrexate has a modest steroid-sparing effect and has been shown to be superior to placebo in maintenance of remission in responders. On the other hand, methotrexate is not associated with improved outcomes when added to infliximab in patients with CD.

Although widely used in clinical practice, the optimal timing and exact therapeutic role of thiopurines in CD is less established. Thiopurines are not effective for induction of remission in CD but have a modest effect in steroid-dependent patients, in the maintenance of remission, and in the prevention of post-operative recurrence of CD. Recent studies from Europe have, however, put into question the benefit of early azathioprine in newly diagnosed CD. The strongest indication for immunomodulators in CD is perhaps as part of combination therapy with anti-TNF biologics. The addition of thiopurines to infliximab results in reduced immunogenicity, higher levels of the biologic agent, reduced inflammatory markers, and improved outcomes. However, the benefit of continued thiopurine therapy in this setting is unclear and should be weighed against possible side effects including an increased risk of lymphoma and non-melanoma skin cancer.
Biosimilars are biologic products ‘sufficiently similar’ but not identical to the reference biologic (‘Originator’). Unlike generic small molecules, biosimilars have much larger and complex structure. Biosimilars aim to substitute for Originators whose patent has expired and are produced by a different company. Because the Originator’s manufacturer maintains the right not to disclose their production line after patent expiration, biosimilars are derived from genetically modified living organisms by different manufacturing process. This includes the creation of a cell bank by isolation of the gene(s) of interest which are transferred to plasmid and then to the selected type of host cells followed by fermentation, purification, formulation and packaging of the final product. It is conceivable that even small changes in this process can cause subtle structural differences between the biosimilar and its originator resulting in considerable deviations in clinical efficacy and safety. Thus, to grant approval and licensing regulatory authorities require extensive quality, nonclinical and clinical data to prove high similarity between the biosimilar and the originator in pharmacodynamics, pharmacokinetics, bioequivalence, comparative efficacy and safety, including immunogenicity. Biosimilars fall into 3 main categories, products similar to natural body substances, monoclonal antibodies, and engineered proteins, but as license requirements differ remarkably between leading authorities (e.g. EMA, FDA and Health Canada), a limited number of biosimilars, namely human growth hormones, erythropoietins and granulocyte colony stimulating factors, has been approved almost exclusively by EMA.

The anti-TNF agents have revolutionized the treatment of IBD as well as of other immune-mediated diseases. However, the cost of treatment is remarkable for public and individual payers. The Biosimilar industry promises enhanced patient access to biologic therapy at a considerable price reduction of both, the biosimilar and the originator. Recently, EMA has approved CT-P13, an infliximab biosimilar (Inflectra® [Hospira, Inc. Lake Forest, IL, United States] and Remsima™ [Celltron, Inc., Incheon, Republic of Korea]) for adult and pediatric CD and UC. Approval was granted by extrapolating results of in vitro and ex vivo nonclinical data and clinical studies in ankylosing spondylitis (AS) and rheumatoid arthritis (RA) which showed comparable major physicochemical characteristics and biological activities of CT-P13 to Remicade. In the efficacy and safety study in active RA, patients in the ITT and PP populations achieved the primary end-point (equivalence in the 95% CI for treatment difference within ± 15% at week 30) and secondary end-points. These effects were further supported by comparable response rates at Week 54. No safety or immunogenicity signals were noticed. Hypothetical models based on pre-defined price reductions suggest considerable savings in Health Care resources which may allow additional patients to access biologic therapy. Some but not all independent studies with the infliximab biosimilar in IBD consisting of small case series and head-to-head comparisons with historical controls are generally encouraging but are far from offering unequivocal evidence for long-term safety and efficacy.
However, EMA’s decision has raised concerns from leading National and International Scientific Organizations. Criticism has focused mainly on extrapolating nonclinical and clinical data from RA and AS to IBD, especially because in the CT-P13 studies neither RA itself nor the selected treatment (combination of infliximab with methotrexate) is an ideal model and treatment, respectively, to support the effect of a biosimilar in IBD patients. Head-to-head comparative studies in IBD, physician-based decisions on substitutability, interchangeability, prescription by brand name, and robust pharmacovigilance including longitudinal immunogenicity monitoring have been suggested for long-term efficacy and safety of the biosimilar.

Biosimilars are expected to penetrate the anti-TNF market and will lead undoubtedly to reduction in the cost of treatment. However, as the driving force in the medical profession is primum non nocere the involved parts, manufacturers, regulatory authorities, and physicians should undertake their own responsibilities to ensure that the quality of production and safety of treatment with the biosimilars are maintained long-term at the level of their originators.

References:

Session VII

New options/treatments goals for IBD therapy
New data on methotrexate

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In 1989 Kozarek et al. were the first to report a beneficial effect of intramuscular methotrexate (MTX) therapy in 21 patients with refractory Crohn’s disease (CD) or ulcerative colitis.\(^1\) It took another 6 years to confirm clinical efficacy of MTX as induction regimen and 13 years as maintenance therapy in patients with CD. Two landmark trials of the North American Crohn’s Study Group Investigators published in 1995 and 2000 established that 25 mg MTX given intramuscularly once weekly for induction and 15 mg MTX given intramuscularly once weekly for maintenance was more effective than placebo in improving clinical symptoms and reducing requirements for prednisone.\(^2,3\) The further exploration of MTX in prospective clinical trials in ulcerative colitis was initially stalled in 1996 by the publication of a negative result of an Israeli multi-center study investigating the clinical efficacy of 12.5 mg MTX given orally in steroid dependent ulcerative colitis.\(^4\) However, starting around the year 2000 MTX was effectively used in patients with ulcerative colitis in clinical practice as shown by numerous retrospective single center analyses.\(^5\) The positive results of these retrospective findings triggered the development of 2 prospective clinical trials, one conducted by the GETAID (Groupe d’Étude Thérapeutique des Affections Inflammatoires du Tube Digestif) in France and one sponsored by the NIH (National Institute of Health) and performed by the CCFA-CRA (Crohn’s and Colitis Foundation of America – Clinical Research Alliance) in the USA. The French METEOR (Comparison of Methotrexate vs Placebo in Corticosteroid-dependent Ulcerative Colitis) trial investigated the clinical efficacy of subcutaneously applied MTX 25 mg once weekly as an induction regimen over 16 weeks. The trial failed to achieve the primary endpoint of a combined clinical and endoscopic remission, but showed a significant advantage of MTX to placebo for the secondary endpoint of clinical remission only.\(^6\) Due to the study design, which did not employ central reading of the endoscopy part of the primary endpoint, the results of METEOR are not as clear-cut as one would have hoped for. MTX could represent a unique and affordable therapy for ulcerative colitis patients in need for an immunosuppressive treatment. Therefore the ultimate proof of the clinical value of MTX in ulcerative colitis will be its efficacy in maintaining steroid free remission. This is the primary endpoint of the US MERIT-UC trial (Methotrexate Response In Treatment of UC), a prospective, randomized, placebo controlled study to analyze the efficacy of MTX to maintain steroid free remission over 54 weeks. This trial is still recruiting and the results are expected in early 2017.
References:


Inflammatory bowel diseases are chronic, progressive and disabling conditions. Conventional treatment strategies, which were based on symptomatic disease control do not appear to significantly alter the disease course. In contrast, the introduction of anti-tumor necrosis factor (anti-TNF) therapies over the past 10 to 15 years, supported by accumulating evidence both from randomized clinical trials and clinical practice, has led to a significant change in patient management, monitoring and new treatment algorithms in inflammatory bowel diseases. An important element of success is early patient stratification and the use of early aggressive medical therapy in a selected group of patients with bad prognostic factors. In addition, results from recent randomized clinical trials (e.g. ACT, EXTEND, POCER, REACT or STORI) underscore the need of continuous objective patient monitoring by looking beyond symptoms and assessing both biomarkers (e.g. CRP and calprotectin) and mucosal status in both Crohn’s disease and ulcerative colitis with the final aim of preventing structural damage and disability. Of note, endoscopic healing was associated with improved outcomes, less hospitalizations or surgery in both CD and UC. Furthermore, hypothesis-driven therapeutic strategy trials provided evidence that therapeutic decision guided by objective measures in addition to symptom assessment only were associated with less complications, surgery or post-operative recurrence in CD. This has led to new treatment goals, instead of focusing on symptomatic clinical response, treatment goals became ambitious and include normalization of biomarkers and mucosal healing. Recently an international consensus recommended also the use of composite endpoints including the above markers as treatment targets in both CD and UC. However, more long-term clinical data/trials are needed to assess whether implementation of therapeutic algorithms based on these targets in clinical practice have the potential to further improve long-term disease outcomes in inflammatory bowel diseases.
Anti-integrins in UC and CD: What is their place?

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Given that the cause of inflammatory bowel disease (IBD) is unknown, therapy is based on the empiric use of anti-inflammatory drugs. However, the recent identification of specific mechanisms that regulate cellular migration into inflamed intestinal tissue has provided novel targets for drug development.

Although the tumor necrosis factor (TNF) antagonists have greatly improved patient care and have a more selective mechanism of action than conventional agents, they are also systemic immunosuppressives that place patients at risk for infection. Ideally, medical therapy should target the pathological immune response in the gut while preserving systemic immunity. Recognition that lymphocyte trafficking to the bowel is governed by highly specific molecular interactions has advanced the concept of gut-specific immunosuppression.

Inhibition of leukocyte trafficking as a treatment for inflammatory disease is based on the concept that recruitment of activated white blood cells is integral to immune homeostasis.

Natalizumab (Tysabri®, co-marketed by Elan and Biogen) is a recombinant IgG-4 monoclonal antibody that blocks the α4 integrin subunit of integrin heterodimers. Consequently, both α4β1/VCAM-1 and α4β7/MAdCAM-1 mediated interactions are antagonized. In 2003, Gosh et al. performed a controlled trial that evaluated 248 patients with moderate to severely active CD. Patients were assigned to receive 2 infusions (week 0 and 4) of either placebo; 3 mg/kg of natalizumab followed by placebo; 2 infusions of 3 mg/kg of natalizumab; or 2 infusions of 6 mg/kg of natalizumab. Although the primary outcome of the study, the proportion of patients in remission (CDAI < 150) at week 6, was significantly different among the treatment groups, more patients in the 6 mg/kg natalizumab group were in remission at weeks 4 (29% vs. 14% in the placebo group, p = 0.028) and week 8 (43% vs. 16%, p < 0.001). Patients assigned to 3 mg/kg of natalizumab also had significantly higher rates of remission at week 4 (29% vs. 14%, p = 0.027, week 6 (44% vs. 27%, p = 0.03), week 8 (41% vs. 16%, p < 0.001) and week 12 (42% vs. 27% in the placebo group, p = 0.042). In 2005, Sandborn et al. reported the results of a large trial (ENACT) that showed a modest benefit of natalizumab induction therapy. However, the maintenance phase of this study showed clinically important differences in response (61% vs. 28%, p < 0.001) and, notably, corticosteroid-free remission (55% vs. 25%, p < 0.05) rates at week 36 in patients who responded to natalizumab induction therapy and continued maintenance therapy. A subsequent induction trial (ENCORE)
ultimately demonstrated the presence of a modest benefit for natalizumab induction therapy.

However the development of PML, a serious viral infection of the brain, proved to be a serious limitation to the use of natalizumab. Recently, JCV serology has been developed that has high sensitivity for detection of latent viral infection. As data accumulate regarding the safety of natalizumab in patients with negative serology, natalizumab therapy may evolve into an acceptable option for the management of refractory CD. However, more attractive alternatives are now available.

Vedolizumab (Millennium Pharmaceuticals Inc.; Takeda, Cambridge, Massachusetts) (previously known as MLN-02, LDP-02, MLN0002) is a humanized IgG-1 monoclonal antibody directed to the integrin $\alpha_4\beta_7$.

Two large multicenter randomized placebo controlled trials evaluated the efficacy and safety of vedolizumab induction and maintenance therapy for UC and CD. GEMINI I evaluated 374 patients with active UC, randomized in a 3:2 ratio to receive either 300 mg of IV vedolizumab or placebo at weeks 0, 2 and 6. 48% of those who received vedolizumab had prior exposure to a TNF-antagonist and 41% had failed treatment with 1 of these agents. At week 6, clinical response was observed in 47.1% of patients assigned to vedolizumab compared to 25.5% of those treated with placebo ($p = < 0.001$). Corresponding remission rates were 16.9% and 5.4% ($p = 0.001$). Higher rates of mucosal healing were also observed (40.9% vs. 24.8%, $p = 0.001$). In the maintenance phase of the trial, vedolizumab responders were re-randomized to receive vedolizumab 300 mg every 4 or 8 weeks or placebo for up to 52 weeks. An additional 511 patients were enrolled in the maintenance study from an open-label trial. A total of 373 patients were equally randomized to 1 of 2 vedolizumab dose regimens or placebo. At week 52, the rates of remission in patients who received vedolizumab every 8 weeks, every 4 weeks or placebo were significantly different in favor of the vedolizumab groups (44.8% vs. 41.8% vs. 15.9%, $p = < 0.001$). No cases of PML were observed and the rates of opportunistic and serious infections were also not different amongst the treatment groups.

In CD GEMINI II evaluated 368 patients with active disease who were randomized, in a 3:2 ratio, to receive induction therapy with 300 mg of IV vedolizumab or placebo at weeks 0, 2 and 6. As was the case for GEMINI I the maintenance phase of GEMINI II comprised of responders from the randomized induction component and from an open label cohort study ($n = 747$). In maintenance, participants received vedolizumab every 4 or 8 weeks or placebo for up to 52 weeks. At the end of the induction phase, the rate of clinical remission was greater in patients who received vedolizumab than in those assigned to placebo (14.5% vs. 6.8%, $p = 0.02$). However, response rates were not different between the 2 groups (31.4% vs. 25.7%, $p = 0.23$). At week 52, remission was present in 36.4% and 39% of patients receiving vedolizumab every 4 weeks ($p = 0.0042$) and every 8 weeks ($p = 0.0007$) compared to 21.6% of those who were assigned to placebo (49). In a second multicenter double-blind phase III, randomized, placebo-controlled induction trial, 416 patients with active CD, the majority of whom had failed a TNF-antagonist ($n = 315$), were randomized to receive 300 mg of vedolizumab or placebo at weeks 0, 2, and 6. In the TNF-antagonist failure population remission was observed at week 6 in 15.2% of patients assigned to vedolizumab and 12.1% of those who received placebo ($p = 0.433$). However, all
secondary endpoint including remission at week 6 in the overall population and at week 10 in TNF antagonist failures and in the overall population, sustained remission in both populations, and CDAI-100 response in the TNF-antagonist failure population were met.

Etrolizumab (RHuMab\(\beta\)7, PRO145223, RG-7413; Genentech, San Francisco) is a humanized IgG-1 monoclonal antibody targeting the \(\beta\)7 integrin. Accordingly etrolizumab blocks both \(\alpha\text{E}\beta\text{7}\) and \(\alpha\text{4}\beta\text{7}\) integrin mediated interactions with their ligands, MAdCAM-1 and E-cadherin respectively. Etrolizumab and several other agents that block lymphocyte trafficking to the gut are currently under evaluation in Phase III trials.

Selected References:


Mucosal healing: How deep is enough?

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Mucosal healing has emerged as an important outcome measure of treatment in inflammatory bowel disease. It is increasingly incorporated in the outcome measures of clinical trials along with patient reported outcomes and used in clinical practice as a therapeutic target or goal. The exact definition of mucosal healing continue to evolve and several scoring systems have evolved, some of which require further validation. Considerable inter-observer variation may also exist in interpretation of mucosal appearance in inflammatory bowel disease. Novel endoscopic techniques demonstrate that even in patients who have achieved mucosal healing by conventional criteria, subtile inflammation may continue to persist. Whether mucosal healing needs to incorporate or reflect histological healing is a topic of intense debate and further studies. In addition, surrogate markers of mucosal healing, such as fecal calprotectin, may serve as a therapeutic target, but there is debate about whether normalization of fecal calprotectin always reflects mucosal healing. Patients with mucosal healing may also continue to have clinical symptoms reflecting visceral hypersensitivity.
Session VIII

Biologicals and beyond
Hematopoietic stem cell transplantation for Crohn’s disease

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Crohn’s disease is characterized by chronic inflammation in segments of the digestive tract and tissue damages. A significant progress has been made over the 2 last decades in the management of Crohn’s disease. However, a fraction of Crohn’s disease patients experiences severe disease, refractory to all available therapies.

Evidence for the feasibility and efficacy of hematopoietic stem cell transplantation (HSCT) has been reported in several types of severe treatment-resistant immune mediated inflammatory diseases, including multiple sclerosis and systemic sclerosis. Analyses of the EBMT database provided evidence for the feasibility and the toxicity of the HSCT procedures in immune mediated diseases. Despite long-term benefits, it is associated with a high morbidity and 2–10% mortality rate, making it an acceptable option for only highly refractory patients. The effect of HSCT on the disease is probably associated with a resetting of specific immune responses.

The first evidence of effectiveness of HSCT in IBD was observed in patients who underwent allogeneic or autologous HSCT for hematological or solid malignancy. Beyond short series, autologous HSCT as primary treatment for Crohn’s disease has been investigated in prospective studies. Prolonged drug-free remission is observed in a high proportion of patients. However, a significant rate of relapse is observed on the long-term in one study, raising questions regarding the benefits over conventional treatments.

Accordingly to the EBMT guidelines, HSCT should be proposed only in patients with active Crohn’s disease refractory to immunosuppressants and biologics, and after consideration of all therapeutic options including surgery.

The ASTIC trial, an international investigator-initiated randomized study, evaluates the early and late effects of autologous unselected HSCT on Crohn’s disease over 5 years. Supported by ECCO and sponsored by EBMT, it was performed in accredited transplant centers from six European countries. Only patients aged 18–50 years with impaired quality of life from active Crohn’s disease not amenable to surgery, despite treatment with ≥ 3 immunosuppressive/biologic agents, could be included. All cases suitable for the trial were discussed by a steering committee, which made suggestions for alternative management in a significant proportion of cases. 48 patients underwent mobilization of stem cells, and 45 patients were randomized to transplantation at 1 month (n = 23) or control treatment (HSCT deferred for 1 year, n = 22). If patients improved, corticosteroids and immunosuppressive/biologic drugs were systematically weaned. CDAI and SES-CD were used to assess Sustained Disease Remission, a composite primary endpoint that required clinical remission (CDAI < 150) without corticosteroids or immunosuppressive/biologic drugs for at least the last 3 months with no endoscopic/radiological evidence of active disease at 1 year. Results at 1 year have been recently presented in international congresses. Among the 23 patients who underwent early HSCT, only 2 HSCT patients achieved all criteria for Sustained Disease Remission vs. 1 in controls. Ten patients were in
clinical remission at 1 year vs. 2 in the control group. A significant higher proportion of patients were off immunosuppressive/biologic drugs for more than 3 months in the HSCT group (61% vs. 23%). There were more serious adverse events in the HSCT group. One patient died following HSCT.

In conclusion, autologous HSCT is successful in inducing drug-free remission in Crohn’s disease patients with severe and highly refractory disease. Despite the risks of this procedure, autologous HSCT may still represent a therapeutic option in highly selected cases. Future research should focus on selection of patients and reduction of risks related to HSCT.
The challenge of intestinal tuberculosis as a differential diagnosis

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Crohn’s disease (CD) and intestinal tuberculosis (ITB) are chronic granulomatous inflammatory diseases with very similar clinical, endoscopic, radiological, and histological features. Misdiagnosis rates between ITB and CD range from 50% to 70%, distinguishing CD from ITB has become a clinical challenge, especially in developing countries. Features indicative of ITB include night sweat, concomitant pulmonary tuberculosis, positive tuberculin skin test, positive antibodies to tuberculosis, abdominal lymphadenopathy, ascites, transverse ulcers, involvement of fewer than four segments, patulous ileocecal valve and scars or pseudopolyps. The features of hematochezia, intestinal obstruction, fistula, anorectal lesions, oral ulcers, longitudinal ulcers, aphthous ulcers, cobblestone appearance and pseudopolyps were more common in CD than in intestinal tuberculosis. Significant differences were noted between ITB and CD with regard histopathologic features: size of granulomas, giant cells, caseation necrosis, confluent granulomas, discrete granulomas, and granulomas with lymphoid cuffs. The pooled sensitivity and specificity of IGRA for the diagnosis of ITB was 81% (95% CI: 75–86%) and 85% (95% CI: 81–89%) respectively. CT enterographic and TB-PCR testing of colonic tissue specimens are also useful. CTE findings, proximal small-bowel involvement, asymmetrical mural thickening, segmental small-bowel lesions, mural stratification, the comb sign, and mesenteric fibrofatty proliferation were significantly more common in CD, whereas mesenteric lymph node change (calcification or central necrosis) and focal ileocecal lesions were more common in ITB. Systematic review showed the pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of IGRA for the diagnosis of ITB was 81% (95% CI: 75–86%), 85% (95% CI: 81–89%), 6.02 (95% CI: 4.62–7.83) and 0.19 (95% CI: 0.10–0.36), respectively.
Surgery or biological therapy: Cost efficacy

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Why compare biological therapy with surgery for IBD? They are neither directly comparable, nor mutually exclusive. Nevertheless, the question often arises, not least when treating localized ileocolic Crohn’s disease (CD). Cost, of course, means many things beyond dollars and cents.

The cost of IBD: In the pre-biologic era, hospitalisation accounted for around half (49–57%), costs were higher with increasing extent of disease\(^1,2\), and surgery contributed 43% to lifetime costs of IBD\(^3\). The direct cost of care vary with the health care system, but have been estimated at, $12,147 for CD in the US, but three times this if hospitalized. In Europe the EC-IBD cohort in 9 countries reported a mean cost of around €6000 for active CD and €3500 for ulcerative colitis (UC). Indirect costs (work productivity, welfare benefits etc.) to society may be double the direct costs of care. Comparability between studies is not a strong point of pharmacoeconomic data. The costs of care for IBD in Asia have not been reported.

The cost of biological therapy: In 1998 along comes biological therapy and in 2007, treatment with adalimumab during a registration trial halved the 12 month risk of hospitalisation (15.7–8.0%). The UK National Institute of Health and Care Excellence (NICE) tries to account for disparate data by calculating the incremental cost effectiveness ratio (ICER) which is the extra cost to produce an extra unit of health, measured by quality adjusted life year. An ICER of < £30,000 is considered by NICE to be ‘cost-effective’. The ICER for 2 years continuing therapy with adalimumab was £10,310 (and £21,300 for infliximab, reflecting hospitalisation for infusion). Meanwhile biosimilars are reducing the costs of infliximab by 30–70% in Europe (2015) and adalimumab biosimilars are round the corner.

The cost of surgery: No comparable data for surgical intervention exist. The patient population and decisions to operate clearly differ from decisions to use biological therapy. Nevertheless, in 2005/6, the mean cost of surgical care for IBD (n = 7375) in Manitoba was $18,749, but for those treated with IFX it was $31,440. Attempts to show that the cost of care has declined since the introduction of biological therapy have been unsuccessful. Indeed the likelihood of surgery after infliximab in the Manitoba IBD cohort was higher than for those given azathioprine – although disease severity clearly differed. Step forth LIRIC, a randomized controlled trial comparing the 12 month cumulative costs and quality of life of surgery or infliximab therapy for recurrent ileal CD. Recruitment of 142 patients is almost complete (June 2015) and results will be presented in 2016.

Conclusions: Debate will continue as biosimilars reduce medical costs. Patient selection is crucial: surgery is a coherent medical decision for some patients with a lifelong disease and not a failure.
References:

Personalising IBD therapy: The Asian perspective

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All patients with inflammatory bowel disease (IBD) share common therapeutic goals, including complete mucosal healing and improvements in long-term outcomes (e.g., reduction in hospitalization, surgery and mortality). However, therapeutic options for achieving these goals are different among patients from no therapy to early introduction of combination therapy with anti-TNF and immunosuppressive agents, because IBD patients have diverse features in terms of severity, phenotypes, clinical courses and responses to therapy. The initial steps of personalized therapy are the selection of the right patients by predicting the clinical course of IBD and then the selection of the right therapy (right medication and right dose) by predicting the response to therapy. The next step of personalized therapy is the adjustment of therapy through therapeutic response evaluation and therapeutic drug monitoring. By personalizing IBD therapy, we may maximize the efficacy of management, minimize the risk of adverse events, and ultimately decrease costs. Of note, current recommendations of personalized IBD therapy are mainly based on study results in Western populations. However, Asian patients with IBD are known to be different from Western patients in many respects including some clinical features, genetic factors, and prognoses. In addition, social and medical systems of Asian countries are not the same as those of Western countries. Therefore, personalized IBD therapy for Asians may differ from that for Westerners in some aspects. This review discusses the current progress of personalized IBD therapy and its application from the Asian perspective.
State-of-the-Art Lecture

The future of IBD therapy: Where do we go from here?

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Theoretically, the ultimate goal of IBD management is to attain mucosal healing (and eventually histological healing) in the early stage of the disease in order to stop disease progression, altering the natural course of the disease. Although we are still far away from this goal at present, the progress, that we have achieved, is leading us to be closer and closer to this goal:

1. “Top-down Therapy”: More aggressive therapy at an earlier stage of the disease may improve the clinical outcome and increase the likelihood of achieving mucosal healing. Identifying risk factors for severity and poorer prognosis of the disease may guide the use of this therapy.

2. “Treating to Target Strategy”: Treatment should be monitored and adjusted by using a predefined objective target in predefined timeframe. Endoscopy may be the gold-standard at present. Efforts are underway to identify less invasive biomarkers as surrogates for endoscopic/histological disease activity.

3. “Therapeutic Drug Monitoring”: Optimization of biologic drugs by monitoring therapeutic drug levels and anti-drug antibody levels may promises to deliver better therapeutic efficacy and less failures. Efforts are underway to identify predictors that can be used to determine which specific therapy should be used for the individuals’ condition, leading to personalized medicine.

4. Development of new biologics and beyond: (Table 1)

5. New strategies in the therapeutic manipulation of the microbiome: With the growing perception of the intestinal microbiota as a major driver of disease pathogenesis, manipulating the microbiome as a means of controlling the disease has emerged.

The future for the IBD patients will certainly improve in the year ahead. The ultimate goal of IBD management will be closer and closer to reality.
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POSTER ABSTRACTS

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Awareness of their disease in IBD patients

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Introduction: There is growing demand by patients with chronic disease such as inflammatory bowel disease (IBD) for more detailed information regarding their disease, its management and prognosis. A number of studies have identified areas of concern for patients with IBD including diagnosis, therapy, role of diet, risk to family, cancer risk etc. Several methods have been utilized to improve patient education including patient groups, published literature, internet, meetings. In this study, we have aimed to measure the basic knowledge of our patients on IBD.

Methods: One hundred consecutive patients consulted in the outpatient clinic between 01. February–24. April 2015 were asked a group of questions related to their disease. The answers were recorded and examined by comparing their health records.

Results: All of the patients were able to pronounce the name of their disease. However 64% of the Crohn’s disease (CD) patients and 31% of the ulcerative colitis (UC) patients were unable to claim the extent of their disease. 91% of CD patients and 95% of UC patients were successful at telling the names and posology of their drugs. Only 56% of CD patients and 62% of UC patients were aware of the colorectal cancer related to their disease.

Discussion/Conclusion: IBD patients seem not to be aware of their illnesses adequately in Turkey. This fact can be due to patients’ low interest and concern about their situation related to the sociocultural factors and incomplete patient education. New strategies to educate IBD patients are needed in our country such as websites, brochures, more IBD nurse consultations, meetings which would also increase adherence to treatment.
Are NSAIDs used for arthropathy safe in inflammatory bowel disease?

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Introduction: One of the most common seen extraintestinal manifestations of inflammatory bowel disease (IBD) is joint involvement which can be seen in two types. Type 2 has a more chronic course and has more impact on quality of life. Although pain killers like paracetamol seem to be safer in IBD regarding induction of IBD bowel symptoms, mostly patients do not benefit from this group of drugs. In this study we evaluated the rate of NSAID use for IBD associated arthropathy and the relation to IBD flare.

Methods: We have an outpatient’s clinic at our unit where only IBD patients are examined three times a week. From January 2014 to October 2014 hospital records were searched for IBD patients at this outpatient clinic and all the drugs prescriptions were reviewed for NSAIDs. All the records were examined whether there was a flare in a 10 days period starting from the date of NSAID prescription. And the first routine follow-up visit was examined thoroughly for symptoms of arthropathy.

Results: During the study period there were a total of 2,198 visits (this includes both first visit and follow-ups) and NSAIDs in low dose were prescribed in 32 patients. No flares associated with NSAIDs were seen. In the first follow-up visit after NSAID use, symptoms related to arthropathy improved in all patients.

Discussion/Conclusion: Low dose of NSAIDs have decreased symptoms of type 2 arthritis in patients with IBD that are in remission and improved quality of life without inducing flare-up. Still they should be used with precaution.
Adipokine leptin in relation to nutritional status in patients with inflammatory bowel diseases

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Introduction: Adipose tissue can be considered as a huge gland producing paracrine and endocrine hormones, the adipocytokines, with immunomodulating and metabolic properties. Data on the production of leptin in patients with inflammatory bowel disease are controversial.

Aim of the study: To investigate serum leptin level in patients with inflammatory bowel disease (IBD) depending on nutritional status.

Methods: 40 patients with IBD (30 with ulcerative colitis [UC] and 10 with Crohn’s disease [CD]) were observed, mean age (37.38 ± 1.94) years. Bioelectric impedance analysis was used to determine the body composition parameters. Leptin level in blood sera was assessed by enzyme immunoassay compared to 10 healthy volunteers.

Results: According to body fat percentage (BFP) the patients were divided into 3 groups: I group included 26 (65.0%) patients with low nutritional status (NS), II – 5 (12.5%) patients with normal NS and III – 9 (47.5%) patients with high NS. The leptin level in the patients studied ranged from 0.2 to 26.3 ng/ml. Average values were (1.76 ± 0.23) ng/ml in men and (5.49 ± 2.91) ng/ml in women compared with the control group: (3.84 ± 1.79) ng/ml and (7.36 ± 3.73) ng/ml, respectively. The value of leptin in the third group of patients exceeded the results of the first group 5 times in men and 8.6 times in women (p < 0.05). In men with CD leptin level was 5 times less compared to UC (p < 0.05). Positive correlation between leptin in sera and age of patients (r = 0.41; p = 0.019), BMI (r = 0.67; p < 0.001), fat mass (r = 0.75; p < 0.001), active cell mass (r = 0.34; p = 0.033) and negative with the degree of malnutrition (r = -0.53; p = 0.002) were established.

Discussion/Conclusion: The data obtained confirmed connection between nutritional status and hormone activity of adipose tissue in patients with IBD.
Clinical study of enteral nutrition on Crohn’s disease combined with pyloric obstruction

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Patients who have Crohn’s disease (CD) associated with pyloric obstruction are usually unable to obtain enough nutrients through normal intake patterns. This clinical study aimed to describe different methods on establishment of enteral feeding pathway and evaluate the effects of enteral nutrition (EN) combined with standard treatments in CD patients with pyloric obstruction.

Methods: Twelve CD patients associate with pyloric obstruction were enrolled in this study. The enteral feeding pathways were established through nasointestinal tube or percutaneous endoscopic jejunosotomy (PEJ). The patients were given EN with standard treatments (proton pump inhibitors, 5-aminosalicylic acid, corticosteroids, immunosuppressive drugs, infliximab). Body weight, body mass index, albumin (Alb), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), CD activity index (CDAI) were recorded before and one month after EN support. The remissions of pyloric obstruction were followed-up with gastroscope.

Results: Enteral feeding pathways were successfully established in all twelve patients. After one month EN with standard treatments, all indices were improved significantly. The results of gastroscope three month later showed that 7 patients were in remission of obstruction; the rest 5 patients received Endoscopic Balloon Dilation. Among these five cases, two cases relieved after treatment, two cases still remain poor after two times expansion, and one case was invalid and received operation therapy.

Discussion/Conclusion: EN could not only improve the nutrient condition of CD patients but also could relief the symptom of obstruction with standard medical therapy. Those non-remission patients after EN with medical treatment might benefit with Endoscopic Balloon Dilation, but still partial patients need operation therapy.

Keywords: enteral nutrition, Crohn’s disease, pyloric obstruction
Correlation analysis of TLR4 Asp299Gly, Thr399Ile and TLR2 gene Arg753Gln,Arg677Trp polymorphisms with inflammatory bowel disease in Chinese Zhuang population of Guangxi Zhuang Autonomous Region

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**Aim:** To study the relationship between TLR4 gene Asp299Gly, Thr399Ile and TLR2 gene Arg753Gln, Arg677Trp polymorphisms and the susceptibility to inflammatory bowel disease (IBD) in Zhuang population in Guangxi Province.

**Methods:** Intestinal tissue samples of seventy Zhuang and seventy-six Han unrelated IBD patients and eighty Zhuang and eighty-four Han unrelated healthy people as controls, were collected in Guangxi region from Feb, 2007 to Oct, 2010. Genomic DNA was extracted from the intestinal tissue by phenol chloroform methodology. TLR4 gene Asp299Gly, Thr399Ile and TLR2 gene Arg753Gln, Arg677Trp were amplified by polymerase chain reaction (PCR), then detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), some PCR products of TLR4 gene Asp299Gly, Thr399Ile and TLR2 gene Arg753Gln, Arg677Trp were sequenced.

**Results:** The mutation genotypes of the TLR4 gene Asp299Gly, Thr399Ile and TLR2 gene Arg677Trp, Arg753Gln were not found among the population.

**Conclusions:** TLR4 gene Asp299Gly, Thr399Ile and TLR2 gene Arg753Gln, Arg677Trp polymorphisms are not associated with IBD in Zhuang population of Guangxi Province.

**Keywords:** Toll-like receptor 2, toll-like receptor 4, inflammatory bowel disease, gene polymorphism
Relationship of ATG16L1 gene polymorphisms with inflammatory bowel disease in Zhuang population of Guangxi

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Objective: To explore the correlation between susceptibility to inflammatory bowel disease (IBD) in Chinese Zhuang population of Guangxi province and ATG16L1 gene single nucleotide polymorphisms (SNP), rs2241880.

Methods: The Intestinal tissue of 146 patients of IBD and 164 healthy people were collected. Genomic DNA was extracted from intestinal tissue using with phenol chloroform metholgy. Polymerase chain reaction was used to amplify the ATG16L1 gene, and products were sequenced using the sequencer. The sequenced results were compared to the normal sequence in Genbank.

Results: No significant differences were noted in the ATG16L1 gene SNP site rs2241880 polymorphisms among the patients with Crohn’s disease, ulcerative colitis and the control subjects (P > 0.05).

Conclusions: The SNP rs2241880 of ATG16L1 are not found to increase the susceptibility of IBD in Chinese Zhuang population of Guangxi province.

Keywords: Crohn's disease, colitis, ulcerative, inflammatory bowel disease, ATG16L1 gene, single nucleotide polymorphism
Oral health in patients with inflammatory bowel diseases

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Introduction: Oral cavity is one of the most commonly involved extraintestinal organs in inflammatory bowel diseases (IBD) patients. Oral abnormalities in IBD patients include aphthous ulcer, gingivitis, orofacial granulomatosis, pyostomatitis vegetans, parotid granuloma, etc. Oral microbiota may differ in IBD from healthy controls. The aim of this study was to investigate oral hygiene and abnormalities in IBD patients.

Methods: 36 IBD patients were enrolled and received oral examinations by dentists.

Results: 26 UC and 10 CD were enrolled, including 14 males and 22 females. Mean age was 44.22 ± 15.33. 14 patients were active and 22 were in remission.
1. Dental caries: 30/36 (83.33%) patients have dental caries (DMF index > 0). The difference of percentage of dental caries was not significant in patients with active IBD and in remission. DMFT index was similar in UC (3.92 ± 3.97) and CD (4.0 ± 1.95).
2. Periodontal conditions: 6/36 (16.67%) patients got healthy gingivae, including 4 remissive IBD and 2 active IBD. 6/36 (16.67%) patients had gingivitis, all in active IBD. 24/36 (66.67%) patients have peridentitis, including 18 active IBD and 6 remissive IBD.
3. Oral mucosa: 2/36 suffered from oral ulcers, 2/36 lichen planus and 2 oral leukoplakia, all active IBD.

Discussion/Conclusion: Oral hygiene in IBD patients may differ from healthy people. Periodontal conditions may be worse in patients with active IBD. Oral health may somehow reflect the course of IBD.
Dysbiosis of oral microbiome in adult Chinese patients with active inflammatory bowel diseases

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Introduction: The imbalance of altered gastrointestinal flora and host’s immune system is the main cause of inflammatory bowel disease (IBD). The diversity of salivary microbiota in healthy human is similar to that of gut microbiota. Given the ease and repeatability of direct sampling of the oral cavity, study of oral microbiome is of particular importance for this special disease with the characteristic of repeated relapse.

Methods: Unstimulated saliva was collected from six patients with active IBD and ten healthy adults respectively. Bacterial DNA from saliva samples was extracted and purified, the v3–v4 hypervariable regions of bacterial 16S rRNA were amplified via PCR, and then pyrosequencing of the PCR products were performed on MiSeq sequencing platform.

Results: Overall diversity of oral microbial communities associated with IBD had a decreasing tend in despite of no significance. Given relative abundance of phylum level, the difference of bacterial compositions between healthy and IBD groups was significant, including Bacteroidetes, Proteobacteria, Fusobacteria with significant decrease in IBD and TM7, Firmicutes with increase. Analysis at the species level showed that Haemophilus parainfluenzae, Neisseria cinerea, Rothia mucilaginosa and Streptococcus porcinus were significantly reduced in IBD group in comparison with healthy control. (Fig. 1).

Discussion/Conclusion: Our data presented there were significant differences of salivary microbiota compositions in active IBD patients and healthy adults, and suggested that the oral microbiome was uniquely altered in patients with active IBD. It can be postulated that the dysbiosis of oral microbiota may participate in the development of IBD, and may be partially responsible for the relapse of the disease. Furthermore, oral microbiota may reflect the development of gut microbiota to some extent, particularly in IBD.
Fig. 1: Decrease in the richness, diversity and evenness of oral microbial communities in IBD.
Risk factors associated with surgery and postoperative recurrence in Crohn’s disease

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Objective: To explore the risk factors for surgery and postoperative recurrence of patients with Crohn’s disease (CD).

Methods: From January 2008 to December 2013, 183 patients were diagnosed as CD, 46 patients who underwent surgery were chosen as surgical group and the remaining 137 nonsurgical patients served as controls. All the patients were followed-up until the study endpoint or death and the follow-up period lasted at least 12 months. We typed the disorder according to the Montreal classification. The risk factors were assessed by Logistic regression.

Results: 25.1% (46/183) patients underwent surgery. The postoperative clinical recurrence rate was 39.1% (18/46) and the rate of patients with clinical or endoscopic recurrence was 52.2% (24/46) in surgical group. Multiple logistic regression analysis showed that structuring (OR = 5.836, 95% CI: 2.199~15.487, \( P < 0.001 \)) and penetrating (OR = 25.706, 95% CI: 7.091~93.190, \( P < 0.001 \)) disease behavior as independent predictors associated with the surgery and perianal disease (OR = 23.550, 95% CI: 1.311~422.912, \( P = 0.032 \)) and no medical prophylaxes (OR = 58.701, 95% CI: 1.803~1991.000, \( P = 0.022 \)) as independent predictors associated with the postoperative clinical recurrence.

Conclusions: Patients with CD have higher rate of surgery and postoperative recurrence. Structuring and penetrating disease behavior are predictors for surgery and perianal disease and no medical prophylaxes are predictors for postoperative clinical recurrence.

Keywords: Crohn’s disease, surgery, postoperative recurrence, risk factors
The incidence trends and clinical features of tuberculous versus Crohn’s anal fistulas: A 12-year review (2003–2014) of a single specialized institution in Korea

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Introduction: In Asian countries, the incidence of Crohn’s disease is recently increasing, and perianal involvement at the time of diagnosis is more common than in western countries. Tuberculous (TB) anal fistula is clinically similar to Crohn’s fistula although it is a very rare form of extrapulmonary manifestation. Therefore, its differential diagnosis has been a challenge to clinicians in TB-endemic Asian countries unlike the West. The aim of this clinical study is to analyze the incidence trends and clinical features of TB and Crohn’s fistula.

Methods: Among 13,872 patients who underwent anal fistula surgery in our institution from 2003 to 2014, we retrospectively analyzed the cases of TB or Crohn’s anal fistula which were newly-diagnosed after surgery. During 12-year period, 87 cases of TB and 116 cases of Crohn’s fistulas were diagnosed as appropriate. We reviewed the clinical, pathologic, colonoscopical and surgical data as well as annual incidence rate per surgery.

Results: The median age is 37 (18–68) years in TB and 24 (13–58) years in CD, respectively. Underlying chronic diseases were common in TB (23%). In TB group, AFB stain was negative in 38 (43.7%) and chest radiologic finding was normal in 35 (40.2%). During this 12-year period, the overall incidence rates per surgery were 0.6% in TB and 0.8% in CD, respectively. When analyzed by 4-year intervals, the mean incidence rates of TB and CD changed, from 0.7% and 0.6% in 2003–2006, to 0.6% and 0.9% in 2007–2010, and to 0.5% and 1.0% in 2011–2014, respectively.

Discussion/Conclusion: While the incidence of Crohn’s fistula is recently increasing over time, TB fistula is in a downtrend but still persistent in Korea now. Therefore, when patients presenting with recurrent complex perianal fistula were encountered in TB-endemic countries, we should prepare for a possibility of TB as well as Crohn’s fistula.
Effect of enteral nutrition in the treatment of ulcerative colitis in rats

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Introduction: 1. To investigate the effect of enteral nutrition in the treatment of ulcerative colitis in rats. 2. To investigate whether there is synergistic effect when enteral nutrition combined with SASP in the treatment of ulcerative colitis in rats. 3. To explore the mechanism of enteral nutrition in the treatment of ulcerative colitis.

Methods: Among the 50 male and female SD rats, 10 rats were randomly selected as the normal control group, and the rest of 40 rats were used the TNBS to induce the rats models of ulcerative colitis. After the success of modeling by TNBS, the rest of 40 rats were randomly divided into 4 groups: model control group, SASP group, enteral nutrition group, enteral nutrition and SASP group (combined treatment group). The normal control group and the model control group received 0.9% saline gavage, while the enteral nutrition group, SASP group and the combination group were given enteral nutrition, SASP, SASP with enteral nutrition respectively. For all the 50 SD rats, the body weight, clinical symptoms, characteristics of stool and the blood in the stools were observed every day to calculate the disease activity index (DAI). After 1 week, all the rats were received cesarean operation after anesthetized, then continue to determine the IFN-γ, TNF-α in the serum of rats by ELISA method. The rats killed after the colon tissue isolation, and take part in colonic mucosa of CMDI score, HE staining and pathological section. All the experimental data were analyzed by SPSS17.0 statistical software.

Results:
1. Compared with the normal control group, the DAI value, CMDI score, serum IFN-γ, TNF-α levels were significantly higher in model control group, there are significant differences (P < 0.05);
2. Compared with the model control group, both enteral nutrition group, combined treatment group and SASP group were able to improve the general state of rats, and reduce the score of CMDI and DAI value, reducing the rat serum IFN-γ, TNF-α, there are significant differences (P < 0.05);
3. Compared with the enteral nutrition group, the combined treatment group can reduce the CMDI score and DAI value, the serum IF IFN-γ, TNF-αt, there are significant differences (P < 0.05);
4. Compared with the SASP group, the combined treatment group can reduce the CMDI score and DAI value, the serum IF IFN-γ, TNF-αt, there are significant differences (P < 0.05);
5. Compared with the enteral nutrition group and SASP group, there is no significant difference in serum IFN-γ, TNF-α, CMDI score and DAI value (P > 0.05).
Discussion/Conclusion:
1. Through the TNBS modeling method can successfully establish the rat model of ulcerative colitis.
2. The body caused by the imbalance of immune regulation of serum IFN-γ and TNF-α increased the content of gamma alpha, is one of the possible mechanisms of ulcerative colitis disease.
3. Enteral nutrition on ulcerative colitis have a certain therapeutic effect.
4. Enteral nutrition combined with SASP therapy in the treatment of ulcerative colitis rats had synergistic effect.
Clinical observation on the changes of sTM, PC and fPS levels in patients with ulcerative colitis

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Objective: To investigate the levels of soluble thrombomodulin (sTM), protein C (PC) and free protein S (fPS) in patients with ulcerative colitis.

Methods: A total of 78 patients with ulcerative colitis were collected and 30 cases of healthy subjects as control group from August 2012 to May 2014. The levels of sTM, PC and fPS were measured by ELISA method.

Results: The levels of sTM and fPS in UC patients were 18.89 ± 1.14 ng/ml and 3.69 ± 1.51 ng/ml, which were significantly higher than that in the control groups 10.28 ± 5.03 ng/ml and 1.67 ± 0.39 ng/ml, respectively. The levels of PC were higher than that in the control groups, but the difference was not statistically significant. In different clinical characteristics, the levels of sTM in active UC patients were higher than that in the remissive UC patients (19.29 ± 11.47 ng/ml vs 5.60 ± 1.06 ng/ml, P = 0.04). Besides, the levels of sTM in severe active UC patients were significantly higher than that in the mild and moderate active UC patients (24.33 ± 13.1 ng/ml vs 16.35 ± 9.68 ng/ml, 24.33 ± 13.1 ng/ml vs 16.78 ± 9.71 ng/ml, both P < 0.05).

Conclusion: The levels of sTM and fPS were significantly increased in UC patients, and it may be correlated with the activity and severity of UC.
Probe the cut-off point of anti-Saccharomyces cerevisiae antibodies (ASCA) in the differential diagnosis of Crohn’s disease

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Introduction: Detection the expression level of ASCA IgG, IgA in Crohn’s disease and to explore the cut-off point in the differential diagnosis of CD.

Methods: The subjects include 109 cases diagnosed with CD, 30 cases diagnosed with UC, according to “The diagnosis and treatment of inflammatory bowel disease Consensus (Guangzhou 2012)” and 25 healthy individuals after endoscopic examination. Detect the ASCA IgG, IgA expression levels, and calculate the cut-off point, sensitivity, specificity, positive predictive and negative predictive value.

Results: The positive rate of ASCA is 47.71%, and the cut-off point of ASCA IgG is 10.5, with a sensitivity of 71.56%, a specificity of 61.82% while the cut-off point of ASCA IgA is 0.415 with a sensitivity of 66.06% and a specificity of 78.18%. Either of the antibodies is positive, the sensitivity is increased to 85.32%. The specificity is improved to 80% while both antibodies are positive.

Discussion/Conclusion: ASCA IgG and ASCA IgA expression levels in Chinese CD patients is low compared with foreign patients, which mean that we need to develop appropriate cut-off point of CD patients in China. Both ASCA IgA and ASCA IgG detected can improve the discovered rate of CD.
The advantage of clinical, endoscopic and CTE scoring system in the diagnosis of Crohn’s disease involving the colon

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Aim: To explore the diagnostic value of clinical, endoscopic and CTE scoring system (CECSS) compared with clinical, endoscopic scoring system (Yao He system) and endoscopic scoring system (Lee system) for Crohn’s disease (CD) involving the colon.

Methods: From January 2009 to February 2014, a total of 85 patients attending in our hospital who were diagnosed with CD involving the colon were enrolled in the study, 33 patients with intestinal tuberculosis (ITB) as a control group at the same period were selected and all the patients were followed-up more than 12 months. Screen out the parameters of CTE which were helpful to distinguish CD and ITB and give them scores based on different diagnostic specificity. To score all patients by using CECSS, Yao He and Lee system, realize the diagnostic status of WHO diagnostic criteria and calculate the diagnostic rate and efficacy of different systems. Comparing the diagnostic rate and efficacy of CECSS with that of Yao He and Lee system.

Results: Diagnostic rates of CECSS, Yao He system, Lee system and WHO diagnostic criteria for CD were 78.4%, 60.8%, 43.2%, 18.9% respectively. The rates of three kinds of systems were significantly higher than that of WHO diagnostic criteria; the rate of CECSS was significantly higher than that of Yao He and Lee system. The areas under ROC curves of CECSS, Yao He and Lee system were 0.924, 0.864 and 0.719 respectively, the Youden index of them were 0.747, 0.571 and 0.358. Among the three systems, the AUC of CECSS was the largest, AUC of Lee system was the minimum, there are significant differences statistically in comparison between any two systems (CECSS VS Yao He system Z = 1.326, P = 0.046; CECSS VS Lee system Z = 3.526, P < 0.001; Yao He system VS Lee system Z = 2.272, P = 0.006).

Conclusion: The diagnostic rate and efficacy of clinical, endoscopic and CTE scoring system for CD involving the colon was superior to that of endoscopic, clinical endoscopic system and WHO diagnostic criteria. It would require further clinical trial.
Research on clinical efficacy of orally administrated mesalazine combined with rectally administrated Kangfuxin fluids in mild or moderate distal ulcerative colitis

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Introduction: To investigate efficacy of orally administrated mesalazine combined with rectally administrated Kangfuxin fluids in ulcerative colitis (UC).

Methods: 96 UC patients who had received treatment in our hospital from Jan 2013 to Dec 2014 were randomly divided into two statistically similar groups. Patients in the control group were given mesalazine 1 g orally, qid, and patients in the treatment group were given oral mesalazine combined with 50 mL of Kangfuxin fluids and 100 ml of 0.9% NaCl solution by retention enema, qn. The treatment was conducted for 4 weeks.

Results: Total response rate of the treatment group was 91.67% (30 patients were partially responsive, 14 were responsive and 4 were irresponsive). Total response rate of the control group was 75.0% (24 patients were partially responsive, 12 were responsive and 12 were irresponsive). The difference between the two groups was statistically significant, P > 0.01.

Discussion: Ulcerative colitis (UC) is a long course disease with high rate of reoccurrence which can significantly jeopardize patients’ quality of life. At present general and local use of salicylic acid is recommended for therapy of distal UC though there are certain drawbacks including high cost and side effects. In the present research, general use of mesalazine combined with Kangfuxin rectal fluids has been proven effective. Kangfuxin fluids can accelerate growth of granulation tissues, promote angiogenesis and improve microcirculation of ulcer, at the same time it can promote the effect of anti-bacterial and immune-enhancement. In summary, the research is effective in improving prognosis and shortening the course of disease with lower cost, which shows superior performance in clinic.
Expression of Toll-like receptor 9, MyD88 and its relationship with IL-6 and TNF-α in patients with ulcerative colitis

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To detect the expression level of Toll-like receptor 9 (TLR9), MyD88, IL-6 and TNF-α in peripheral blood of patients with ulcerative colitis (ulcerative colitis, UC), and explore the relationship between TLR9, MyD88 and IL-6, TNF-α.

Methods: The expression levels of TLR9 mRNA and MyD88 mRNA in peripheral blood of patients with active UC and the normal control group were detected by RT-PCR. The IL-6 and TNF-α protein expression levels in serum of different groups were detected by enzyme-linked immunosorbent assay (ELISA).

Results: The expression levels of TLR9 mRNA and MyD88 mRNA in peripheral blood lymphocytes of patients with active UC were higher than that in remission and normal control group, and the difference was statistically significant (p < 0.05). There was no statistically significant difference (p > 0.05) between patients in remission and the control group. The expression levels of TLR9 mRNA and MyD88 mRNA in severe UC group were higher than that in the mild or moderate group (p < 0.05). The TNF-α and IL-6 concentration in serum of active UC group was statistically different compared with the remission group and the control group (p < 0.05). Their concentration between the remission group and the control group has no statistical significance (p > 0.05). Their concentration in the severe UC group was higher than that in the mild or moderate group which is of statistically significance (p < 0.05).

Discussion/Conclusion: The expression levels of TLR9, MyD88, IL-6 and TNF-α of UC patients are significantly higher than that of remission and normal control group, and the severity of UC is positively correlated to the factors, suggesting that it’s related to the activity of the UC disease.
A case of primary intestinal lymphangiectasia

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Case presentation: A 28-year-old man presented to our hospital with a history of abdominal girth increasing and edema in eyelids and lower limbs for 20 days. About 20 days prior to this admission, the patient complained of edema in eyelids. Simultaneously, abdominal distention and the double lower limbs symmetrically pitting edema were occurred. No diarrhea and increasing foams in urine were found. He denied hair loss, rash, skin erythema, oral ulcers, photosensitivity, joints pain, palpitations, night sweats, chest pain, paroxysmal nocturnal dyspnea, insomnia, irritability and apathy. His physical examination demonstrated malnutrition and edema in eyelids and lower limbs. Routine analysis of blood, urine and stool were normal. Investigation showed hypoalbuminemia (serum albumin 21.1 g/l) and hypogammaglobulinemia (globulin 16.5 g/l). The high-sensitivity-C-reactive protein, erythrocyte sedimentation rate, immunoglobulin, serum complement, autoantibody and 24-hour urinary protein excretion were normal. 99Tcm labelled albumin intestinal imaging showed the protein loss in distal ileum. Enhanced abdominal CT images demonstrated the bowel was generally thick. Colon endoscopy showed the asperous mucosa and erythema discrete scattered in the terminal ileum. The biopsy of terminal ileum displayed the chronic inflammatory of mucosa, and eosinophil was 40 per high power field. Capsule endoscopy showed that villi edema were present in the small intestinal (especially in the duodenum and jejunum) mucosa. Finally, it was diagnosed as primary intestinal lymphangiectasia.

Discussion: Primary intestinal lymphangiectasia is a rare disorder characterized by exudative enteropathy resulting from morphologic abnormalities of the intestinal lymphatics. Common symptoms of IL are hypoproteinemia steatorrhea, peripheral edema, lymphocytopenia and malabsorption. An increase in the pressure of the lymph channels has been suggested to be a possible cause of enteric protein loss. The characteristic endoscopic and pathology features have been documented thereby greatly facilitating an accurate diagnosis.
Distribution of the CD45+ lymphocytes in stroma and lamina propria of UC and CD tissues

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Introduction: Inflammatory diseases of the large intestine accompanied by chronic inflammation which determines the activity and extent of changes in the glandular epithelial basement membrane and the surrounding stroma. The chronic infiltration components included mononuclear cells (lymphocyte T, B, NK) and plasmocytes. CD45 (leucocyte-common antigen) is a transmembrane glycoprotein of the leucocyte-specific receptor-like protein tyrosine phosphatase (RPTP) family. It plays a significant role in the positive regulation of antigen-receptor pathways in B and T lymphocytes that lead to modulation of the immune response and apoptosis. The aim of study was assessed the expression of CD45 in stromal cells and in lamina propria of glandular epithelium of UC and CD tissues in correlation with clinicopathomorphological features.

Materials and methods: The study group obtained 32 patients with UC and 10 patients diagnosed with CD. The mean age of UC and CD patients were 33.75 y and 39.28 y. The expression of CD45 was evaluated by immunohistochemistry and found in surface on T and B lymphocytes localized in stroma and lamina propria. The distribution of CD45+ cells in stroma was scored as absent (lack of positive cells), weak (0–25%), moderate (25–50%) and strong (> 50% of positive cells). The presence of CD45+ lymphocytes in lamina propria was classified as an absent (< 5 positive cells) and present (> 5 positive cells).

Results: The CD45+ lymphocytes in stroma was found to infiltrate on moderate and strong in 3 and 29 of UC, and in 4 and 6 of CD (p = 0.0446). The CD45+ cells were present in lamina propria of 10 UC cases and in 4 of CD (p = 0.299). The positive expression of CD45 on stromal lymphocytes was correlated with disease localization (R = 0.349, p = 0.05) whereas the presence of CD45+ cells in lamina propria negatively correlated with the extent of disease and the distribution of eosinophils in lamina propria in UC patients (R = -0.365, p = 0.040; R = -0.445, p = 0.012). In CD cases, the epithelium damage, architectural changes and the presence was positively associated with CD45+ cells in stroma and negatively correlated with positive CD45 lymphocytes in lamina propria (R = 0.769, p = 0.006; R = 0.606, p = 0.048; R = 0.769, p = 0.048; R = -0.670, p = 0.024; R = -0.805, p = 0.03; R = -0.670, p = 0.024).

Conclusion: The presence of CD45+ lymphocytes in stroma of CD patients participate in remodeling and damage of glandular epithelium but their distribution in lamina propria help to protect the structure maintenance of epithelium cells in either CD and or UC patients.
Epidermal growth factor receptor activation mediates intestinal mucin production stimulated by a *Lactobacillus rhamnosus* GG-derived protein: Potential treatment for inflammatory bowel disease

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**Background and aim:** The mucus layer coating the gastrointestinal tract serves as the first line of intestinal defense against inflammation and injury. Probiotics promote mucin production by goblet cells in the intestine. p40, a *Lactobacillus rhamnosus* GG (LGG)-derived soluble protein, has been shown to transactivate the epidermal growth factor receptor (EGFR) in intestinal epithelial cells, which is required for inhibition of apoptosis and preservation of barrier function in the colon, thereby ameliorating colitis. The purpose of this study was to investigate the effects and mechanisms of p40 regulation of mucin production.

**Methods:** LS174T cells which could continuously produce high levels of Muc2, one of the major products of goblet cells were treated. The effects of p40 treatment in wild type and EGFR⁵ mice which have a negative mutation in the EGFR kinase domain were compared. Mucin production was also evaluated in ulcerative colitis patients.

**Results:** p40 activated EGFR and its downstream target (Akt) in a concentration-dependent manner in LS174T cells, and p40 stimulated Muc2 gene expression and mucin production, which were abolished by inhibition of EGFR kinase activity, down-regulation of EGFR expression by EGFR siRNA transfection, or suppression of Akt activation. Treatment with p40 increased mucin production in the colonic epithelium, thus thickening the mucus layer in the colon of wild type, but not of EGFR⁵ mice. In addition, mucin production was significantly decreased in ulcerative colitis patients compared to the normal controls.

**Conclusion:** p40-stimulated activation of EGFR mediates up-regulation of mucin production, which may play a role in regulation of intestinal epithelial homeostasis and prevention against inflammatory bowel disease.
Evaluation of the presence of A–allele HERC2 (rs916977) and the presence of perianal fistula in Egyptian Crohn’s disease

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Introduction: Crohn’s disease (CD) is a multifactorial disease with a genetic background. (1) Perianal fistulæ in CD rarely heal by themselves and lead to significant morbidity. (2) Till now, predicting the course of CD including the development of perianal complications has been a challenge. (3) An accurate prediction of the subgroups of patients most likely to have the worst outcomes will be very useful to individualize the management and select the ideal strategy for each patient. (4) Using genetic markers for risk stratification are more appealing compared to serologic markers or clinical parameters. And that is because they are present long before the disease onset and before any environmental factor plays a role. (5) Recent genome-wide association studies identified homozygosity for the A-allele at HERC2 (rs916977) was found to be associated with perianal penetrating disease behavior. (6) The prevalence of CD is rapidly rising in Egypt and there is no information about this polymorphism frequency in the Egyptian population. (7)

Methods: The AIM is to evaluate the presence of A-allele at HERC2 (rs916977) and its relation to the presence of perianal fistula in Egyptian patients having CD. We studied 50 CD patients in which, 10 cases were presented by Crohn’s complicated with perianal disease and 50 healthy controls. All included subjects were Egyptian in whom genotyping for the previously mentioned HERC2 SNP was performed. Clinical and demographic features were characterized.

Results: Analysis of the allele and genotype frequencies at (rs916977) on the HERC2 gene, showed no association with CD in Egyptian patients (P = 0.636); odds ratio = 0.588; CI 95% (0.191–1.814). Also, there was no association between HERC2 genotype variant and disease phenotype based on the Montreal classification. Also, there was no association with gender, smoking history, surgical history perianal fistulæ, and presence of extra-intestinal manifestations.

Discussion/Conclusion: These results suggest that the polymorphisms at (rs916977) on the HERC2 gene seem not to be involved in the genetic predisposition to CD in Egyptian population, and confirm that there are ethnic differences in the genetic background of CD. Replication studies by independent groups are necessary to elucidate the contribution of susceptibility genes to CD in different ethnic populations.
References:


Disclosure of Interest: None Declared

Keywords: Crohn’s disease, genetic polymorphisms, IBD, perianal disease
Clinical, laboratory, endoscopical and histological characteristics predict severe ulcerative colitis

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Introduction: Ulcerative colitis is a remitting and relapsing chronic inflammatory disorder of the colon with a mortality rate of 7% from acute severe UC.

Methods: A retrospective study of the correlation of clinical indicators, laboratory indicators, endoscopical features, and histological features with clinical severity of UC was conducted in 125 UC cases.

Results: Diarrhea, mucous and pus in the stool, fever, anemia, weight loss and tachycardia symptoms and the erythrocyte sedimentation rate, concentration of C-reactive protein, amount of white blood cells and platelets, and positive occult blood test positively correlated with the severity of disease. Whereas, serum total protein, albumin, and hemoglobin levels negatively correlated with the severity of UC. The endoscopic observations of mucosa bleeding, granular mucosa, pseudopolyps, pouch lighter or disappeared and luminal stenosis as well as the grade and extent of disease were significantly associated with the severity of UC. Histological grade and granular mucosa were significantly associated with the severity of UC. Failure of conservative treatment, severely low gastrointestinal bleeding, and the discovery of a suspicious cancer in the biopsy are the main indicators for colectomy.

Discussion/Conclusion: Significant reduction in serum total protein, albumin, and hemoglobin concentration is a relatively specific indicator of severe UC.
Analysis of psychologic status and the related influential factors of 86 cases of ulcerative colitis

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Introduction: To explore the mental and psychological status and the related influential factors in the ulcerative colitis (UC).

Methods: Eighty six UC patients (UC group) and eighty six healthy adults (control group) were scored by using Anxiety and Depression Scale (HAD). The scores were compared between two groups. The scores were also compared among different degree of UC patient. The influential factors were analyzed.

Results: The HAD scores of UC patients was markedly higher than that of control group (P < 0.05). With the increasing of the severity of the disease, HAD score increased gradually. HAD score in severe UC patients was significantly higher than that in mild and moderate UC patients. The anxiety score of moderate UC patients was significantly higher than that of mild UC patient (P < 0.05), but there was no significant difference in depression score between mild and moderate UC patients (P > 0.05). There was no significant difference in the incidence of anxiety and depression among UC patient with different gender and age (P > 0.05). Compared with patients with low education background, the patients with high education background were easier to have anxiety and depression (P < 0.05). The incidence of anxiety and depression in different economic status had no statistical significance (P > 0.05). The incidence of anxiety and depression in brain workers was higher than that in manual workers (P < 0.05)

Discussion/Conclusion: The incidence of anxiety and depression in UC patients is apparently higher than that in healthy people. Psychological abnormality in severe UC patients is more obvious UC patients with high education background or brain workers are apt to have anxiety and depression.
Researching the use of azathioprine in the treatment of inflammatory bowel disease

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Introduction: The objective is to investigate the efficacy and safety of azathioprine (AZA) in patients with active inflammatory bowel disease.

Methods: Find active IBD patients. All patients initially received AZA combined with steroids therapy. Treatment with AZA then continued after the steroids were withdrawn. Clinical efficacy, the endoscopic healing of mucosa and adverse reactions were assessed at the end of the 12th, 24th, 48th and 96th weeks.

Results: 80 patients with active IBD (60 UC patients and 20 CD patients) were collected. After the CD patients had been treated for 12 weeks, no differences were found in their ESR, CRP, WBC count, HCT, Hb and CDAI levels in comparison to the patients’ previous treatment (p > 0.05). At week 24, the ESR and CRP levels were significantly lower than before AZA therapy had been received (p < 0.05). However, there was no difference in the WBC count, HCT, Hb and CDAI levels at week 24 in comparison to before treatment had started (p > 0.05). At week 48, the ESR, CDAI and CGSCD levels were significantly lower than before AZA therapy had begun (p < 0.05). In contrast, the CRP, WBC count, HCT and Hb levels remained the same as before (p > 0.05). After the CD patients had been treated for 96 weeks, the ESR, CRP, HCT, Hb, CDAI and CGSCD levels were significantly lower than those before AZA therapy had been administered (p < 0.05).

Discussion/Conclusion: AZA is effective in the treatment of active UC, especially during steroid withdrawal, and maintains remission. There was no difference in the curative effect between the 1 mg/kg/d dose and the 2 mg/kg/d dose. AZA treatment also effectively maintains long-term steroid-free remission in CD patients, reduces the recurrence rate and minimizes the dosage of steroid. AZA can effectively promote and maintain mucosal healing in UC and CD. Although the rate of adverse reactions is relatively high, the rate of severe adverse reactions is fairly low.
The correlation of inflammatory cytokines and peptide YY in patients with irritable bowel syndrome

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Introduction: To understand the pathogenesis of irritable bowel syndrome (IBS) we detected the serum levels and the colonic mucosa expression rate of tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10) and peptide YY (PYY) and observed the correlation of inflammatory cytokines and PYY in patients with IBS.

Methods: Using ELISA to detect 22 cases of diarrhea-type IBS (D-IBS), 18 cases of constipated-type IBS (C-IBS), 20 healthy controls’ serum of TNF-α, IL-10 and PYY. Using immunohistochemistry to detect those patients colorectal mucosa’s expression about TNF-α, IL-10 and PYY.

Results:
(1) The serum levels and the colonic mucosa expression rate of TNF-α in D-IBS group were significantly higher than that in normal group (P < 0.05), but those expression of TNF-α in C-IBS group did not significantly differ from in normal group (P > 0.05).
(2) The serum levels and the colonic mucosa expression rate of IL-10 in D-IBS group were significantly lower than that in normal group (P < 0.05), but those expression of IL-10 in C-IBS group did not significantly differ from in normal group (P > 0.05).
(3) The serum levels and the colonic mucosa expression rate of PYY in D-IBS group were significantly higher than that in normal group (P < 0.05), but those expression of PYY in C-IBS group did not significantly differ from in normal group (P > 0.05).
(4) TNF-α and PYY were positively correlated in the D-IBS group (r = 0.876, P < 0.05), but IL-10 and PYY levels were negatively correlated in the D-IBS group (r = -0.867, P < 0.05).

Discussion/Conclusion: The changes of inflammatory cytokines caused the change of PYY and PYY may regulated those inflammatory cytokines, thereby improving low-grade inflammation in IBS.
The correlation of inflammatory cytokines and tight junction protein in patients with irritable bowel syndrome

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Introduction: To understand the pathogenesis of irritable bowel syndrome (IBS) we detected the serum levels and the colonic mucosa expression rate of tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10) and tight junction protein-1 ( Claudin-1) and observed the correlation of inflammatory cytokines and tight junction protein in patients with IBS.

Methods: Using ELISA to detect 22 cases of diarrhea-type IBS (D-IBS), 18 cases of constipated-type IBS (C-IBS), 20 healthy controls’ serum of TNF-α, IL-10 and Claudin-1. Using immunohistochemistry to detect those patients colorectal mucosa’s expression about TNF-α, IL-10 and Claudin-1.

Results:
(1) The serum levels and the colonic mucosa expression rate of TNF-α in D-IBS group were significantly higher than that in normal group (P < 0.05), but those expression of TNF-α in C-IBS group did not significantly differ from in normal group (P > 0.05).
(2) The serum levels and the colonic mucosa expression rate of IL-10 in D-IBS group were significantly lower than that in normal group (P < 0.05), but those expression of IL-10 in C-IBS group did not significantly differ from in normal group (P > 0.05).
(3) The serum levels and the colonic mucosa expression rate of Claudin-1 in D-IBS group were significantly lower than that in normal group (P < 0.05), but those expression of Claudin-1 in C-IBS group were significantly higher than in normal group (P < 0.05).
(4) TNF-α and Claudin-1 were negatively correlated in the D-IBS group (r = -0.867, P < 0.05), while IL-10 and Claudin-1 were positively correlated (r = 0.868, P < 0.05).

Discussion/Conclusion: The changes of inflammatory cytokines caused the change of Claudin-1, which caused the symptoms of diarrhea.
Upregulated expression of hITF in Crohn’s disease

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Introduction: To study the expression of human intestinal trefoil factor (hITF) mRNA in Crohn’s disease.

Methods: Seventy-eight patients underwent DBE examination in Xiamen Zhongshan Hospital. Of these patients, 33 were female and 45 were male; their ages ranged from 20 to 69 years. Mean age was 52.5 years. DBE with biopsy was performed on 39 patients with Crohn’s disease and 39 patients who served as normal controls. The cases were diagnosed as Crohn’s disease based on medical history, physical examination, and endoscopic and histological findings. The specimens were obtained immediately after DBE with biopsy and frozen in liquid nitrogen and stored at -80°C before mRNA isolation. The present studies were performed retrospectively using frozen tissue from these patients. Total RNA was extracted from the sample using TRIzol reagent. Total RNA were reverse-transcribed using the PrimeScript™ RT Reagent Kit according to the manufacturer’s instructions. qRT-PCR was performed for hITF and β-actin using the following primers pairs: hITF, forward primer: 5’-AGCCACGACGAGATCTATGACA-3’; reverse primer: 5’-AAGGCGCAGGCCCGCAAT-3’. The fragment amplified was 326 bp. β-actin, forward primer: 5’-GACAGCACCATGTACCCT-3’; reverse primer: 5’-CTGGGCCATTCTCCTTAGAG-3’. The fragment amplified was 557 bp. qRT-PCR analysis was performed. All samples were run in triplicate to reduce the experimental variability. The amplification results were detected and analyzed using qRT-PCR detection system. The gene signals were standardized against the corresponding β-actin signal, and results were expressed as the ratio of each molecule to β-actin. All analyses were performed using the SPSS software package, version 13.0.33

Results: Thirty-nine Crohn’s disease patients and thirty-nine normal controls were diagnosed via DBE with biopsy (Figure 1). The expression of hITF mRNA in Crohn’s disease was significantly increased compared with the normal controls (P < 0.05) (Table 1, Figure 2, 3).

Discussion/Conclusion: The expression of hITF mRNA is increased in Crohn’s disease.
Figure 1: The Expression of hITF mRNA in Small Intestinal Mucosa

Figure 2: Histotype comparison between Crohn's disease and normal controls.
Colonic microflora in patients with irritable bowel syndrome

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Analyzing the condition of colonic microflora is indispensable to defining tactics for the complex therapy of irritable bowel syndrome (IBS) and for preventing further relapses of the disease.

**Aim:** To learn about factors that disturb the colonic microflora of patients with IBS.

**Materials and methods:** The colonic microflora of 36 patients with IBS was studied. The microflora to be researched was obtained by means of fibrocolonoscopy with the large intestine being scraped in three areas, namely the transverse colon, the descending colon and the rectum.

**Results:** The analysis has shown that the microflora is disturbed in IBS patients, as indicated by a conditional increase in pathogenic flora (E. coli 20.1 + 4.3 $10^6$), a reduction in the quantity of bifidobacterium (287.3 + 26.6 $10^6$), and, in some cases, the occurrence of pathogenic microorganisms (staphylococcuses [24.2 + 2.5 $10^5$] and lactosanedegatives esheriy [16.6 + 1.2%], etc.). It should be noted that the most frequently found disturbance in the microbial environment of the colon was the catarrhal-erosive form of lesions in the slimy colon.

Three kinds of flow were established when analyzing the degree of manifestation of dysbacteriosis. The insulated phylum of dysbacteriosis was detected in 8 patients (22.3%), and was characterized by a change in quantity of bifidobacterium and latent flow. The combined phylum of dysbacteriosis of the intestine conditioned by the availability of staphylococcuses and conditionally of pathogenic flora (lactosanedegatives esheriy) was found in 16 patients (44.4%), owing to the fact that they had the moderately expressed local form of clinical flow. In 12 patients (33.3%), in which the deployed phylum of dysbacteriosis had been established, the expressed clinical flow conditioned by the availability of pathogenic microbial association was observed.

**Conclusions:** The research conducted by us demonstrates that in 23.3% of the patients the insulated phylum of dysbacteriosis was observed. However, in 33.3% of the patients the deployed phylum of dysbacteriosis followed by expressed clinical flow owing to the availability of microbial association took place. This highlights the necessity of applying local and systemic therapy for a complex of medical measures.
CD15 positive cells in glandular epithelium and inflammatory cells of UC and CD patients

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Introduction: Inflammation of intestinal mucosa subject to the inflammatory infiltrate consisting primarily of neutrophils and lymphocytes impairs its integrity and leads to the conversion architecture of intestinal villi. CD15 is expressed on the surface of human leukocytes, mainly in neutrophils and it binds to the E-selectin of endothelial cells which leads to these cells migration into tissue. The aim of study was to evaluate CD15 expression in intestinal glands and inflammatory cells in UC and CD patients in correlation with histopathological features.

Materials and methods: The study group consists of 39 cases with UC and 10 with diagnosed with CD. The expression of CD15 was performed by immunohistochemical technique and assessed in membrano-cytoplasmic color reaction in glandular epithelium (gCD15) and polynuclear inflammatory cells (mainly in neutrophils) (iCD15). Expression of gCD15 was defined as negative (< 25% positive cells) or positive (> 25% positive cells) whereas iCD15 was classified as negative (0%), weak (0–25%), moderate (25–50%) and strong (> 50% of positive cells).

Results: Positive gCD15 expression was observed in 29 of UC and in 8 of CD cases but it was not statistically different (p = 0.7422). Expression of iCD15 was weak in 15 cases, moderate in 15 and strong in 6 of UC and it was statistically differ from CD patients (weak in 3 cases and strong in 7 cases) (p =0.003). In UC cases, the gCD15 expression was found to correlate with chronic inflammatory infiltrate (R = -0.306, p = 0.048) whereas iCD15 expression was associated with the presence of neutrophils in lamina propria (R = 0.311, p = 0.048). Statistical analysis confirmed that positive gCD15 cases correlated with the architectural epithelium changes and the presence of erosion in CD patients (R = 0.829, p = 0.003; R = 0.666, p = 0.035).

Conclusion: Our results showed that the positive gCD15 and iCD15 cells may be responsible for inflammatory response in UC and architectural damage of CD tissue.
The epitopes of human and microbial transglutaminases are similarly recognized by celiac disease sera

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Introduction: The use of microbial transglutaminase (mTg) from Streptovercillium mobaraense in the food industry is expanding on a great scale and mTg is ingested in large amounts in the common Western diet, including by celiac patients. Being a member of the human endogenous tTg, the mTg shares multiple functional similarities. However, immunogenic comparison of the two enzymes in celiac disease (CD) is lacking.

Methods: Complexing mTg and gliadin results in mTg neo-epitope (mTg neo). These complexes were purified by asymmetric field flow field fractionation and confirmed by multi angle light scattering and SDS-PAGE. Sera from an in house cohort of 81 CD patients (mean age 30 ± 17) and 81 healthy blood donors (mean age 29 ± 21) were analysed using the following ELISAs: AESKULISA® tTg New generation (tTg-neo-epitopes) IgA and IgG, AESKULISA® Gliadin IgA and IgG, and AESKULISA® DGP IgA and IgG as well as AESKULISA®s against mTg and mTg neo-epitopes (Research use only (RUO) Kits as IgA and IgG).

Results: Purified mTg-neo IgG and IgA (AUC = 0.92, 0.93, respectively) showed an increased immunoreactivity compared to single mTg and gliadin (p < 0.001) but similar immunoreactivity to the tTg-neo IgG and IgA ELISA (AUC = 0.94, 0.95, respectively). Using a competition ELISA, the mTg- and tTg-neo-epitopes have identical outcomes with regard to CD sera both showing a decrease in optical density of 55 ± 6%, (p < 0.0002). Comparing the antibodies’ levels of the individual CD patients, sera with high antibody titre [U/ml] against the tTg neo-epitope show also high antibody activities of the mTg neo-epitope and vice versa indicating the presence of similar epitopes within the Tg-gliadin complexes.

Discussion/Conclusion: Even without overall homology, mTg and tTg display a comparable immunopotent epitope. mTg neo-epitope IgA and IgG antibodies are immunogenic in CD. If substantiated it will impact the food industry additive policy, food products labelling, consumer awareness and public health implementation.
Mesalazine: Potential in the treatment of inflammatory bowel disease

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Background: Inflammatory Bowel Disease (IBD), mainly comprising Crohn’s disease (CD) and ulcerative colitis (UC), is a chronic condition that primarily affects the intestine and is characterized by leukocytic infiltration. Blocking the migration of leukocytes from the circulation is therefore a reasonable therapeutic goal. Budesonide and mesalazine (mesalamine) are commonly used in the medical management of patients with mild to moderate IBD. Mesalazine is a 5-aminosalicylic acid derivative that has been widely used to treat patients with IBD. Accumulating evidence indicates that mesalazine has a very low rate of adverse drug reactions and is well tolerated by patients. However, a few cases of pulmonary and cardiac disease related to mesalazine have been reported in the past, though infrequently, preventing clinicians from diagnosing the conditions early.

Aim: Our aims were, to assess the effect of mesalazine on irritable bowel syndrome (IBS) symptoms.

Conclusion: We describe the 78 cases with UC in the Department of Gastroenterology of Inner Mongolia People’s Hospital. At the time of admission, mesalazine dose was 3.0 g/d for four weeks. Four weeks after admission, 90% patients’ symptoms were improved after mesalazine single-dose treatment. 10% patients had less effective after treatment, and then continuous therapy by mesalazine 3.0 g/d plus methylprednisolone 10 mg for 4 weeks. Most patients get symptoms improved, no bloody purulent stool, abdominal pain and diarrhea. Our patients with IBS treatment with mesalazine appeared to show benefit but this still need confirmation in a larger group. More precise subtyping based on underlying disease mechanisms may allow more effective targeting of treatment in IBS.

Keywords: inflammatory bowel disease (IBD), mesalazine, potential
Fecal microbiota transplantation (FMT) for fungi-infected, high fever UC patients

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Introduction: Ulcerative colitis (UC), as a kind of inflammatory bowel diseases (IBD), is generally not as complicated as Crohn’s disease (CD). However, for the hospitalized UC patients might have severe symptoms like high fever, more frequency of bloody stool, and so on. Some of the hospitalized UC patients with high fever might not only because of the progression of the disease, but also a sign of infection. Besides the infection of bacteria, like C. difficile infection or the infection of virus, like cytomegalovirus (CMV), we have found some high fever UC patients with fungi infection. The fungi infection would be ever cultured from the stool, or detected as a sign of increase of 1,3-β-D glucan. Though anti-fungi infection medicine would be helpful, concerning the potential renal toxicity, some of the patients might not be suitable for anti-fungi infection medicine.

Fecal microbiota transplantation (FMT) is a booming method for a lot of intestinal diseases, like IBD, diarrhea, constipation, and so on. Randomized controlled trial (RCT) had been published to prove its effectiveness in C. difficile infection originally, and on UC just recently.

Methods: FMT has been used for the treatment of refractory IBD patients in our center as well. Especially in recent experience, FMT has been used for the fungi-infected, high fever UC patients. After carefully screening the donor and suitable patients, FMT was performed through endoscopy. And body temperature, frequency of stool, circulation blood test, stool test, stool cultivation, as well as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin, 1,3-β-D glucan were monitored.

Results: Seven patients (5 male and 2 female) have been applied, with the mean age 48.7 ± 18.6 (20–74 years). Four of the patients have been cultured candida albicans from the stool. The 1,3-β-D glucan (picogram/milliliter) (normal 0–60) has been dropped from 148 ± 79.8 to 22 ± 10.5. The white blood cell (white-cell count [per mm³]) (normal 1800–6300) decreased from 9547.9 ± 2242.5 to 5759.3 ± 1586.2. All the patients have excluded the infection of respiratory, urinary, nervous and recirculating systems, meanwhile a negative assay of TB, CMV and C. difficile infection. Antibiotic and probiotics have been used for the patients with out of limits white blood cell. FMT have been applied once or twice from healthy donors or the selected healthy relatives. Finally, the peak body temperature decreased from 38.4 ± 0.7 to 36.9 ± 0.2. And all the other examinations like erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin and stool frequency have been improved.

Discussion/Conclusion: Though needs more practice and RCT data, FMT might be a new, safe and effective method for fungous infection treatment of the IBD patients.
Diminished expression of H2-calponin enhanced intestinal inflammation and development of colitis-associated cancer

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Introduction: H2-calponin is an actin filament-associated regulatory protein expressed in smooth muscle and non-muscle cells. It functions as a regulator of smooth muscle contraction in smooth muscles have been recognized already, but its function in non-muscle cells has not been elucidated yet.

Methods:
H2-calponin knock-out mice was induced by DSS for colitis model, and AOM-DSSA for colitis-associated colon cancer model. Mice body weight, stool consistency, stool frequency, bloody stool as well as related immune response, transduction signals were investigated.

Results: It’s found that that H2-calponin plays an essential role in maintaining persistent activation of STAT-3 that leads to colon inflammation and CAC development. We have identified that lack of H2-calponin increases macrophages and neutrophils infiltration, leading to more IL-6 and MPO secretion, thus triggers STAT-3 phosphorylation and development of colon colitis and CAC. The human white blood cells counterpart, H2-calponin predominate expresses in monocytes and there is a dramatic decrease of H2-calponin expression in UC patients.

Discussion/Conclusion: These results suggest that H2-calponin may represent a functional link between the CAC and the immune system, which opens up a new sight for the treatment of inflammation-associated cancer in human.
Natural history of Crohn’s disease in China

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Introduction: To analyze characteristics of clinical data in patients with CD, progression of the disease pattern and risk factors of prognosis.

Methods: We collected the information of CD in our province diagnosed between January 1997 and January 2011, information and data of patients were collected by the questionnaire. We evaluated the activity of disease according to CDAI, recorded treatment and surgery during follow-up. The association with the development of severe CD was assessed by multivariate analyses using the logistic regression analysis.

Results: The peak age of onset for CD occurrence is 17–40 years old, with 115 cases (58.4%). The location mainly affected is ileocolon the distal ileum with 82 patients (41.6%). Non-stricturing non-penetrating behavior accounts for 44.7% of CD when diagnosed. Follow-up of 60 months was completed in 172 patients. After follow-up of 60 months, patients affected in ileocolon was 86 cases (50%). And non-stricturing non-penetrating behavior accounts for 29.7% of CD. In recent 5 years, the number of CD patients received steroids and biological agents in our province were not increased significantly (P > 0.05). Use of immunosuppressive drugs is increasing (P < 0.05). The cumulative risk for abdominal surgical procedure was 7.0%, 11%, and 21.5% at years 1, 3 and 5, respectively. Male, age less than 40 years, location of ileocolon, stricturing and penetrating behavior, the need for steroid treatment in the first year of diagnosis, didn’t received immunosuppressive drugs early were all risk factors that predicted a “disabling course” of CD.

Discussion/Conclusion: The disease location and behavior evolved over time. In recent 5 years, treatment of CD had changed. CD patients had increased risk of operation during the course disease.
Platelet indices in patients with ulcerative colitis in China

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Introduction: Ulcerative colitis (UC) and Crohn’s disease (CD) are non-specific inflammatory bowel diseases (IBD) of unknown etiology. Many serum biomarkers such as hypersensitive C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR) have been studied for monitoring of disease activity in IBD. Blood platelets play an important role in inflammation and the repair of damaged tissues.

Methods: MPV, PDW, hsCRP, ESR, white blood cells (WBC), platelets (PLT) and red blood cells (RBC) were measured in 476 active patients and 229 healthy control donors. UC activity was assessed by Truelove-Witts criteria. UC diseased region was divided according to Montreal criteria.

Results: MPV was significantly decreased in patients with active patients compared to healthy control donors (p = 0.001). Significant negative correlation between disease indexing and MPV in patients with active UC was observed, however there was a relationship between diseased region and MPV. Moreover, MPV and PDW sensitivity and specificity were 73%, 73%; 78%, 75%.

Conclusions: MPV and PDW is reduced in active UC patients compared to healthy donors in China. The present report revealed that changes of platelet indices in IBD are note-worthy. The study shows that MPV and PDW are associated with active UC. So we think that MPV and PDW may be useful markers of the activity and lesions of UC.
Periodicity patterns for ulcerative colitis in China

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\textbf{Introduction:} The occurrence of many diseases such as gastrointestinal bleeding, diabetes mellitus, metabolic syndrome and encephalorrhagia are related to certain climate and seasons. Similarly we noticed that the incidence of ulcerative colitis (UC) is variable according to different seasons. Several international investigations drewed contrary conclusions about the seasonality of inflammatory bowel disease. But there still aren’t such reports in China. One aim of this study was to detect the seasonality of UC in China.

\textbf{Methods:} Retrospective analysis: Clinical data of UC patients of the Tai’an Central Hospital from the year 2008 to 2012 were collected. They included the date of birth, gender, age, duration of hospitalization, time of onset, site of lesion, clinical stage, place of residence and smoking status.

\textbf{Results:} There was no association between season of the year and births of UC. The distribution of months of admission showed no periodicity changes. We found no statistical difference in birth distribution in four seasons. However, we found that the nadir number of admissions for UC patients occurred in September. And gender, smoking and residence does not affect the trend changes. There was statistical difference in onset months on a monthly basis. As far as the distribution in months of onset on a seasonally basis is concerned, seasonality was observed in UC population as a whole. The onsets of UC patients occurred more frequently in the winter-spring period than summer-autumn period.

\textbf{Conclusions:} There is periodicity in the birth months and the onset months of ulcerative colitis patients, but these data doesn’t support an association between periodicity and admissions. Environmental factors play an important role in the development of ulcerative colitis.
Seasonal patterns for inflammatory bowel disease: A systematic review and update

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Introduction: The clinical course of inflammatory bowel disease (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC), is marked by exacerbation and morbidity. Seasonal variations of IBD analyzed in some previous publications are showing conflicting data.

Methods: This review was performed according to the standard guidelines for systematic reviews of observational studies. We searched the following databases until December 2012: Pubmed and Scopus databases by using the following subject heading terms and/or text words to increase the sensitivity of the search: inflammatory bowel disease, Crohn’s disease, ulcerative colitis, seasonal, seasonality, periodicity, birth, onset, flare, relapse, and admission. The data extracted included the first author, the year of publication, country of the population studied, the number of cases, sex, age of patients, case-control, study variables, statistical analysis and main findings.

Results: A total of 17 publications about seasonality of birth, onset, flares, relapse and admission were included in this review. 10 were excluded after review.

Conclusions: We found a seasonal pattern of relapse and a little evidence of a monthly and seasonal trend in birth, onset and flare but did not find seasonality in admission for IBD. The inconsistency that we found in seasonal patterns of IBD with respect to birth, onset and flare does not exclude the important role that environmental factors are playing in IBD occurrence. More rational and longer observations and cohort studies are required to research the seasonal patterns for IBD.
Quality of life and disease-related factors in patients with ulcerative colitis in remission

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Objective: To investigate the health-related quality of life (HRQoL) of patients with ulcerative colitis (UC) in remission as well as its influencing factors.

Methods: A total of 42 UC patients in remission and 50 controls were enrolled in our study from 2011 to March 2012. Demographic data collected, were requested by fill in the Quality of Life Scales, Medication Compliance Scales, and Hospital Anxiety and Depression Scales (HAD-A, HAD-D).

Results: The total score of IBDQ for the UC patients was 170.26 ± 43.67, total score of SF-36 110.60 ± 18.82, score of HDA-A 5.21 ± 3.72 and score of HAD-D was 4.79 ± 3.81; while those scores for the controls were 210.54 ± 7.30, 123.48 ± 8.68, 3.14 ± 1.40 and 3.42 ± 1.84 respectively. There were significant differences in the total scores of SF-36 and IBDQ between the two groups, and dimension scores, HAD-A and HAD-D for the UC patients were much higher than those for the controls. Course of disease, medication compliance and status of anxiety and depression were much more important factors affecting HRQoL of the patients.

Discussion/Conclusion: The quality of life for patients with UC in remission is lowered in the aspects of bowel symptoms, systemic symptoms, emotional function and social function and the scores for anxiety and depression scale are significantly higher than in normal individuals.
Epidemiological and clinical characteristics of inflammatory bowel disease in Kazakhstan

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Background: Research Institute of Cardiology and Internal Diseases, a tertiary center, provides special inflammatory bowel disease (IBD) service. Previously data on epidemiology of IBD in Kazakhstan was not available. This research features epidemiologic and clinical characteristics of ulcerative colitis (UC) and Crohn’s disease (CD).

Methods: Between 2011 and 2013 years, 69 cases of IBD hospitalized patients were analyzed retrospectively in mono-center, hospital-based study in Kazakhstan. Frequencies and proportions were calculated by using SPSS version 12.0. Nominal data on the cases were assessed using the Pearson and Fisher tests.

Results: Fifty five patients (79.7%) had UC and fourteen (20.2%) – CD. Mean age was 36.4 ± 11.6 years (UC) and 34.7 ± 13.9 (CD), age at the time of first presentation was 32.4 ± 11.5 years (UC) and 30.8 ± 14.2 years (in 35.7% CD cases first symptoms started in the age under of 19 years). Male to female ratio was 1:1.1 (UC) and 1:1.5 (CD). Urban citizens were more predisposed to UC and CD (70.9% and 71.4% accordingly).

Mean duration of UC symptoms was 51.3 months (from just presented to 23-years anamnesis), time from diagnosis – 13.6 ± 4.7 months (9 months maximum). Incorrect initial diagnosis were: 5.4% – infection colitis, 1.8% – irritable bowel syndrome, 12.7% – chronic hemorrhoid. In CD mean time from first presentation – 44.6 ± 35.8 m, time from diagnosis – 10.9 ± 2.8 months. Almost half of the CD patients (40%) initially were diagnosed with ulcerative colitis.

Mean activity indexes were: Mayo score 7.9 ± 2.4, CDAI – 252.8 ± 159.0. Rate of relapse/year amounted to 1.98 ± 1.2 times (UC), 3.22 ± 2.1 (CD), (p < 0.01).

Inflammation localizations in UC were: 27.2% – distal, 34.5% – left-side and 38.1% – total colitis. Complications in anamnesis: 30.9% – bleeding, 1.8% – bowel perforation, 5.4% – toxic megacolon, 1.8% – colon cancer, 3.6% – high grade dysplasia. Extra-intestinal complications: 3.6% – primary sclerosing cholangitis, 5.4% – rheumatoid arthritis, 3.6% – skin lesions.

In CD in 28.5% colon involved, in 35.7% – ileocolitis, 42.8% – terminal ileum, 28.5% – jejunum and distal segments of colon, 7.1% – proctitis. In 28.5% of cases patients had fistulizing type, perianal complications – 21.4%, stenosing type in 21.4%. 35.7% patients had surgical treatments. The extraintestinal complications were: 14% sacroileitis, 7.1% rheumatoid arthritis.

Analysis of incorrect initial diagnosis with the presence of intestinal complications of IBD proved a weak correlation (0.385 Fisher's test). Additionally, a negative correlation was established between the age of the first appeared CD symptoms with the presence of perianal lesions (Pearson test -0.616) and operative treatment (Pearson test -0.750). Complicated forms of IBD were accompanied by malabsorption syndrome (Pearson test 0.692 to 0.519 for UC and CD).
**Conclusions:** The majority of IBD cases were diagnosed amongst young people (20 to 40 years) with female predominance. Poor awareness about IBD amidst healthcare specialists and patients could affect in late diagnosis (up to 1 year), which in turn may lead to the higher frequency of intestinal complications.
Unnecessariness of enema preparation for sigmoidoscopy in moderate-to-severe ulcerative colitis patients

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Introduction: Sigmoidoscopy are very useful in the diagnosis, differential diagnosis, and management of inflammatory bowel disease. However, the optimal bowel preparation of sigmoidoscopy for with ulcerative colitis (UC) patients is not defined. Also the efficacy of enema for preparation of UC patients is controversial. The aim of this study was to investigate the efficacy of bowel preparation for sigmoidoscopy in active UC patients.

Methods: From January 2010 to July 2012, UC patients scheduled for flexible sigmoidoscopy were retrospectively enrolled to 2 groups: group 1: one enema 2h pre-procedure; group 2: no enema for procedure. The endoscopic images were reviewed by two expert endoscopists. The two endoscopists assessed the quality of bowel preparation and endoscopic disease activity by Mayo UC endoscopic score.

Results: For this study, 105 patients were reviewed (group 1 = 50; group 2 = 55). No difference was noted between the groups with regard to age, gender. The disease activity of UC in group 2 (no enema) was more severe (mayo score 8.4) than group 1 (one enema, mayo score 3, p = 0.04). There was no significant difference in bowel cleansing grade between group 1 and 2 (p = 0.12). There was no significant difference between the groups in terms of depth of insertion (p = 0.42). Inter-observer variations (k value) on endoscopic activity of UC are similar (0.73 in group 1 and 0.70 in group 2).

Discussion/Conclusion: In moderate and severe disease patients, the enema preparations were not needed. The enema gives no significant improvement in efficacy of bowel preparation in active disease status UC patients.
Difficult cases to diagnose as Crohn’s disease or intestinal tuberculosis

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Introduction: Some intestinal erosions or ulcers on colonoscopy are not so typical that endoscopic finding is very confusing to finalize the diagnosis as Crohn’s disease or intestinal tuberculosis.

Methods: We analyzed the clinical and endoscopic data retrospectively about the cases diagnosed at both Crohn’s disease and intestinal tuberculosis at the time of colonoscopy from 2007.1.1. to 2015.1.1.

Results: During 8 year-period, we can find 7 patients who met the above inclusion criteria. The final diagnosis was 4 Crohn’s disease and 3 intestinal tuberculosis. The male to female was 5 to 2 and mean age was 34. Colonoscopy showed the cases with more than 5 segment involvement were more frequent in Crohn’s disease (50% vs 33%). The mainly transverse ulcers can be found more easily with intestinal tuberculosis than Crohn’s disease (100% vs 50%). Pseudopolyps was also frequent in intestinal tuberculosis than Crohn’s disease (66% vs 25%).

Discussion/Conclusion: Although many specific endoscopic findings are already known, several cases with atypical endoscopic presentation at the time colonoscopy are still very difficult to decide the diagnosis. We suggest the differentiation could be aided by the clinical symptoms and the results of laboratory tests and the response to therapeutic trials.
The use of mesenchymal stromal cells in order to achieve deep (biological) remission of ulcerative colitis

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Currently, the concept of remission ulcerative colitis (UC) should be defined as a condition in which there is no biological and histological signs of inflammation – remission beyond symptoms. Biological remission UC involves the absence of symptoms, healing of intestinal mucosa, as well as normalization of serum and fecal biomarkers active inflammation.

Objective: To study the effect of mesenchymal stromal cells (MSCs) of bone marrow to achieve biological remission in patients with ulcerative colitis.

Methods: 68 patients with UC were divided into two groups. The first group of patients (n = 36) received standard anti-inflammatory therapy with 5-aminosalicylic acid (5-ASA) and glucocorticosteroids (GCS) + MSCs. Age – 19 to 58 years old (ME-29). The second group of patients (n = 32) received the standard anti-inflammatory therapy with 5-ASA and corticosteroids. Age of this group 20 to 62 years (ME-28). Immuno-biological treatment efficacy were assessed by the level of CRP and fecal calprotectin (FCP). Histopathology evaluation was performed on the index Geboes. Evaluate the effectiveness of therapy was performed at 2, 6 and 12 months. Baseline CRP in acute disease in the 1st group was 28.6 ± 2.4 mg/l, in the 2nd – 28.0 ± 3.0 mg/l (p = 0.363). Baseline FCP in the 1st group was 730 ± 23.4 mcg/g, in the 2nd – 810 ± 30.1 mcg/g (p = 0.086). Index Geboes in the 1st group was 4.2 ± 0.2 points in the 2nd – 4.1 ± 0.3 points (p = 0.107).

Results: After 2 months, the level of CRP in patients in group 1 was 10.6 ± 1.1 mg/l, in the 2nd – 11.0 ± 1.1 mg/l (p = 0.139). The level of the FCP in patients in the 1st group was 110 ± 12.0 mcg/g, in the 2nd – 120 ± 12.0 mcg/g (p = 0.001). Index Geboes in 1st group was 0.9 ± 0.1 points, in the 2nd – 1.1 ± 0.1 points (p < 0.001). After 6 months, the level of CRP in patients in 1st group was 6.5 ± 0.6 mg/l, in the 2nd – 8.9 ± 0.1 mg/l (p < 0.001). The level of the FCP in patients of 1-st group was 80 ± 5.0 mcg/g, in the 2nd – 95 ± 0.5 mcg/g (p < 0.001). Index Geboes in 1st group was 0.9 ± 0.1 points, in the 2nd – 1.0 ± 0.1 points (p < 0.001). After 12 months, the level of CRP in patients in 1st group was 8.6 ± 1.2 mg/l, in the 2nd – 9.4 ± 1.0 mg/l (p = 0.004). The level of the FCP in patients of 1st group was 75 ± 5 mcg/g, in the 2nd – 80 ± 5 mcg/g (p < 0.001). Index Geboes in 1st group was 0.6 ± 0.1 points, in the 2nd – 1.0 ± 0.1 points (p < 0.001).

Conclusions: Inclusion of MSCs in a comprehensive anti-inflammatory therapy UC contributes to a deeper immunobiological and histological remission UC.
Comparative assessment of the safety of stem cells and standard anti-inflammatory therapy of Crohn’s disease

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Mesenchymal stromal cells (MSCs) are now widely used in clinical studies with various diseases, providing a positive effect due to the immunomodulatory and paracrine mechanisms. However, the safety profile of these cells remains unproved.

Objective: To compare the safety of treatment of the patients with Crohn’s disease (CD), receiving comprehensive anti-inflammatory therapy with the application of MSCs standard therapy with 5-aminosalicylic acid (5-ASA), glucocorticosteroids (GCSs) and immunosuppressive agents (IS).

Materials and methods: Within the period from 2008 to 2013 the system transplantation of allogenic MSCs was carried out in 64 patients with CD. 47 patients were included in the first group, the average monitoring time averaged 62 ± 4 months. 19 of them (40.4%) were men and 28 (59.26%) women. The average age was 30.4 ± 1.2 years. 124 patients with CD, who received standard anti-inflammatory therapy with 5-ASA and GCSs, were included in the second, control group. Out of them 56 (45.2%) were men and 68 (54.8%) women. The average age was 36.8 ± 1.5 years. The patients, who received anticytokine therapy, were not included in this group. The safety of the used therapy was assessed by the presence of complications, arising during the observation, infectious complications, exacerbation of chronic inflammatory diseases, serious infectious complications, a malignant transformation, a lethal outcome.

Results: In the first group of patients with CD the development of non-severe infectious complications or exacerbation of chronic inflammatory diseases were registered in 7 patients out of 56, that totaled 12.5%, in the second – in 14 (16.7%) patients out of 84. When comparing the two groups, no differences were found in the risk of the development of infectious complications and exacerbation of chronic inflammatory diseases on the background of the standard anti-inflammatory CD therapy or with the introduction of the MSCs (RR 0.75, 95% CI 1.5–23.58; x²=0.16; p = 0.66). Severe infectious complications (pneumonia, pleurisy, activation of latent TB) in the first group were detected in 1 patient (1.8%) out of 56, and in the second group in 5 (5.9%) out of 84. When comparing the two groups no differences in the risk of this type of complications were also found (RR 0.3; 95% CI 0.04–2.5; x²=0.59; p = 0.44). Colorectal cancer was registered only in one she-patient from the first group (1.8%). The time between the introduction of the MSCs and diagnosed colon cancer was 10 days. In the second group of patients over the 5 years of follow-up, malignant transformation was observed in 4 (4.8%) patients out of 84 (RR 0.5, 95% CI 0.05–4.96; x²=0.01; p = 0.97). Within 5 years of follow-up in the first and second groups of patients, fatal outcomes were registered on one occasion in each group, 1.8% and 1.2% respectively (RR 1.5, 95% CI 0.1–23.49; x²=0.19, p = 0.66).
Conclusion: The analysis did not reveal any differences in the development of severe infectious complications, exacerbation of chronic inflammatory diseases, serious infectious complications of malignant transformations and deaths in patients with CD, who received the MSCs and the standard anti-inflammatory therapy.
The combination of mesenchymal stromal cells and infliximab increases the anti-inflammatory effect of the treatment of ulcerative colitis

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Mesenchymal stromal cells (MSCs) have a high immunosuppressive potential. Concentration of azathioprine, methotrexate, 6-mercaptopurine, infliximab (IFX) no effect on the viability, differentiation, phenotype MSC and ability to suppress proliferation of peripheral blood mononuclear cells. These results are important for the clinical application of MSCs in combination with immunomodulators and anti-TNF-α therapy. However, little is known about the effectiveness of the combined use of MSC and immunomodulatory drugs in the treatment of IBD.

**Aim:** Assess the clinical and endoscopic efficacy of combination therapy of ulcerative colitis (UC) with concurrent use MSC and IFX.

**Methods:** 1st group patients (n = 28) who were administered MSCs twice a month at intervals of 1 week + after 6 months from the date the first administration of MSCs. 2nd group patients with UC (n = 26) received IFX. 3rd group of patients with UC (n = 10) received MSC and IFX. Follow-up was 24 months. To assess the clinical activity of ulcerative colitis, we used the index Rachmilevitz, to assess the endoscopic activity. Analysis of the effectiveness of different biologic therapy of patients with UC after 2, 6 and 12 months of therapy. Initial level clinical activity index before treatment was in group 18.98 ± 0.38 points in the 2nd – 9.1 ± 0.4, and 3rd, respectively, – 9.1 ± 0.6, the level of endoscopic activity index before treatment was in the 1st group 7.46 ± 0.2 points, in the 2nd – 7.62 ± 0.16, in the 3rd – 7.6 ± 0.4 (p > 0.05).

**Results:** After 2 months of clinical activity index decreased significantly from baseline in 1st group to 1.53 ± 0.24 points in the 2nd – to 1.27 ± 0.12, in the 3rd to 1.1 ± 0.17 points (p > 0.05 between groups). After 6 months of clinical activity index was in group 11.64 ± 0.24 points in the 2nd – 1.35 ± 0.14 points, 3rd – 0.7 ± 0.15 points, which was significantly lower than in the 1st and 2nd groups (p < 0.05). After 12 months of clinical activity index was in group 11.68 ± 0.8 points in the 2nd – 1.62 ± 0.16 points, 3rd – 0.5 ± 0.16 points, which was significantly lower than in the 1st and 2nd groups (p < 0.05). Index Mayo after 2 months decreased significantly from baseline in the 1st, 2nd and 3-d groups of up to 1.57 ± 0.24, 1.65 ± 0.25, 1.22 ± 0.2 scores (p < 0.05), respectively. After 6 months the index Mayo in 1st group was 1.6 ± 0.24 points, in the 2nd – 1.65 ± 0.19, in the 3rd – 1.1 ± 0.2 points. After 12 months, the index of the Mayo patients 3rd group was 0.8 ± 0.2 points, which was significantly lower (p < 0.05) than in 1st group – 1.46 ± 0.22 points and 2nd – 1.43 ± 0.1, groups of patients with UC.

**Conclusion:** Combined biological therapy of inflammatory bowel disease contributes to more stable clinical and endoscopic remission compared to monotherapy with biological agents after 1 years.
The industrial food additive microbial transglutaminase is immunogenic in celiac disease children

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Introduction: Microbial transglutaminase (mTg) is capable of cross-linking numerous molecules thereby revolutionizing industrial food product qualities. It is a family member of human tissue transglutaminase (tTg), the autoantigen in CD. Despite declarations of the safety of mTg, direct evidence for immunogenicity of the enzyme in celiac patients is lacking.

Methods: The serological activity of mTg, tTg, gliadin complexed mTg (mTg neo-epitope) and gliadin complexed tTg (tTg neo-epitope) were studied in: 95 pediatric celiac patients (CD) mean age 8, 99 normal children (NC) mean age 8.5 and 79 normal adults (NA) mean age 28.1. Sera were tested by ELISAs, detecting IgA, IgG or both IgA and IgG: AESKULISA® tTg (tTg), AESKULISA® tTg New Generation (tTg neo-epitope, tTg-neo), microbial transglutaminase (mTg) and mTg neo-epitope (mTg-neo). The results were correlated to the degree of intestinal injury, using Marsh criteria.

Results: Comparing pediatric CD patients with the 2 normal groups: mTg-neo IgA, IgG and IgA + IgG antibody activities exceed the comparable mTg ones (p < 0.0001). All mTg-neo and tTg-neo levels were higher (p < 0.0001). tTg IgA and IgG + IgA were higher than mTg IgA and IgA + IgG (p < 0.0001). The levels of tTg-neo IgA/IgG were higher than tTg IgA/IgG (p < 0.0001). The sequential antibody activities, reflecting best the increased intestinal damage, going from M0 to M3c were: tTg-neo IgG ≥ mTg-neo IgG > mTg-neo IgA + IgG > tTg-neo IgA > tTg IgA > mTg-neo IgA. Taken together, mTg-neo IgG and tTg-neo IgG correlated best with intestinal pathology (r² = 0.989, r² = 0.989, p < 0.0001, p < 0.0001, respectively). mTg-neo IgG had higher sensitivity than tTg-neo IgG, with lower specificity.

Discussion/Conclusion: mTg is immunogenic in children with CD and by complexing to gliadin its immunogenicity is enhanced. Anti-neo-epitope mTg antibodies correlate with intestinal damage to the same degree as anti-tTg. In view of the pathogenic role allocated to tTg antibodies, further studies are needed to explore the pathogenic potential of anti-mTg antibodies in CD.
Effect of thalidomide on the TNBS-induced colitis in rats and research on its mechanism

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Introduction: To observe the effects of thalidomide on trinitrobenzene sulfonic acid (TNBS) induced colitis in rats and explore the possible pharmacological mechanism.

Methods: 32 rats were randomly divided into four groups (n = 8): normal control group (receiving 0.9% NaCl solution); colitis was induced in 24 rats by rectal administration of TNBS dissolved in ethanol; model control group (no treatment), thalidomide low-dose group (treated with 100 mg/kg thalidomide) and thalidomide high-dose group (treated with 200 mg/kg thalidomide). After 1-week-intervention, the colonic macroscopic damage index (CMDI) and tissue damage index (TDI) were evaluated, the colonic expression of interleukin-6 (IL-6), IL-17 and IL-23 were determined by immunohistochemistry and the mRNA levels of IL-6, IL-17 and IL-23 were determined by real time PCR.

Results: Compared with the model control group, the CMDI and TDI decreased (1.92 ± 0.38 and 1.08 ± 0.38 vs 3.50 ± 0.50, and 4.00 ± 0.58 and 2.54 ± 0.48 vs 5.00 ± 0.52, respectively; all P < 0.05). The colonic expression levels of IL-6, IL-17 and IL-23 also declined (low-dose: 0.27 ± 0.04, 0.34 ± 0.02 and 0.24 ± 0.02, respectively, all P < 0.05; high-dose: 0.24 ± 0.03, 0.26 ± 0.02 and 0.21 ± 0.02, respectively, all P < 0.05). The mRNA levels of IL-6, IL-17 and IL-23 declined (low-dose: 4.66 ± 0.54, 8.20 ± 0.90 and 3.77 ± 0.52, respectively, all P < 0.05; high-dose: 2.10 ± 0.32, 4.42 ± 0.16 and 1.98 ± 0.08, respectively, all P < 0.05).There were significant differences in colonic expression and mRNA levels of IL-6, IL-17 and IL-23, but no in the CMDI and TDI.

Discussion/Conclusion: Thalidomide can attenuate the symptoms and colonic inflammatory damage in TNBS-induced experimental colitis in rats possibly via a mechanism associated with inhibition of Th17 cell activation, downregulation of IL-6, IL-17 and IL-23.
The peri-appendiceal inflammation in Chinese ulcerative colitis patients

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Introduction: Many reports have described ulcerative colitis (UC) patients had inflammation surrounding the appendiceal orifice. The clinical significance and prognostic implications of this finding are still unclear. The aim of the study was to evaluate the clinical characteristics of peri-appendiceal inflammation (PAI) in Chinese patients undergoing colonoscopy for diagnosis or surveillance of ulcerative colitis.

Methods: Patients with a clinical diagnosis of UC, underwent colonoscopy twice or more times at Peking University Third Hospital were included in a retrospective study. Demographic data and colonoscopy results were reviewed.

Results: A total of 247 patients were included. 83 (33.6%) patients had endoscopically described PAI. The other 164 (66.4%) patients were included in control group. Of the 83 patients in PAI group, 45 (54.2%) were male and 38 (45.8%) were female, which were similar with control group (97 male and 67 female, p = 0.459). Both group had similar average time of follow-up (28.9 ± 24.1 months and 28.7 ± 24.1 months, respectively, p = 0.953). However, PAI group were younger than control group: the average age in PAI group was 38.9 ± 13.6 years old while 43.6 ± 15.4 years old in control group, p = 0.017). 15 patients (18.1%) in PAI group progressed during the period of follow-up while 23 patients (14.0%) in control group, which was no significant difference (p = 0.794). 3 patients (3.6%) in PAI group progressed to pan-colitis while 3 patients (1.8%) in control group, too.

Discussion/Conclusion: We found a higher incidence rate of PAI in Chinese UC population and UC patients with PAI were younger than those without PAI. Patients with PAI seemed to be more likely to progress to pan-colitis, although there was no significant difference compared with control group. The clinical significance of PAI needs further investigation.
The effects of Baizhufuling Tang in different ratios on the cytokine of rats with Crohn’s disease

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Objective: To research the effect of Baizhufuling Tang in the ratios 1:1, 2:1 and 1:2 on the cytokine of rats with Crohn’s disease (CD).

Methods: The internationally recognized Morris’s methods were used to develop the rat model and the rats with CD were cured with Baizhufuling Tang dosed in different ratios. An ELISA kit was used to determine the TNF-α, IL-1β, IL-4 and IL-10 in the rats’ blood serum.

Results: Compared to the blank group, the TNF-α and IL-1β levels increased distinctly (p < 0.05), while there was no significant different in the IL-4 and IL-10 levels. Compared to the model group, the TNF-α level was reduced remarkably in the 1:1 group (p < 0.05), the IL-1β level was reduced remarkably in the 1:2 group (p < 0.05) and the TNF-α level and the IL-1β level were reduced simultaneously in the 2:1 group (p < 0.05). The three different ratios were unable to adjust the IL-10 level but were able to return the IL-4 level to normal over time. This was more apparent in the 2:1 group.

Conclusion: Baizhufuling Tang is better at adjusting the TNF-α and IL-1β levels when it is dosed in the ratio 2:1 than when it is dosed in the ratios 1:1 and 1:2. This shows that different ratios of Baizhufuling Tang have different effects on the imbalanced immunity of Th1/Th2.

Keywords: Baizhufuling Tang, ratios, cytokine immune, Crohn’s disease
Serum S100A12 may be a useful biomarker in ulcerative colitis

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Introduction/Background: S100A12, a calcium-binding proinflammatory protein secreted by granulocytes, has been associated with inflammatory bowel disease (IBD).

Aims: The present study aimed to investigate the serum S100A12 levels in patients with ulcerative colitis (UC) and irritable bowel syndrome (IBS).

Methods: S100A12 serum levels were determined in 60 patients with UC, 50 with IBS-D and 50 healthy individuals, by means of an enzyme-linked immunosorbent assay.

Results: The serum level of S100A12 was significantly increased, 48.756 ± 17.315 ng/ml for UC patients, 36.093 ± 22.315 ng/ml for IBS-D group and 30.477 ± 18.492 ng/ml for normal group (P < 0.001 in both cases). Moreover, ROC curve analysis showed that the optimal cut-off of S100A12 for the prediction of UC was 29.8 ng/ml, with a 90% sensitivity and a 71% specificity. The area under the curves (AUCs) were 0.81 (95% CI: 0.74–0.88) and statistically significant (P = 0.001). We allocated the UC patients into three groups of upon Truelove criteria and Witts criteria. The serum S100A12 levels of mild, moderate and severe subgroup were respectively 37.52 ± 2.51 ng/ml, 48.55 ± 3.25 ng/ml and 60.21 ± 4.02 ng/ml. The statistically significant differences were observed between the three groups (P < 0.001, respectively). However, the serum S100A12 levels were 42.805 ± 5.228 ng/ml for E1 groups, 47.809 ± 3.282 ng/ml for E2 groups, 51.210 ± 3.602 ng/ml for E3 groups. Although patients with E3 disease seemed to exhibit an increased level of S100A12 compared to that of patients with E2 and E3. This difference did not prove significant (P = 0.259 and P = 0.480, respectively).

Discussion/Conclusion: Increased levels of circulating S100A12 are found in UC, compared to IBS-D. When used to distinguish UC from IBS-D adult patients, serum S100A12 levels exhibit moderate performance. On the other hand, serum S100A12 may serve as an inflammatory marker in UC.
Clinical efficacy of mesalazine oral combined with suppositories on the left half of ulcerative colitis

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Introduction: To explore the clinical efficacy of mesalazine oral combined with suppositories on the left half of ulcerative colitis.

Methods: Thirty-seven cases who has the left half of ulcerative colitis in our hospital outpatient and hospitalized were recruited from January 2013 to June 2013. These cases were divided into observation group (20 cases) and control group (17 cases), which were given oral mesalazine enteric-coated tablets and at the same time was given mesalazine suppositories on the observation group. The treatment period lasted for four weeks. And compared the two groups among the general efficiency rate, endoscopic mucosal improvement rate and adverse reaction.

Results: Compared to those in the control group, the general efficiency rate and endoscopic mucosal improvement rate of observation group were significantly higher, and the difference between the groups was significant (P < 0.05). There was no significant difference in adverse reaction between the two groups (P > 0.05).

Conclusion: Mesalazine oral combined with suppositories on the left half of ulcerative colitis can increase intestinal local drug concentration and can improve the treatment efficiency, which has low incidence of adverse reactions, it is worthy of clinical application.
**Therapeutic effect of Qingchangshuan in treating experimental colitis mice mediated by Rig-I**

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**Introduction:** Rig-I knockout mice are with the characteristics of the increasing CD4+ effector T cells and the colonic inflammation. We designed this study to investigate the immunoregulatory mechanisms of Qingchangshuan with the efficacy of clearing heat and removing blood stasis to treat the experimental colitis mediated by Rig-I.

**Methods:** Wildtype (WT) and Rig-I knockout (KO) male 129Sv mice were randomly separately divided into control (C) group, model (M) group, Qingchangshuan (QCS) group, 5-ASA group. The mice were given 5% dextran sulfate sodium ad libitum for 7 days to establish experimental colitis model and administrated with appropriate drugs for another 7 days. The general conditions, the disease activity index (DAI), colon length and index, the ratio of colon weight and length, colonic histopathology and the expression of CD44, CD62L on CD4+T splenocytes (assessed by Flow Cytometry), as well as the mRNA and protein expression of Rig-I, Gαi2 in the colon tissue (assessed by Real-time PCR and Western blotting) was measured.

**Results:** The DAI score of QCS group in WT mice was significantly decreased (P = 0.01). The splenic CD4+ effector T cells (CD4+ CD44^{high} CD62L^{low}) of QCS group (P = 0.002) and 5-ASA group (P < 0.001) was significantly decreased, while CD4+ memory T cells of QCS group (CD4+ CD44^{high} CD62L^{high}) was significantly higher (P < 0.001). The expression of Rig-I protein was significantly lower in QCS and 5-ASA group (P = 0.008, P = 0.007), while Gαi2 protein only in QCS group was significantly lower (P = 0.011). The DAI score of 5-ASA group was significantly decreased (P = 0.005). The CD4+ effector and memory T cells of spleen in QCS group was significantly lower (P = 0.018).

**Discussion/Conclusion:** Qingchangshuan markedly improved the general condition of colitis in mice, reduced the CD4+ effector T cells in spleen and the expression of Rig-I, Gαi2 in colon tissue, reducing the inflammation at local or overall. It confirmed that Qingchangshuan has immunomodulatory effects.
Measurement and clinical significance of IL-6, IL-10 levels in sera from patients with ulcerative colitis

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Introduction: Through measuring IL-6, IL-10 levels in sera from patients with UC, this thesis investigate that changes of IL-6, IL-10 levels in sera function on ulcerative colitis and the relationship between that and severity.

Methods: To measure IL-6, IL-10 levels in sera in 52 cases of UC patients and 40 cases of healthy physical by ELISA.

Results: Serum IL-6, IL-10 levels of UC patients were obviously higher than those in the other group (P < 0.05); serum IL-6 level in severe ulcerative colitis patients was higher than moderate and mild ulcerative colitis patients (P < 0.05). Serum IL-10 level in severe UC patients was lower than moderate and mild UC group (P < 0.05).

Discussion/Conclusion: Measuring serum IL-6, IL-10 levels of UC patients has important clinical significance on judging severity and imbalance of IL-6, IL-10 levels in sera has effect on ulcerative colitis.
Correlation of R702W, G908R and L1007fs polymorphisms of the NOD2/CARD15 gene with susceptibility to inflammatory bowel disease in Zhuang population in Guangxi, China

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Aim: To investigate the relationship between R702W, G908R and L1007fs polymorphisms of the NOD2/CARD15 gene and susceptibility to inflammatory bowel disease (IBD) in a Zhuang population in Guangxi, China.

Methods: Intestinal tissue samples of 70 Zhuang and 76 Han unrelated IBD patients and 80 Zhuang and 84 Han unrelated healthy people were collected in Guangxi from February 2007 to October 2010. Genomic DNA was prepared from these intestinal samples and used to genotype the R702W, G908R and L1007fs polymorphisms of the NOD2/CARD15 gene by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: None of the patients with IBD and healthy controls had heterozygous or homozygous SNP variants. The distributions of genotype and allele frequencies were not significantly different between the IBD group and healthy control group. No significant differences were noted in the NOD2/CARD15 gene R702W, G908R and L1007fs polymorphisms among patients with Crohn’s disease, ulcerative colitis and control subjects in Zhuang and Han populations in Guangxi (all P > 0.05). Gene mutation genotypes of the NOD2/CARD15 gene R702W, G908R and L1007fs polymorphisms were not found in these populations.

Conclusion: R702W, G908R and L1007fs polymorphisms of the NOD2/CARD15 gene are not associated with susceptibility to IBD in the Zhuang population in Guangxi.

Keywords: inflammatory bowel disease, NOD2/CARD15, single nucleotide polymorphism
Association between PTPN2 polymorphism rs2542151 and ulcerative colitis in northeast Chinese population

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We investigated the association between ulcerative colitis (UC) and single nucleotide polymorphism (SNP) rs2542151 of PTPN2.

Introduction: Ulcerative colitis (UC) as a form of chronic and recurrent bowel disease, the etiology is unknown. Pieces of evidence suggest that UC should be evolved as a result of inappropriate and ongoing activation of the mucosal immune system driven by the commensally luminal microflora in a genetically susceptible host. Protein tyrosine phosphatase non-receptor type 2 (PTPN2) plays an important role not only in inflammatory pathway, also in the development of UC. In recent years, association the study of PTPN2 gene gene loci polymorphism with susceptibility to ulcerative colitis has become a focus in Western counties, but the studies are controversial in southern China. This paper is a study on the association between PTPN2 polymorphism rs2542151 and ulcerative colitis in northeast Chinese population.

Methods: The studied population comprised 115 subjects, including patients with UC (UC cases, n = 115) and subjects without UC (healthy controls, n = 99). The target SNP was directly sequenced by Taqman genotyping assays. We use SPSS ver17 to do statistical analysis

Results: The allelic frequency of rs2542151 were 79.13% and 20.87% in patients with UC disease respectively. 85.35% and 14.65% in normal population respectively (P value > 0.05). But in genotype frequency there was significant difference between ulcerative colitis patients and normal population (P = 0.042). The polymorphisms of rs2542151 loci did not correlate with age with ulcerative colitis.

Discussion/Conclusion: Our study demonstrated that rs2542151 of PTPN2 was associated with ulcerative colitis susceptibility in the northeast Chinese population.
Misdiagnosis of Crohn’s disease as intestinal tuberculosis: A case report and review of the literature

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Differential diagnosis between two digestive diseases, Crohn’s disease (CD) and intestinal tuberculosis (ITB), is always a difficult problem in clinic and induce a delay in appropriate treatment (immune suppression versus anti-tuberculosis therapy), as the clinical symptoms of two diseases are so similar.

One patient was hospitalized for the pain in the right lower abdomen, and was performed the appendectomy. Later, he underwent the resection of ileocecum for that intestine fistula occurred after the appendectomy. The pathological diagnosis was intestinal tuberculosis and the anti-tuberculosis therapy was commenced on the patient for one year.

Afterwards, the patient was readmitted to the hospital for the right lower abdominal mass. A CT revealed intestinal fistula, abdominal abscess and abdominal wall gas. We performed the right hemicolecotomy on the patient for the reason of intestinal fistula and secondary infection. Postoperative diagnosis we made was CD, which is based on the history and the pathological examination. According to the CDAI (Crohn’s disease activity index), the patient is at high-risk. After the assessment, the patient was treated with infliximab. The patient has remained in complete remission and made a good recovery at the times of a 12-month follow-up.

The diagnosis between ITB and CD is difficult, and the misdiagnosis may lead to serious consequences and increase the rates of recurrence and reoperation. The postoperative biologic therapy should be considered as the high risk factors exist.

Keywords: Crohn’s disease, intestinal fistula, intestinal tuberculosis
Amiloride may ameliorate DSS induced colitis in mice via inhibiting the level of uPAR

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Introduction: It is reported that uPAR antagonist amiloride has an effect on experimental colitis. In this research it is investigated if amiloride ameliorate DSS induced colitis in mice via inhibiting expression of uPAR.

Methods: 5% DSS was given to mice for inducing experimental colitis. Before induction of colitis, amiloride (10 mg/kg), VSL#3 (5 g/kg) and normal saline were administered by gavage to mice in three groups (named amiloride group, VSL#3 group, DSS group respectively, n = 5 in each group) respectively, and then through day 1 to day 6. Disease activity index (DAI) score was recorded every day. Mice were sacrificed on day 6. Histology score was rated and uPAR mRNA and protein was measured using RT-PCR, immunohistochemistry and western blot respectively.

Results: DAI score through day 1 to day 6 of mice in amiloride group and VSL#3 group were all lower than DSS group (all P < 0.05). After sacrificing, histology score of mice in amiloride group and VSL#3 group were all lower than DSS group (5.2 ± 2.2 and 5.6 ± 2.1 vs 8.8 ± 1.9, P < 0.01 and < 0.05, respectively). uPAR mRNA level in amiloride group (1.08 ± 0.03 relatively to β-actin) and VSL#3 group (1.01 ± 0.06 relatively to β-actin) were all lower than DSS group (1.33 ± 0.05 relatively to β-actin, both P < 0.01). A large number of uPAR positive inflammatory cells were seen in intestinal lamina propria of mice in DSS group, and the number was markedly decreased in amiloride group and VSL#3 group (9.6 ± 1.1 and 10.4 ± 2.5 vs 18.4 ± 3.4, both P < 0.01). Measuring using western blot, uPAR protein was significantly increased in DSS group, and markedly decreased in amiloride group, while only slightly decreased in VSL#group.

Discussion/Conclusion: Amiloride may relieve DSS induced colitis in mice via inhibiting the expression of uPAR. And posttranslational regulation may involve in this effect.
Clinical efficacy of mesalazine enema combined with triple live bacterial agent of Clostridium butyricum, Streptococcus faecalis and Bacillus mesentericus in patients with mild-to-moderate distal ulcerative colitis

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Introduction: To evaluate the clinical efficacy of mesalazine enema combined with triple live bacterial agent of Clostridium butyricum, Streptococcus faecalis and Bacillus mesentericus in patients with mild-to-moderate distal ulcerative colitis (UC).

Methods: Forty-six patients with active mild-to-moderate distal UC were randomly divided into either a mesalazine group (control group, n = 23) or a combination group (trial group, n = 23). Patients in the mesalazine group were treated with mesalazine enema, and on the basis of this, the patients in the combination group were additionally given triple live bacterial agent of Clostridium butyricum, Streptococcus faecalis and Bacillus mesentericus. The course of treatment was four weeks. Disease activity index (DAI), endoscopic score, response rate, histopathological changes, and adverse reactions were compared between the two groups.

Results: DAI decreased from 7.72 ± 0.66 to 2.84 ± 2.35 in the trial group and from 7.17 ± 0.94 to 3.41 ± 2.58 in the control group, and the decrease was statistically significant between the two groups (t = 2.340, P = 0.018). The endoscopic score decreased from 3.20 ± 0.82 to 1.80 ± 0.90 in the trial group and from 3.10 ± 0.72 to 2.50 ± 0.86 in the control group, and the decrease was statistically significant between the two groups (t = 2.051, P = 0.040). The response rate was significantly higher in the trial group than in the control group (91.30% vs 65.22%, \( \chi^2 = 4.608, P = 0.036 \)). The histopathological changes showed no significant difference between the two groups (P > 0.05).

Discussion/Conclusion: Combined therapy with mesalazine and triple live bacterial agent could effectively alleviate clinical symptoms and colonoscopic manifestations in patients with mild-to-moderate distal UC.
6-Thioguanine nucleotide concentrations optimize individualized azathioprine maintenance therapy in patients with Crohn’s disease

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Introduction: It is still controversial that whether red blood concentration of 6-thioguanine nucleotide (6-TGN) based dose adjusting can be beneficial in optimizing azathioprine (AZA) therapy. This study is designed to assess the role of 6-TGN concentrations in maintaining clinical remission in Chinese patients with Crohn’s disease (CD).

Methods: We performed a prospective observational study of 83 eligible patients of CD treated with AZA in The First Affiliated Hospital of Anhui Medical University since January 2008 to September 2014. 69 patients achieving maintenance stage obtained stable AZA dose at least 6 months prior the enrolment after induction by steroids or infliximab. The dose of AZA initiating at 50 mg per day with corticosteroids or infliximab firstly used was adjusted by white blood count (WBC) and 6-TGN concentrations at month 3, 6 and 12 respectively. Demographic material, Crohn’s disease activity index (CDAI), 6-TGN concentration and laboratory tests were recorded at each visit.

Results: The mean 6-TGN concentrations of patients in remission group (n = 60) were 301.66 ± 116.23 (mean ± SD, mean AZA dose was 1.47 ± 0.58 mg/kg/d) vs. 264.94 ± 164.53 pmol/8× 108 RBC in those with active disease (n = 9, mean AZA dose was 1.75 ± 0.66 mg/kg/d, P = 0.41). No significant difference was found among the different levels of 6-TGN concentrations and remission rate (P = 0.12). According to CDAI, 44 of 49 (89.80%) patients receiving AZA alone as maintenance treatment sustained steroid free clinical remission while 16 of 20 (80.00%) patients treated by combination of AZA and infliximab remained remission. Adverse effects occurred in 21.74% (15/69) patients, including 13 leucocyte decrease and 2 abnormal liver function. A high 6-TGN level (> 400 pmol/8× 108 erythrocytes) was associated with the decrease of leukocyte (P < 0.001). Only two patients discontinued AZA intake due to leukopenia.

Discussion/Conclusion: Azathioprine dose adjusted by 6-TGN level may be a potential method in individualized therapy of maintaining remission in Chinese patients.
Characteristics and differential diagnosis of intestinal flora in Crohn’s disease and intestinal tuberculosis

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Objective: To analyze the characteristics of intestinal flora in Crohn’s disease (CD) and intestinal tuberculosis (ITb), and to find potential identification features to differentiate these 2 diseases.

Methods: Fifteen CD patients, 23 ITb patients, and 21 healthy volunteers (controls) were enrolled from June 2007 to November 2009. Selective culturing was used for the enumeration of bacteria count.

Results: The intestinal flora was mainly composed of Bifidobacteria, Bacteroids, Escherichia coli and Staphylococcus aureus both in CD and ITb patients. Lactobacillus and Bifidobacteria decreased obviously but Bacteroid increased in CD patients compared with the control (P < 0.01). Lactobacillus, Bifidobacteria and Escherichia coli decreased obviously (P < 0.05), but Bacteroid increased in ITb patients compared with the control (P < 0.01). Bacteroid increased in ITb patients compared with CD patients (P < 0.05). No difference in Enterococcus, Staphylococcus aureus and Saccharomyces was found among the 3 groups (P < 0.05).

Conclusion: Intestinal flora disorder occurred in either CD or ITb patients. The alteration of Bacteroid and Escherichia coli can help to differentiate the 2 diseases.
Introduction: To observe the changes of PYY and PYY receptors in rats with ulcerative colitis (UC), we detected not only the serum level of PYY but also jejunal epithelial cell in UC rats and estimated two important parameters of PYY receptor.

Methods: Rats were randomly divided into UC group, D-IBS group and control group. The serum level of PYY was measured by radioimmunoassay (RIA), and did receptor radioligand analysis to detect the epithelial cell membrane, getting the two basic parameter reflecting the character of PYY receptor: dissociation constant (Kd) and maximum binding capacity (Bmax).

Results: The serum level of PYY in UC and D-IBS was higher than that in normal group (P < 0.001) and the serum level of PYY in UC higher than in D-IBS (P < 0.001). The value of Kd and Bmax of UC compared with that in D-IBS and normal group P > 0.05.

Discussion/Conclusion: The serum level of PYY in UC was significantly higher than that in normal group and D-IBS, so we presume that the change of the serum level of PYY may not only relate to the symptom of diarrhea, but also inflammation. No matter the UC, D-IBS group, their Kd and Bmax were no significant difference compared with that of normal group, so we presumed that the symptom and inflammation in UC may have nothing to do with the change of PYY receptor.
Association of P268S, JW1 and N852S polymorphisms of NOD2/CARD15 gene with Zhuang patients with Crohn’s disease in Guangxi, China

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Aim: The aim of this study was to assess the relationship between P268S, JW1 and N852S polymorphisms of NOD2/CARD15 and susceptibility to CD population from Guangxi Zhuang Autonomous Region, China.

Methods: Intestinal tissues of 102 Zhuang and 100 Han unrelated inflammatory bowel disease (IBD) patients and 72 Zhuang and 78 Han unrelated healthy people were collected in Guangxi Region from March 2009 to March 2013. Genomic DNA was extracted from intestinal tissues by phenol chloroform method. P268S, JW1 and N852S of NOD2/CARD15 gene were amplified by polymerase chain reaction (PCR), then detected by restriction fragment length polymorphism (RFLP) and verified by gene sequencing.

Results: Heterozygous mutation of P268S was detected in 10 cases of CD including 6 Zhuang and 4 Han, 2 Han ulcerative colitis (UC) and 1 Zhuang healthy control. Genotype and allele frequencies of P268S mutation in Zhuang and Han CD were higher than that in UC and normal control group (P < 0.05). Eight cases of CD patients carrying P268S gene mutation were less than or equal to 40 years of age (P = 0.040). Gene mutation genotypes of JW1 and N852S were not found among CD, UC and control groups (P > 0.05).

Conclusions: P268S of NOD2/CARD15 gene may be associated with susceptibility and some clinical characteristics of CD in Zhuang population in Guangxi Zhuang Autonomous Region, China. JW1 and N852S of NOD2/CARD15 gene may not be related to susceptibility to these CD patients.

Keywords: Crohn’s disease, NOD2/CARD15, single nucleotide polymorphisms
The pathogenic role of MUC2 in animal models of inflammatory bowel disease

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The incidence of inflammatory bowel disease (IBD) is increased year by year, already is the world’s digestive system problems, mainly divided into UC and CD, the exact pathological mechanism is unclear, which may be related to intestinal flora, organization of immune-mediated mucosa injury related to the comprehensive effect of various factors such as genetic susceptibility, the destruction of the mucous membrane barrier also plays an important role, mucin MUC2 is composed of the main component of the intestinal mucosa. By observing the chronic colonic histological changes in IBD animal models, testing its CBir1, MUC2 expression level, and giving different interventions to the model groups. The DAI score, HI score and the expression level of CBir1e in TNBS + 50% ethanol group, Ketotifen + TNBS + 50% ethanol group and LPS + OVA + TNBS + 50% ethanol group were higher than those in the normal group. PAS stain MUC2 expression and immunohistochemical MUC2 expression, all of which in the TNBS + 50% ethanol group were lower than in the TTF + TNBS + 50% ethanol group. The expression level of MUC2 in the TTF + TNBS + 50% ethanol group was lower than in the LPS + OVA + TNBS + 50% ethanol group. These results indicate that the MUC2 expression of BALb/c mouse model for IBD is lease, it may be related to IBD. TTF can activate mast cells to release induce intestinal inflammation.
A case of thymoma characterized as colonic ulcer

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Case presentation: A 65-year-old man presented to our hospital with a history of recurrent mucopurulent bloody stool for 2 years and aggravated for 2 months. In the 2 recent years, the recurrent mucopurulent bloody stool occurred. Stool frequency was about 3–4 times one day. Two months ago, the symptoms was getting worse accompanied by dizziness. Investigation showed severe anemia (Hb 38 g/L) and colonoscopy showed ulcerative colitis in local hospital. The patient had ecphyadectomy for 6 years. The treatment with mesalazine and kangfuxin liquid was ineffective. The second colonoscopy examination showed that proliferative lesions distributed diffusely in the ascending and transverse colon and multiple, isolated ulcers with mucosa hyperplasia were presented in descending colon, sigmoid colon and rectum. Pathological examination of lesions displayed chronic inflammation and local neutrophil infiltration in the colon mucosa. Investigation showed hypoimmunoglobulinemia (globulin 16.5 g/L) and cytomegalovirus (CMV) DNA detection was positive (5.32 x 10^4 IU). The anemia improved more slowly than expected after blood transfusion and which was not matched with hematochezia. Therefore, we did bone marrow aspirate examination which indicated the pure red-cell anemia (PRCA). The chest CT displayed that there was a lump in the upper mediastinum. The disease improved gradually after tumor resection and anti-CMV treatment. Thymoma was confirmed by postoperative pathology eventually.

Discussion: Thymoma is one of the most common tumor in the mediastinum. The concurrent disease usually included myasthenia gravis, PRCA, hypogammaglobulinemia. Approximately fifty percent of patients with PRCA also suffered from thymoma, which was helpful for thymoma diagnosis. Meanwhile, as a kind of T-cell lymphoma, thymoma may induce bowel lesions, such as ulcer, mucosa hyperplasia and hemorrhage, which is similar to inflammatory bowel disease.
Dose azathioprine maintains remission in patients with steroid-dependent ulcerative colitis?

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Introduction: Studies assessing the efficacy of azathioprine in steroid-dependent ulcerative colitis are still unclear. We aimed to evaluate the long-term efficacy and safety of azathioprine in patients with steroid-dependent ulcerative colitis.

Methods: 33 patients with steroid-dependent inactive ulcerative colitis who received azathioprine therapy between January 2005 and December 2012 were included in this study and followed up until December 2014. Azathioprine was started at 50 mg/kg/d, and was adjusted according to clinical response and occurrence of adverse events, aiming for a target dose of 1.5–2.0 mg/kg/d. Steroid therapy was tapered according to protocol. The primary endpoint was the rate of clinical remission (include complete remission and partial remission) to azathioprine at 6, 12 and 24 months. Secondary endpoints included mucosal healing, steroid dose and safety of treatment.

Results: On an intention-to-treat basis, the proportion of patients remaining in clinical remission to azathioprine (mean dosage, 1.41 ± 0.36 mg/kg/d) at 6, 12 and 24 months was 81.8% (complete remission, 45.5%; partial remission, 36.3%), 72.7% (complete remission, 30.3%; partial remission, 42.4%), 69.7% (complete remission, 48.5%; partial remission, 21.2%), respectively. At 24 months 39.4% were in steroid-free remission and mucosal healing. Steroid withdrawal was attained in 48.5% and 51.5% of patients at 6 and 12 months respectively. Median time to complete steroid withdrawal was 6 months. An adverse event occurred in 39.4% of patients. Approximately 1/3 of patients (30.3%) experienced leukopenia. None of the patients experienced severe infections, neoplasms and deaths.

Discussion/Conclusion: Azathioprine appears to be safe and effective in about 70% of patients with steroid-dependent ulcerative colitis. Although side effects may limit long-term use, azathioprine has potential to maintain clinical remission.
Systematic review and meta-analysis: The diagnostic value of computed tomography enterography and magnetic resonance enterography in Crohn’s disease

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Introduction: Computed tomography enterography (CTE) and magnetic resonance enterography (MRE) are common examinations for patients with Crohn’s disease (CD). They have been shown to have a high and comparable diagnostic accuracy for diagnosis of CD. The aim of this study was to compare the diagnostic value of CTE with MRE in patients with suspected or established CD.

Methods: Embase, Medline and Cochrane databases were searched for studies. Segmental intestinal wall thickening and strengthening were taken as image diagnostic indicators in CD, with endoscopic and histopathologic findings as diagnostic standard. Pooled sensitivity, specificity, the weighted area under the curve (AUC) and other diagnostic indices were evaluated.

Results: A total of 486 patients known or suspected CD from 14 different studies were analyzed. All the papers were blinded and over 10 with QUADAS-scale-scoring. The pooled sensitivity and specificity for CTE group in diagnose CD was 87% (95% confidence interval [CI] 83–90) and 87% (95% CI 81–91) respectively. The pooled positive likelihood ratio (LR) was 4.14 (95% CI 2.75–6.22) and pooled negative LR was 0.21 (95% CI 0.15–0.29). The AUC under the summary receiver-operating characteristic (sROC) of CTE group was 0.897. While the pooled sensitivity and specificity for MRE group was 81% (95% CI 72–88) and 84% (95% CI 74–91). The pooled positive LR was 4.35 (95% CI 2.67–7.10) and pooled negative LR was 0.24 (95% CI 0.16–0.37). The AUC was 0.888. There is much overlap of the AUC 95% CI between CTE group and MRE group. The results are not statistically significant.

Discussion/Conclusion: Although CTE has lower false positive and false negative than that in MRE, there is no obvious difference between CTE and MRE in diagnosis value of CD. We hope more studies about analysis of diagnostic value in CD between different clinical examinations to clinical treatment.
TLR 2, 4, 6 as a tool for predicting the risk of developing early relapse of ulcerative colitis

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Introduction: Investigations of the influence of innate immunity on the development of ulcerative colitis (UC) and Crohn’s disease (CD) are actually today. Progress has been achieved in the study of the role of TLR (Toll-like receptors) in innate and adaptive immunity, which defined new concepts of the nature of the immune processes. Certainly, the study of TLR has a value in understanding the pathogenesis of UC and CD.

Methods: We studied 86 patients with UC aged 19–75 years (39.0 ± 1.4 years) depending on the localization of the inflammatory process were divided into three groups: 1–15 (17.4%) patients with distal UC form, 2–42 (48%) patients with left-sided colon cancer lesions and 3–29 (33.7%) of the patients with total form of the disease. The control group consisted of 20 healthy volunteers (15 women, 5 men) aged 26.2 ± 8.3 years. TLR expression on peripheral blood monocytes was determined by immuno-fluorescence assay with monoclonal antibodies TLR2 (CD282), TLR4 (CD284) and TLR6 (CD286), conjugated with FITC (Hycultbiotechnology, The Netherlands) and the corresponding isotype controls during the medication-induced relapse and remission. 

Results: Expression of TLR 2, 4, 6 during relapse UC was 82.5 ± 0.7%, 12.6 ± 0.5%, 11.7 ± 0.3%, respectively, in clinical remission: 68.0 ± 0,8%, 6.9 ± 0.7%, 5.4 ± 0,2% respectively (p < 0.05). In the control group these indexes were 66.7 ± 0,8%, 3.7 ± 0,3%, 3.4 ± 0.2% respectively, which was significantly different from the expression of TLR 2, 4, 6 during relapse (p < 0.05), and had no significant differences compared with values during clinical remission (p < 0.05). Analysis of changes in expression of TLR 2, 4, 6 remission indicates decreased activity of the innate immune response in patients with UC. The expression of TLR 2, 4, 6 depending on the severity of the inflammatory process and long term morbidity revealed significant differences.

On the basis of the identified relationships we calculated the risk of relapse of UC based on the values of TLR 2, 4, 6 using non-linear regression. It was found that the risk of relapse UC is directly dependent on the expression of TLR 2, 4, 6, and both increased expression of receptors increases the likelihood relapse UC. We get a table for calculating the risk of relapse of UC based on the expression TLR 2, 4, 6.

Discussion/Conclusion: Expression of TLR 2, 4, 6 represents phase severity and activity of inflammation in UC. Rise expression of TLR 2, 4, 6 leads to an increased risk of relapse UC. Composite increase in the expression of TLR 2, 4, 6, associated with the development of early relapse. Determination of the expression of TLR 2, 4, 6 can be used as a marker of clinical and endoscopic remission and early prediction of relapse UC.
Comparison of the reliability of celiac disease serology to reflect intestinal damage

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Introduction: In view of the increasing importance of the serological biomarkers for the screening and diagnosis of celiac disease, their differential performance, and the lack of head to head comparison, we undertook the task to evaluate the reliability of those isolated or combined antibodies to reflect the intestinal damage in children with CD.

Methods: 95 pediatric CD patients (mean age 8.3 ± 4.4), 45 nonspecific abdominal pain children (AP) (mean age 7.3 ± 5.1), 99 normal children (NC) (mean age 8.5 ± 4.2) and 79 normal adults (NA) (mean age 28 ± 5.1) were tested by the following ELISAs, detecting IgA, IgG or both, IgA and IgG: AESKULISA® Gliadin (AGA), AESKULISA® tTg (tTG; RUO), AESKULISA® DGP (DGP) and AESKULISA® tTg New Generation (Neo-epitope tTg complexed to gliadin = tTg-neo). The results were compared to the degree of intestinal injury, using revised Marsh criteria, where M0 is normal and M3c is maximally affected. Scatter diagrams and regression analysis comparing the 12 antibodies’ OD activities to the degree of the intestinal damage were correlated.

Results: In general, the comparison showed that most of the assays are able to differentiate patients with low and high degree of intestinal damage. Comparing the different correlations between CD associated IgA and IgG antibodies’ isotypes, the tTg neo IgA ($r^2 = 0.968$, $p < 0.0025$) and tTg-neo/DGP IgGs ($r^2 = 0.989$, $p < 0.0001$; $r^2 = 0.985$, $p < 0.0001$, respectively) stood out, significantly, as the best indicators of the intestinal damage in CD.

The highest optical density (OD) values (medium OD 2.94 ± 1.2, $p < 0.0001$) were achieved by using the tTg-neo IgA ELISA in patients with Marsh 3c.

Discussion/Conclusion: Therefore, it is suggested that tTg-neo IgA/IgG antibodies should be preferably used to reflect intestinal damage during screening, diagnosing and monitoring compliance in childhood CD.
Antibodies against neo-epitope tTg complexed to gliadin are more reliable than anti-tTg for the diagnosis of pediatric celiac disease

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Introduction: The new guidelines of ESPGHAN for the diagnosis of pediatric celiac disease (PCD) rely on anti-human tissue transglutaminase (tTg) as the prime and unique antibody for screening of the suspected PCD population. Despite the extended CD associated serological repertoire, none of them has challenged tTg premiership. tTg complexed to gliadin presents neo-epitopes resulting from the enzyme-substrate interaction and antibodies against the complex are called tTg neo-epitope (tTg-neo).

Aim: To compare reliability of anti-tTg and tTg-neo antibodies in diagnosis of PCD.

Methods: 95 pediatric CD patients (mean age 8.3), 99 normal children (NC) (mean age 8.5) and 79 normal adults (NA) (mean age 28) were tested using the following ELISAs detecting IgA, IgG or both IgA and IgG: AESKULISA® tTg (tTg; RUO) and AESKULISA® tTg New Generation (Neo-epitope tTg complexed to gliadin). The results were compared to the degree of intestinal injury, using revised Marsh criteria. Sensitivity, specificity, positive and negative predicted values were calculated.

Results: A significantly higher OD activity was detected for tTg-neo IgA, IgG and IgA+IgG than for tTg (p < 0.0001, p < 0.0001, p < 0.001, respectively). tTg-neo IgA, IgG correlated better with intestinal damage than tTg ($r^2 = 0.968, 0.989$ compared to $0.909, 0.488$ (p < 0.001), respectively). The table summarizes some other parameters:

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predicted value</th>
<th>Negative predicted value</th>
<th>AUC</th>
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<td>tTg-neo IgA+IgG</td>
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<td>98.99</td>
<td>98.91</td>
<td>96.08</td>
<td>0.984</td>
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<tr>
<td>tTg IgA+IgG</td>
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<td>100</td>
<td>100</td>
<td>86.09</td>
<td>0.961</td>
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<td>Significance p &lt;</td>
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Discussion/Conclusion: The tTg-neo IgA, IgG and IgA+IgG isotypes exhibited a higher OD activity and better reflected intestinal damage in PCD, compared to tTg isotypes. The tTg-neo combined IgA + IgG ELISA kit had higher sensitivity and a comparable specificity for the diagnosis of childhood CD. It is suggested that the revised ESPGHAN criteria should include tTg neo in the diagnostic flow chart.
The detection of the fecal inflammatory markers in the ulcerative colitis

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Objectives: Due to the damages of intestinal mucosal barrier of ulcerative colitis (UC) patients, many inflammatory biomarkers flow out with the/into the feces. Detecting the levels of fecal inflammatory markers contributes to the assessment of intestinal inflammation activity. The aim of this study is to investigate the levels of intestinal alkaline phosphatase (IAP), calprotectin (Cal), matrix metalloproteinase-9 (MMP-9), myeloperoxidase (MPO), neopterin (Npt) in UC patients feces.

Methods: From June 2013 to May 2014, 50 UC patients diagnosed by the Department of Gastroenterology of The First Affiliated Hospital of Anhui Medical University were enrolled, 50 healthy subjects as normal control. 50 copies of the fresh stool specimens from healthy subjects and UC patients before and after treatment were collected. The fecal IAP levels was detected by the p-NPP methods, the fecal Cal, MMP-9 and Npt levels were detected by ELISA methods, the fecal MPO level was detected by the spectrophotometry methods.

Results: The level of IAP in UC patients feces was lower than that in control group (P < 0.01). The levels of IAP in the feces of UC patients increased after treatment significantly (P < 0.01). The level of Cal, MMP-9, MPO, Npt in the feces of active UC patients were higher than that in the remissive UC patients and the control group. There was significant difference between the levels of Cal, MMP-9, MPO and Npt in the feces of active UC patients with different severity (P < 0.01). There was a significant correlation between the levels of Cal, MMP-9, MPO and Npt in the feces of UC patients and the DAI score (r = 0.81, P < 0.01). The levels of Cal, MPO, MMP-9 and Npt in the feces of UC patients decreased after treatment significantly (P < 0.01).

Conclusion: Detection of the fecal markers contribute to evaluate intestinal inflammation in UC patients.
Determination of fractalkine/CX3CL1 levels in plasma of the Crohn’s disease

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Objective: To investigate the differences of the plasma levels of Fractalkine/CX3CL1 and ICAM-1, VCAM-1 between control group and Crohn’s diseases (CD) group to elucidate the clinical significance.

Methods: From January 2013 to August 2014, 96 CD patients and 48 healthy subjects as normal controls were enrolled in the Department of Gastroenterology of The First Affiliated Hospital of Anhui Medical University. According to the Crohn’s disease activity index (CDAI), the disease activity severity were assessed. The plasma levels of Fractalkine/CX3CL1 and ICAM-1, VCAM-1 were tested by ELISA method, the differences of the plasma levels of Fractalkine/CX3CL1 and ICAM-1, VCAM-1 between CD and control group were analyzed.

Results: Compared with control group, the plasma levels of Fractalkine/CX3CL1 in CD patients increased obviously (0.8872 ± 0.1570 ng/ml vs 1.8828 ± 0.5489 ng/ml, P < 0.01). But there was no association with the clinical features of CD. Compared with control group, the plasma levels of ICAM-1 in CD patients increased significantly (1684.08 pg/ml ± 420.21 pg/ml vs 3936.94 pg/ml ± 1058.90 pg/ml, P < 0.01). The plasma levels of ICAM-1 between the different location in CD patients were 4222.17 ± 1013.21 pg/ml, 3582.79 ± 1206.85 pg/ml and 4081.10 ± 877.26 pg/ml. Compared with normal group, the plasma levels of VCAM-1 in CD patients increased obviously (0.7187 ng/ml ± 0.0885 ng/ml vs 1.6595 ng/ml ± 0.4145 ng/ml, P < 0.01); The plasma levels of VCAM-1 in CD patients with mild, moderate and severe group according to the disease activity of CD were 1.2360 ± 0.3057 ng/ml vs 1.6154 ± 0.3720 ng/ml vs 1.9122 ± 0.3199 ng/ml (P < 0.01); It was confirmed that there was possible correlation between the plasma levels of ICAM-1,VCMA-1 in CD patients.

Conclusion: The plasma levels of Fractalkine/CX3CL1 and ICAM-1, VCAM-1 in CD patients increased obviously, and may partly have possible correlation with the biological behavior of CD disease.
Environmental factors in inflammatory bowel disease in Yunnan province: A nested case-control study

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Objective: To examine environmental risk and protective factors prior to patients developing IBD (including UC and CD) in Yunnan province in a nested case-control study.

Methods: The newly diagnosed IBD cases were recruited from January 1, 2008 to December 31, 2013, controls were matched sex and age with 1:4 case-controls. Environmental factors were completed by using questionnaires.

Results:
1. Had intestinal infectious disease and using antibiotics frequently before the age of 14 years, taking non-steroidal anti-inflammatory drugs other than aspirin less than 1 month before diagnosis, brain work, occupational stress, dining not on time more than 3 times a week, eating fried foods, salted foods or foods stored in the refrigerators more than 3 times a week were associated with increased risk of UC. While smoking, regular physical activity 1 to 2 times a week and more than 3 times a week, drinking tea, eating sweets and eating fruits 1 to 2 times a week, especially consumption of fruits more than 3 times a week were protective for the development of UC.
2. Appendectomy before diagnosis and dining not on time more than 3 times a week increased the risk of CD. Regular physical activity 1 to 2 times a week and more than 3 times a week were associated with reducing development of CD.

Conclusions:
1. Environmental factors had been identified as the indispensable part in the development of IBD, especially in UC.
2. We reported for the first time in a nested case-control study in Yunnan province. Regular physical activity was a protective factor, while dining not on time acted as the risk factor. Some dietary habits, life style, occupational factors and childhood factors may play important roles in IBD, especially in UC.

Keywords: ulcerative colitis, UC; Crohn’s disease, CD; environmental factors; nested case-control study
Association of Fas/Apo1 gene promoter (-670 A/G) polymorphism in Tunisian patients with IBD

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To detect a possible association between the polymorphism of the (-670 A/G) Fas/Apo1 gene promoter and susceptibility to Crohn’s disease (CD) and ulcerative colitis (UC) in the Tunisian population.

Introduction: Inflammatory bowel disease (IBD) is a chronic disorder of the gastrointestinal tract characterized by immune dysregulation and leukocyte recruitment. IBD may manifest as either Crohn’s disease (CD) or ulcerative colitis (UC), which are two distinct forms of IBD with some common clinical, epidemiological and immunological features, but they can be distinguished by anatomical and histological features as well as by serologic markers.

Methods: The (-670 A/G) Fas polymorphism was analyzed in 105 patients with CD, 59 patients with UC and 100 controls using the polymerase chain reaction restriction fragment length polymorphism method.

Results: Significantly lower frequencies of the Fas-670 A allele and A/A homozygous individuals were observed in CD and UC patients when compared with controls. Analysis of (-670 A/G) Fas polymorphism with respect to sex in CD and UC showed a significant difference in A/A genotypes between female patients and controls (P corrected = 0.004 “in CD patients” and P corrected = 0.02 “in UC patients”, respectively). Analysis also showed a statistically significant association between genotype AA of the (-670 A/G) polymorphism and the ileum localization of the lesions (P corrected = 0.048) and between genotype GG and the colon localization (P corrected = 0.009). The analysis of IBD patients according to clinical behavior revealed no difference.

Discussion/Conclusion: Fas-670 polymorphism was associated with the development of CD and UC in the Tunisian population.
Study on the prevention and therapeutic effects of Faecalibacterium prausnitzii on colitis of experimental rats

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Introduction: To explore the therapeutic effects and the mechanisms of Faecalibacterium prausnitzii (Fp) on trinitro-benzene-sulfonic acid-induced colitis.

Methods: Sixty Sprague-Dawley rats were divided into healthy control group, colitis model control group, Fp pretreated group, Fp supernatant pretreated group, Fp treated group and Fp supernatant treated group. Disease activity index (DAI), histological injury of colonic tissue, the content of butyrate in feces, forkhead box protein 3 (Foxp3) regulatory T cells (Treg) in peripheral blood and spleen and the level of interleukin (IL)-17 and IL-6 in serum were evaluated. All the data were statistical analyzed by single factor analysis of variance.

Results: Compared with colitis model control group, DAI significantly lowered and histological injury obviously improved in Fp and Fp supernatant groups. The effects of Fp pretreated group were better than those of Fp treated group and Fp supernatant pretreated group were better than Fp supernatant treated group. There was significant difference between Fp pretreated group and other groups on the concentration of butyrate (F = 49.796, P < 0.01). The peripheral blood level of Foxp3+ Treg in Fp supernatant pretreated group was highest. The spleen level of Foxp3+ Treg in Fp pretreated group and Fp supernatant pretreated group were significantly higher than that of other groups. The serum level of IL-17 and IL-6 in Fp pretreated group, Fp supernatant pretreated group, Fp treated group and Fp supernatant treated group was significantly lower than that of colitis model group.

Discussion/Conclusion: Fp plays a role in promoting the repair of intestinal inflammatory reaction in colitis model rats. The mechanism may be related with butyrate producing, the peripheral blood and spleen level of Foxp3+ Treg up-regulating, suppressing the secretion of proinflammatory cytokine IL-17 and IL-6. Rebuilding the balance of Treg/Th17 to reduce local intestinal inflammation.
The use of probiotics in the treatment of rectal stump inflammatory and ulcerative process

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Aim: The development of optimal therapeutic regimens aimed at restoring the quantitative and qualitative composition of intestinal microflora using probiotics and increase the effectiveness of integrated treatment of the stump of the rectum with ulcerative colitis after total colectomy.

Materials and methods: Due to the ineffectiveness of conservative treatment of surgical interventions were performed in 332 (58%) patients, including 103 (18%) due to the poor state of the first stage produced a total colectomy with ileostomy formation of single-barrel and suturing the stump of the rectum. Depending on the type of treatment in these patients postoperatively divided into two groups: The study group consisted of 50 (48.6%) patients who received postoperative basic (sulfosalazin, salofalk, corticosteroids) and bracing therapy and probiotics. The control group consisted of 53 (51.4%) patients who received only basic and restorative therapy.

Results: Before treatment all patients had significant violations of the intestinal microflora with the presence of opportunistic bacteria. In most cases disbiotic changes were accompanied by a decrease in the number of bifidobacteria and lactobacilli and lactopositive E. coli, as well as an increase in the number of representatives of conditionally pathogenic flora. Thus, in the second group the intestinal microflora in the cult of the rectum normalized or decreased in numbers to the severity of dysbiosis of I degree in 33 patients. In the first group dysbiosis II, III degree was observed in 30 patients.

Thus, on the basis of these data suggest that the combination of basic therapy with probiotics allows for reducing the inflammatory activity in the cult of the rectum and, of course, reduce the time of preparation for the recovery operation.
Two case reports of Crohn’s disease of upper gastrointestinal tract

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Introduction: Ileocecal region is the most common area of Crohn’s disease while Crohn’s disease of upper gastrointestinal tract is relatively rare and sometimes may be missed diagnosis and misdiagnosis.

Methods: Here we report two cases with Crohn’s disease of upper gastrointestinal tract. The two patients are all young males and the chief complaint of one patient was bellyache, vomit and haematemesis for two days, of another patient was bloating, vomit and emaciation for two months. Diagnosis of Crohn’s disease of duodenum and pyloric obstruction was confirmed by endoscopy and biopsy.

Results: The former patient received glucocorticoids and PPI treatment, the latter patient received mesalazine and PPI treatment. All the two patients have got remission and recovery now.

Discussion/Conclusion: Crohn’s disease of upper gastrointestinal tract commonly affects the duodenum and be identified by duodenal ulcer and pyloric obstruction. Endoscopy and biopsy are important for the diagnosis. In addition to PPI, glucocorticoids or mesalazine is need in treatment.
HSF2 inhibited proinflammatory cytokines expression induced by LPS via MAPK and NF-κB pathways in Caco-2 cells

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Introduction: Heat shock transcription factor (HSF) was responsible for maintaining intestinal epithelial cell homeostasis through activation of some protection proteins termed heat shock proteins. Our previous study has demonstrated that HSF2 was a difference expression protein in ulcerative colitis (UC), and its levels was associated with the severity of UC. However, the detailed mechanism of HSF2 in UC is undefined. Thus, we carried out this study to reveal the role of HSF2 in inflammation regulation.

Methods: HSF2 siRNA and HSF2-FLAG recombinant plasmid were transfected into Caco-2 cells by Lipofectamine means. Pro-inflammation cytokine expression was induced by LPS. Nitric oxide (NO) were measured by Griess reagent. The mRNA transcription levels of inducible nitric oxide synthase (iNOS) was analyzed by quantitative real-time PCR. The concentrations of IL-1β, and TNF-α in the supernatants of transfected Caco-2 cells were determined by ELISA. The expression of COX2 and phosphorylation levels of ERK1/2, JNK, p38, and NF-κB in nuclear were measured by Western Blotting.

Results: The expression of COX2, NO, iNOS, TNF-α and IL-1β in Caco-2 cells induced by LPS were markedly increased after silenced HSF2 expression by RNA interference. On the contrary, the expression of aforesaid pro-inflammation cytokines were reduced after enhanced HSF2 expression by HSF2-FLAG recombinant plasmid transfection. In addition, silenced HSF2 expression could increase phosphorylation levels of P38, JNK and ERK1/2 especially, thus, increase the expression of NF-κB in nuclear. Enhanced HSF2 expression was quite the contrary. In total, these findings suggested that HSF2 inhibited LPS-induced pro-inflammation cytokines by reducing the expression of NF-κB in nuclear via down-regulation phosphorylation of ERK1/2, JNK and p38 pathways.

Discussion/Conclusion: These studies revealed, in part, HSF2 has a potential anti-inflammatory properties thought MAPK and NF-κB pathways. This result might be a novel clue to reveal the pathogenesis of UC and a potential target for regulation the inflammatory response.
The expression of Keratin1 in colonic mucosa is associated with the severity of Crohn’s disease

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Introduction: The morbidity of Crohn’s disease (CD) is increasing in China year by year. In addition, there is a lack of accurate diagnostic indices with which to evaluate the activity of the disease. We aimed to identify CD-associated proteins as biomarkers for the diagnosis, and objective assessment of disease activity.

Methods: Differential expression of serum proteins from CD patients compared to normal controls was analyzed by two-dimensional electrophoresis (2-DE) and matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF-MS). The expression of Keratin1 (KRT1) in colonic mucosa in Crohn’s disease, Behcet’s disease, ulcerative colitis, intestinal tuberculosis, infective enteritis, intestinal lymphoma and normal controls was investigated by immunohistochemistry (IHC).

Results: KRT1 was differentially expressed in CD patients compared to normal controls. The expression of KRT1 was significantly lower in the intestinal mucosa of CD patients compared to Behcet’s disease, ulcerative colitis, intestinal tuberculosis, infective enteritis, intestinal lymphoma and normal controls. The results of immunohistochemistry showed that the expression of KRT1 decreased in parallel with the severity of CD.

Discussion/Conclusion: KRT1 appears to be a potential novel molecular marker for CD activity, and may provide a basis for studies on the pathogenesis and novel therapeutic targets for CD-
Calprotectin, NGAL-MMP-9 complex and NGAL as biomarkers in the diagnosis of inflammatory bowel disease (IBD) in children

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Introduction: The current standard for diagnostics of inflammatory bowel diseases remains endoscopy. Therefore, there is a need for novel, non-invasive serum markers specific for IBD.

Aim: To evaluate serum NGAL-MMP-9 complex, NGAL and calprotectin as surrogate markers of inflammation in children with Crohn’s disease (CD) and ulcerative colitis (UC) and to compare them with the disease activity index scores.

Methods: Blood samples were obtained from children with Crohn’s disease (n = 42), and ulcerative colitis (n = 43) for the diagnostic examinations. Concentration of NGAL-MMP-9 complex, NGAL and calprotectin were determined with commercially available kits.

Results: Serum NGAL-MMP-9 complex concentrations were highly elevated in patient with Crohn’s disease (105 ± 62.8, range: 10.1–307 ng/ml, n = 42 ) or ulcerative colitis (103 ± 70.4, range: 8.99–476 ng/ml, n = 43), relative to apparently healthy volunteers (40.3, range: 8.7–164 ng/ml, n = 35). There was significant correlation between NGAL-MMP-9 complex and calprotectin (r = 0.53) and NGAL (r = 0.85). Correlation of evaluated biomarkers with score of disease activity were moderate to strong (NGAL-MMP-9: r = 0.45 and r = 0.41; NGAL: r = 0.60 and r = 0.33; calprotectin: r = 0.68 and 0.28, for Pediatric UC Activity Index and Pediatric CD Activity Index, respectively).

Discussion/Conclusion: Children with IBD exhibit significant increase of the serum NGAL-MMP-9 complex, calprotectin and NGAL. Significant correlations, especially with pediatric UC activity indexes, suggest their possible use in IBD diagnosis. However, this topic requires further clinical studies.
Novel valuable biomarkers in the diagnosis of inflammatory bowel disease in children

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Introduction: Diagnosis of inflammatory bowel diseases rely still on assessment of changes in endoscopy and measurements of nonspecific acute phase proteins as surrogate markers of inflammation. Novel non-invasive biomarkers are thus needed for the identification of patients with IBD. Aim of the study was to evaluate three modern markers: serum NGAL-MMP-9 complex, serum neutrophil gelatinase B-associated lipocalin (NGAL) and fecal calprotectin as surrogate markers of inflammation in children with Crohn’s Disease (CD) and ulcerative colitis (UC) and to compare with the common indices of IBD.

Methods: Blood samples were obtained from children with IBD: Crohn’s disease (n = 42), and ulcerative colitis (n = 43) for the diagnostic examinations. Concentration of NGAL-MMP-9 was determined with ELISA kit (R & D Systems, USA), NGAL with ELISA kit (BioVendor, Czech Republic), calprotectin with quantitative immunochromatographic point-of-care test (Bühlmann Laboratories AG, Switzerland).

Results: Serum NGAL-MMP-9 concentration was highly elevated in patient with IBD (104 ± 66.7, range: 8.99–476 ng/ml, n = 85), relative to apparently healthy volunteers examined by manufacturer (40.3, range: 8.7–164 ng/m, n = 35). Serum NGAL level was significantly elevated (p < 0.05) in children with IBD (97.9 ± 42.0, range: 25–252 ng/ml, n = 85) as compared with the level in healthy controls (median: 42.0, range: 18.1–107 ng/ml, n = 126). For fecal calprotectin the following results were obtained: 535 ± 522 μg/g stool, range: 30–1800, n = 85 as compared with the cut-off value (< 50 μg/g). There was a significant correlation between NGAL-MMP-9 and calprotectin (r = 0.53), NGAL-MMP-9 and NGAL (r = 0.85) and between NGAL and calprotectin (r = 0.66). All three markers correlate well with other biochemical parameters.

Discussion/Conclusion: All three parameters were highly elevated in patient with IBD as well as in each subgroup (Crohn’s disease or ulcerative colitis). Thus, may be useful as valuable clinical biomarkers in IBD pediatric patients.
Pulse wave velocity, intima media thickness and flow-mediated dilatation in patients with normotensive normoglycemic inflammatory bowel disease

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Introduction: IBD patients have lower traditional cardiovascular risk factors than general population. However, some studies suggested that IBD patients have increased risk for cardiovascular events and atherosclerosis. Chronic inflammatory process may predispose to atherosclerosis. We aimed to investigate subclinical atherosclerosis in patients with IBD, by measuring cf-PWV, CIMT and FMD compared to matched normal controls.

Methods: A total of 192 cases, consisting of 74 patients with UC, 52 patients with CD and 66 healthy control subjects, were included in the study. Patients with previous cardiovascular disease, DM, HT, chronic renal failure, infectious and inflammatory disorders other than CD and UC were excluded. PWV was calculated using an automatic device. Measurements of FMD and CIMT were performed with B-mode ultrasonography, by using a high resolution, 18 MHz linear-array transducer.

Results: The cf-PWV levels were 8.13 ± 1.61 m/s in the UC patients, 8.16 ± 1.74 m/s in the CD patients and 6.85 ± 0.95 m/s in the healthy subjects. The levels of cf-PWV were significantly higher in CD and UC patients than control groups (P < 0.001), but there was no significantly difference between UC and CD (P > 0.05). We found significantly decreased FMD levels in patients with UC and CD (9.6 ± 5.1% vs 10.8 ± 4.4%), when compared with control subjects (15.1 ± 9.7%) (P < 0.05), but FMD levels did not differ significantly between UC and CD patients (P > 0.05). On the other hand, no difference in CIMT was detected between UC, CD and controls groups. We did not find any significant relationships between disease extent, cf-PWV, FMD and CIMT (P > 0.05). There was a significant correlation between cf-PWV and disease duration (P = 0.001, r = 0.297).

Conclusion: The present study suggest that IBD patients, without traditional cardiovascular risk factors have increased risk of endothelial dysfunction and atherosclerosis. Structural changes in arterial vessel wall occur because of long-term exposure to inflammation or cardiovascular risk factors after endothelial dysfunction.
Acute visual field defect depending on occipital infarction in a patient with ulcerative colitis

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Introduction: Extraintestinal manifestations and thromboembolic complications are seen more than in one-third of patients with inflammatory bowel disease (IBD). While the incidence of venous thromboembolic events such as deep venous thrombosis, and sinus venous thrombosis are estimated to be 0.26% in IBD, arterial thromboembolism is seen less frequently. We presented here a newly diagnosed case of ulcerative colitis (UC) that was admitted with acute visual loss due to occipital infarction. To the best of our knowledge, this is the first report regarding with occipital infarction depending on UC.

Case report: A 32-year-old male patient was admitted with massive bloody diarrhea and abdominal cramps for ten days. Laboratory results were normal except iron deficiency anemia, increased platelets levels, and elevated sedimentation. Based on colonoscopic and histopathologic findings, he was diagnosed as having severe UC. Five days after initiation of mesalazine treatment, the patient was suffering from acute visual field problem and headache. The right homonymous superior temporal quadrantanopia (mean deviation: -14.94 dB for left eye, mean deviation:-9.85 dB for right eye) was detected on visual field test. The infarction of left occipital area was found in cranial computerized tomography. Antiplatelet therapy (300 mg/day) was started in addition to mesalazine. Two months later, the complaint of visual field problem and the mean deviation on visual field test (-11.58 dB for left eye, -7.56 dB for right eye) was reduced. Additionally contrast enhanced magnetic resonance showed chronic ischemic encephalomalacia in medial side of the left occipital lobe.

Discussion: Cerebral vascular events usually occur during acute exacerbation of IBD. The prognosis of IBD patients with cerebral arterial thrombosis is worse than IBD patients without cerebral arterial thrombosis. Antiplatelet therapy recommends to prevention and treatment of cerebral arterial infarctions in IBD, but these patients should be carefully monitored for relapse of IBD.
Correlation of NOD2, IRGM, ATG16L1 and STAT4 gene polymorphism with Crohn’s disease in Chinese Han population

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**Introduction:** The etiology and pathogenesis of Crohn’s disease (CD) has not yet been clarified. In recent years related studies published abroad have demonstrated the correlation of NOD2, IRGM, ATG16L1 and STAT4 gene mutation with CD. To analyze the correlation of NOD2, IRGM, ATG16L1 and STAT4 gene polymorphism with CD in Chinese Han population.

**Methods:** Sixty-six consecutive CD patients with Han nationality were enrolled from Jan. 2007 to Jan. 2010 in Suzhou Municipal Hospital. Sixty-six healthy subjects served as normal controls. All the subjects were genotyped by PCR and direct sequencing to determine the genotype of related single nucleotide polymorphisms (SNP) in the above-mentioned genes and the genotype and allele frequencies were determined.

**Results:** The genotype and allele frequencies at NOD2 SNP of rs82066842, IRGM SNP of rs13361189, ATG16L1 SNP of rs82241880 and STAT4 SNP of rs87574865 of CD patients and normal controls were in Hardy-Weinberg equilibrium. There were no significant differences in the genotype and allele frequencies between the two groups.

**Discussion/Conclusion:** Gene polymorphism of NOD2, IRGM, ATG16L1 or STAT4 is not associated with CD in Chinese Han population.
Efficacy and safety of probiotics combined with mesalamine in the treatment of patients with ulcerative colitis

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Introduction: This study investigated the clinical efficacy and safety of probiotics combined with mesalamine in the treatment of patients with mild or moderate ulcerative colitis and compared several laboratory index changes before and after treatment.

Methods: 42 confirmed cases of mild or moderate ulcerative colitis were divided into two groups, with a randomized control study method. The treatment group (probiotics Yakult and mesalamine Etiasa) was 20 cases (Yakult: 1 bottle/time, Etiasa: 1.0 g/time, 3 times/day), the control group (Etiasa: 1.0 g/time, 3 times/day) were observed in 22 cases for 6 months. The clinical manifestations, safety and several laboratory indices of two groups of patients were compared before and after treatment.

Results: The research showed that the total effective rate of clinical treatment was 90% in the treatment group, 81.82% in the control group. The complete remission rate in the treatment group was 45%, 31.8% in the control group. The complete remission rate and total effective rate in the treatment group were significantly higher than those in the control group (P < 0.05). The total relapse rate of the former is significantly lower than that of the latter (P < 0.05). No obvious side effect was observed. After 6 months treatment, the hemoglobin, hematocrit and serum albumin levels in the treatment group were significantly increased (P < 0.05), while in the control group after treatment, hemoglobin, serum albumin and hematocrit were not changed significantly (P > 0.05); ESR and C-reactive protein in the treatment group were very significantly reduced (P < 0.01), and ESR and C-reactive protein were significantly reduced in the control group (P < 0.05); serum TNF-α, IL-17 and IL-23 cytokines in the treatment group were very significantly decrease (P < 0.01), while in the control group, the serum TNF-α, IL-17 and IL-23 cytokine were decreased significantly(P < 0.05); After 6 months treatment, there were significant difference in all the above indicators between the two groups (P < 0.05). In the treatment group, hemoglobin, hematocrit and serum albumin levels were significantly higher than those in the control group. ESR and C-reactive protein in the treatment group were significantly lower than those in the control group. The serum TNF-α, IL-17 and IL-23 cytokines in the treatment group were significantly lower than those in the control group.

Discussion/Conclusion: This study revealed that probiotics combined with mesalamine can significantly reduce the level of pro-inflammatory cytokines in the treatment of patients with mild or moderate ulcerative colitis, there are stronger effects in induction remission and maintenance of remission in patients with active ulcerative colitis, and these effects are more obvious than mesalamine treatment alone. Better safety and effective treatment are showed. The data suggest that the probiotics have a good role of adjuvant therapy for ulcerative colitis.
Predictors of urgent findings on abdominopelvic CT in patients with Crohn’s disease presenting to the emergency department

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Background: Patients with Crohn’s disease (CD) are frequently exposed to diagnostic radiation, mainly as a result of abdominopelvic computed tomography (APCT) examinations. However, there are limited data on the impact of APCT on clinical management in this population.

Aim: To investigate clinical predictors of urgent findings on APCT in patients with CD who presented to the emergency department (ED).

Methods: A retrospective study was performed among patients with CD presenting to 11 EDs with a gastrointestinal complaint. The primary outcome, OPAN (obstruction, perforation, abscess, or non-CD-related urgent findings), included new or worsening CD-related urgent findings or non-CD-related urgent findings that required urgent or emergency treatment. Variables with p < 0.1 in univariate analyses were included in a multivariable logistic regression model.

Results: Of the 266 APCTs performed, 103 (38.7%) had OPAN and 113 (42.5%) required changes in treatment plan. Stricturing or penetrating disease (odds ratio [OR] 2.72, 95% confidence interval [CI] 1.21–6.13), heart rate > 100 beats/min (OR 2.33, 95% CI 1.10–4.93), leukocyte count > 10,000/mm³ (OR 4.38, 95% CI 2.10–9.13), and CRP > 2.5 mg/dL (OR 3.11, 95% CI 1.23–7.86) were identified as the independent predictors of OPAN, whereas biologic agent use (OR 0.37, 95% CI 0.15–0.90) was identified as the negative predictor in patients with CD.

Conclusions: Only 39% of the APCTs performed in the ED among patients with CD showed urgent findings. Stricturing or penetrating disease, tachycardia, leukocytosis, and high CRP level were predictors of urgent CT findings, while biologic agent use was a negative predictor. To reduce unnecessary radiation exposure, the selection process for CD patients referred for APCT must be improved.
Association between red cell distribution width and disease activity in patients with inflammatory bowel disease

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**Background:** Recent studies have suggested that a higher red blood cell distribution width (RDW) is associated with disease activity in patients with inflammatory bowel disease (IBD). However, the RDW in IBD patients without anemia has not been investigated.

**Aim:** This study aimed to determine whether or not RDW could be used for the assessment of disease activity in IBD patients with and without anemia.

**Methods:** The serum C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), hemoglobin concentration, platelet and white blood cell counts, and RDW were assessed in 221 IBD patients, comprised of 120 patients with ulcerative colitis (UC) and 101 patients with Crohn’s disease (CD). Disease activity was determined for UC and CD with the Mayo score and the Crohn’s disease activity index, respectively.

**Results:** The CRP level, ESR, hemoglobin concentration, hematocrit, and RDW increased according to disease activity in patients with and without anemia (all p < 0.05). Multivariate analysis demonstrated that RDW was the best independent indicator for predicting disease activity in CD patients without anemia (odd ratios [OR], 1.702; 95% confidence interval [CI], 1.185–2.445; p = 0.004) and UC patients without anemia (OR, 4.921; 95% CI, 2.281–10.615; p < 0.001). Also, ROC curve analysis showed the RDW to be the most significant indicator of non-anemic active IBD (area under curve [AUC] in CD, 0.852, p < 0.001; AUC in UC, 0.827, p < 0.001).

**Conclusion:** The association between increased RDW and active IBD was evident in IBD patients with and without anemia.
The role of Gab1, Gab2 and Hook1 in regulating the pathogenesis of ulcerative colitis

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Objectives: To study the role of three adaptor proteins – Gab1, Gab2 and Hook1 in regulating the pathogenesis of ulcerative colitis.

Methods: Colon mucosa samples were collected from 5 ulcerative colitis patients and 5 healthy controls. The mRNA levels of Gab1, Gab2 and Hook1 were evaluated by real-time quantitative PCR.

Results and Conclusions: Gab1, Gab2 and Hook1 was down regulated in the intestinal epithelium of ulcerative colitis patients compared to healthy individuals, suggesting their possible participation in the pathology of ulcerative colitis.

Plans: We plan to further investigate the molecular mechanisms that these adaptor proteins modulating ulcerative colitis development or progression by taking advantage of both mouse models and clinical specimens.
The role of phosphatase SHP2 in regulating the function of intestinal macrophages in inflammatory bowel disease

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Object: To study the role of phosphatase SHP2 in regulating the function of macrophages in inflammatory bowel disease.

Methods: We generated macrophage-specific SHP2 knockout mice (MΦ-SHP2 KO mice) using LysM-Cre/SHP2<sup>flox/flox</sup> system, and adopted dextran sulfate sodium (DSS)-induced acute colitis model. Disease Activity Index (DAI) and histological scores were compared between MΦ-SHP2 KO mice and their SHP2 WT littermates.

Results and Conclusions: MΦ-Shp2 KO mice developed more severe colitis induced by DSS than their WT littermates. MΦ-Shp2 KO mice displayed more weight loss, shortened colon length and higher grade of inflammatory infiltration. Furthermore, we found that the inhibition of SHP2 attenuated the phagocytic capacity of macrophages, suggesting that macrophage-expressed SHP2 was important for the maintenance of intestinal homeostasis.

Plans: Further research will be carried out to clarify more detailed mechanisms that SHP2 modulates macrophage function in IBD. Meanwhile, we will explore the correlation between Shp2 expression and the pathology of IBD as well as IBD-derived colon cancer using clinical specimens.
Quantitative analysis of intestinal flora of Uygur and Han ethnic Chinese patients with ulcerative colitis in Xinjiang

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Introduction: To identify correlations between intestinal flora and ulcerative colitis (UC), we analyzed differences in amounts of Bacteroides, Fusobacterium, Clostridium, Bifidobacterium spp, and Faecalibacterium prausnitzii in the intestinal microflora of Uygur and Han ethnic Chinese patients with ulcerative colitis and healthy controls.

Methods: Bacterial genomic DNA extracted from fecal samples was used for quantitative analysis by real-time fluorescence quantitative polymerase chain reaction (PCR) to analyze the amounts of Bacteroides, Fusobacterium, Clostridium, Bifidobacterium spp, and Faecalibacterium prausnitzii.

Results: Compared with healthy, controls the amount of Bacteroides (P = 0.026) significantly increased, while the amounts of Clostridium (P = 0.004), Bifidobacterium spp (P = 0.009), and Faecalibacterium prausnitzii (P = 0.008) significantly decreased when the Uygur and Han UC patient populations were combined. In the group of UC patients, compared with the remission, Bacteroides population was significantly increased in the acute UC patients (P ≤ 0.05), while the amounts of Clostridium, Bifidobacterium spp, Fusobacterium and Faecalibacterium prausnitzii significantly decreased in the acute UC patients (P ≤ 0.05). Either UC group or control group, the amounts of each of the 5 bacteria, no significant differences were observed between the Han group and the Uygur group.

Discussion/Conclusion: Variations in microbial loads of the five bacterial strains may be associated with the occurrence of UC in Uygur and Han populations; however, these variations were not associated with ethnic differences.
Effects of probiotics on Toll-like receptors expression in UC rats induced by 2, 4, 6-trinitro-benzene sulfonic acid

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Introduction: Evidence suggests the association of ulcerative colitis (UC) with intestinal flora disorder and abnormal immune response. To investigate the regulatory effects of probiotics on Toll-like receptors (TLRs) expression in an UC rat model, and to discuss the role and possible mechanisms of probiotics in the development of UC.

Methods: Rats were assigned into the healthy control, model, Golden bifid treatment and TLR4mAb intervention groups. UC rat model was established using 2, 4, 6-trinitro-benzene sulfonic acid (TNBS). Rats’ general status and histological changes were scored using the disease activity index (DAI) and the histopathological scoring (HPS) method, and their expression of TLR4 and TLR2 were measured using RT-PCR.

Results: The expression of TLR4 and TLR2 in model group was significantly higher than the healthy control, but rats received Golden bifid treatment or TLR4mAb intervention exhibited significantly decreased (P < 0.05) level of TLR4 and TLR2 mRNA comparing to the model rats.

Discussion/Conclusion: The development of UC is associated with abnormal intestinal immune response. Probiotics alleviated inflammatory reactions in rats with UC, and the mechanisms might be associated with the expression of TLRs as well as the subsequent inflammatory cytokines.
Comparison of two experimental ulcerative colitis models that induced by DSS and TNBS in rat

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Introduction: To compare animal models of colitis that induced by dextran sodium sulfate (DSS) and 2, 4, 6-trinitrobenzene sulfonic acid (TNBS).

Methods: DSS and TNBS were used to establish animal models of experimental ulcerative colitis in rats. The disease activity index (DAI), weight index of colon, spleen, thymus, lesion score and myeloperoxidase (MPO) activity were measured in different periods of two models.

Results: Six rats died in the DSS group and one rat died in the TNBS group in the whole experiment process. DAI score was highest at 7th day in DSS group and highest at 2nd day in TNBS group. Then DAI score was lower in both groups. The period of inflammation of DSS-induced colitis was short. The period of inflammation of TNBS-induced colitis was longer. The histological injury of colon was more severe and lesion score was higher in TNBS group.

Discussion/Conclusion: Both DSS and TNBS could induce ulcerative colitis in rat. The period of inflammation of TNBS-induced colitis was longer and was a transformational dynamic process of acute inflammation to chronic inflammation.
Immunohistochemical analysis of Fascin-1 protein expression in IBD

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Introduction: Fascin-1 is a protein that organizes actin filaments in the bundles with a minimum ratio of 4.1:1 (actin/fascin). It plays an important role in creating microspikes, folding the cell membrane and stress fiber. This process is important in the formation of a diverse set of cell protrusions such as a filopodia, as well as cell motility and migration. Fascin is found in the most distal regions of filopodia and lamellipodia and the cellular distribution of Fascin within actin bundles appears to vary depending upon the extracellular substrate. In literature Fascin-1 is described as marker of cancer aggressiveness (breast, lung and also colorectal cancer). Fascin-1 activity is not clear, it affect in different ways for various cancers. Therefore the aim of our study was to evaluate the expression of Fascin-1 in inflammatory bowel diseases.

Materials and methods: The study consisted of 40 patients with ulcerative colitis (UC) and 12 patients with Crohn’s disease (CD). Endoscopic materials were taken from archival paraffin-embedded tissue. Sections were stained with H&E and subjected to routine histological evaluation. According to Geboes classification, an analysis of the severity changes (architectural changes, the assessment of crypt destruction, erosions and ulcers, infiltration of inflammatory cells) was performed. The expression of Fascin-1 protein in tissue sections was assessed by immunohistochemical methods. The color reaction was observed in cytoplasm of the glandular epithelium and inflammatory cells. The staining reaction in a 4-point scale was assessed as absent, weak, medium and strong. Weak-expression in < 25% cells; medium-expression in ≥ 25% and ≤ 50% cells; strong-expression in ≥ 50% cells. For statistical analysis we divided reaction as absent or present (weak, medium, strong).

Results: Patients with ulcerative colitis showed no expression of Fascin-1 in epithelial cells in 45% cases, weak, medium and strong in 55% (12.5%, 20% and 22.5%, respectively). In inflammatory cells of UC we observed rather positive reaction of this protein (72.5%). Patients diagnosed with Crohn’s disease had a 100% positive reaction of Fascin-1 in epithelial cells (weak in 75%, medium in 16.7% and strong in 8.3% cases). The positive reaction of inflammatory cells to Fascin-1 was observed in up to 58.3% of patients with Crohn’s disease. Moreover, in the normal glands of healthy mucosa the 100% positive expression of Fascin was noted. Statistical analysis showed a correlation between the presence of protein expression in epithelial cells and inflammatory cells in UC (p < 0.001), but not in CD. We also observed that positive reaction of Fascin-1 in epithelial cells is more often in CD than UC (p = 0.003), but expression of this protein in inflammatory cells in UC and CD is similar. In addition, expression of Fascin-1 in inflammatory cells in CD was positively correlated negatively with patients age (p = 0.003). It was also observed that increased degree of architectural changes in CD when the protein expression in inflammatory cells was present (p = 0.027).
**Conclusion:** Decreased Fascin-1 expression seems to play a role in ulcerative colitis development. Inflammatory cells expressing Fascin-1 may affect on architectural disorders in Crohn’s disease.
Fecal microbiome transplantation for Crohn’s disease: Report on a case series

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Introduction: The link between the microbes in the human gut and the development of Crohn’s disease (CD) is becoming clearer. We examined the effect of fecal microbiome transplantation (FMT) instilled into the gastrointestinal tract for CD.

Methods: During January to December 2014, patients with mild-to-moderate CD (CDAI of 150–450) and did not respond to mesalazine or corticosteroid were treated with FMT by gastroscopy or colonoscopy. The end points were 1 week, 2 weeks and 4 weeks after the procedure.

Results: A total of 18 patients were enrolled, and the clinical remission rate was 66.7% (12/18), 61.1% (11/18) and 33.3% (6/18) at the points of 1 week, 2 weeks and 4 weeks after transplantation. The percentage of patients who had their ESR and Hs-CRP decreased for more than a half was 61.1% (11/18), 77.8% (14/18), 27.8% (5/18), and 55.6% (10/18), 72.2% (13/18), 22.2% (4/18), at the end points respectively. Meanwhile, 3 patients (16.7%) reported mild abdominal pain and 2 patients (11.1%) reported transient fever (37.9°C and 38.4°C). There was no statistical difference in efficiency of fecal microbiome between donors under 14 years of age and those aging 14 and older (p > 0.05). The fecal microbiome from family member and that from unrelated donors didn’t yield statistically different clinical remission rate (p > 0.05).

Discussion/Conclusion: FMT improves the clinical remission rate of CD and shows the best effects in the second week after FMT. Also, the donor’s age and relationship with the patient does not affect the curative effects.
A randomized controlled trial of two different dosing regiments of azathioprine in the treatment of active Cohn's disease

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Objective: To compare the efficacy and safety of different dosing of azathioprine (AZA) in long term treatment of patients with active Crohn’s disease (CD) in China through a randomized controlled trial.

Methods: From 2012 to 2014, fifty patients with active CD who need to be treated with systemic steroids were recruited. The patients were randomized divided into two arms: 1 mg/kg/d AZA vs. 2 mg/kg/d AZA (n = 25 per arm). All patients initially received AZA combined with steroids therapy and AZA was maintained for treatment after withdrawal of steroids. Clinical efficacy and adverse events were assessed at the end of the 12th, 24th, 48th weeks.

Results: Analysis was done by intention to treat (ITT) and per-protocol (PP). The complete remission (CR) rates and the response rates (RR complete remission rates plus partial remission rates) at week 12 in 1 mg/kg/d arm and 2 mg/kg/d arm were proved to be with no significant difference (CR n = 4 vs. 5, ITT: P = 0.941, PP: P = 1.000; PR n = 18 vs. 20 ITT: P = 0.242, PP: P = 0.920). At week 24 the clinical efficacy was different (CR n = 6 vs. 14, ITT: P = 0.011, PP: P = 0.027; PR n = 11 vs. 17, ITT: P = 0.042, PP: P = 0.0.112).

The Clinical efficacy became statistically significant at week 48 (CR n = 3 vs. 11, ITT: P = 0.007, PP: P = 0.017; PP n = 4 vs. 13, ITT: P = 0.004, PP: P = 0.008). In 1 mg/kg/d arm four Patients (16%) had adverse events, one of whom had pancreatitis, one had arthritis, one had flu-like illness, two had leukopenia. While in 2 mg/kg/d arm five Patients (20%) had adverse events, four of whom had leukopenia, one had arthritis. There were no differences in the rate of adverse events between the treatment groups (P = 1.000).

Conclusion: AZA at the dose of 2 mg/kg/d is more effective compared to 1 mg dosing in active Crohn’s disease in long-run, without impaired safety.

Keywords: Crohn’s disease, azathioprine, dose, efficacy, adverse effect
Analysis of epidemiological and clinical characteristics of inflammatory bowel disease over 15-year period

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Background and Aims: The prevalence of inflammatory bowel disease (IBD) is increasing rapidly in China. We aimed to explore the trends in epidemiological and clinical characteristics of IBD in Eastern China over the 15-year period.

Methods: This is a multi-center retrospective study. Newly diagnosed IBD cases from January 1995 to December 2009 (n = 427) in Eastern China were included. Study protocol was approved by Institutional Review Board. Disease severity was assessed by Montreal classification. It was divided into two periods: 1995–2004 and 2005–2009. The epidemiological and clinical characteristics of ulcerative colitis (UC) and Crohn’s disease (CD) were compared in these two periods, respectively.

Results: The mean inpatient CD incidence had 2.5-fold increment with P < 0.05 while incidence of UC did not change significantly over the two periods (P > 0.05). The incidence growth of CD is significantly associated with the growth of gross domestic product (GDP) in China (P < 0.001). There were no statistically significant difference regarding the mean age at diagnosis, gender ratio and mortality rate (P > 0.05) between the two periods among both UC and CD. Meanwhile, the rate of applications of immunomodulators and biologics was higher in 2005–2009 than those in 1995–2004 (P < 0.05).

Conclusions: During 1995–2009, age at diagnosis, gender and the familial occurrence of IBD did not change significantly in Eastern China. The incidence in inpatient CD has increased 2.5-fold and significantly associated with the GDP growth. This study provides insight into the possible local epidemiological and clinical patterns of IBD.

Keywords: change, epidemiology, clinical characteristics, inflammatory bowel disease
Expression and significance of nerve growth factor in ulcerative colitis

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Objective: To discuss the expression and significance nerve growth factor (NGF) in intestinal tissue and serum of ulcerative colitis (UC).

Materials and methods: All 40 cases of patients which were diagnosed with UC from the Digestive Department of outpatient and inpatient in the First Hospital of Shanxi Medical University, at the same time selected 10 patients with colon polyps and 10 cases healthy check-up as control groups, take intestinal mucosa and venous blood as the specimen. Immunohistochemical staining and ELISA methods were used respectively to detect the expression in intestinal mucosa tissue and serum of NGF in UC patients and the control groups.

Results:
1. Test results of immune histochemical method: The expression of NGF in UC mucosa was higher than in the control group, the grey value respectively (167.035 ± 12.216, 188.713 ± 5.924), the difference was statistically significant (P < 0.01); expression of NGF were differences between mild and moderate, and severe UC (P < 0.05); the expression of NGF was no differences between mild and severe UC (P > 0.05); NGF expression in intestinal mucosal tissue of UC was positively correlated with the degree of UC (r = 0.505, P < 0.05); NGF expression characteristics in the mucosa of UC unrelated to lesions.
2. Test results of enzyme-linked immunosorbent assay method: Expression of NGF in serum of the UC group and the healthy control group was not statistically significant (P > 0.05); NGF expression in the serum of UC patients with NGF positive expression intensity in the intestinal mucosa of UC patients was negative correlation (r = -0.529, P < 0.05).

Conclusion: The high expression of NGF in UC mucosa may be related to the occurrence and development of UC, which may be a bridge to connect the nervous system and the immune system, and is positively correlated with the extent of the disease; NGF expression in the serum of patients with UC may help determine the extent of disease.

Keywords: nerve growth factor, ulcerative colitis, intestinal mucosa, serum
Effect of oxymatrine on expression of Toll-like receptor 9 and nuclear factor-κB mRNA in colonic tissue of rats with ulcerative colitis

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To investigate the regulative mechanism of oxymatrine on the expression of Toll-like receptor 9 (TLR9) and nuclear factor-κB (NF-κB) mRNA in colonic tissue of rats with ulcerative colitis (UC).

Methods: Seventy-fifth grade of adult SD rats randomly divided into 5 groups randomly: control group, oxymatrine group, mesalazine group, oxymatrine and mesalazine combined group and model group. One week later of the experiment, three rats in each group were randomly selected and executed for observing colonic histological changes. On day 15, the remaining rats were executed after fasting 24h to detect the expression of TLR9/NF-κB mRNA in colon tissue by reverse transcription polymerase chain reaction.

Results: The expression of TLR9 in UC model rat colon tissue are higher than in treated groups and normal control group (P < 0.01). In the treated groups, the oxymatrine + mesalazine combined group shows a lower expression of NF-κB mRNA than the oxymatrine group and the mesalazine group, the difference was statistically significant (P < 0.05 to P < 0.01 ), but between the oxymatrine group and the mesalazine group, the difference has no statistically significant (P > 0.05).

Discussion/Conclusion: Oxymatrine can regulate TLR9 and NF-κB mRNA expression in inflammatory colonic mucosal cells, thereby inhibits the inflammatory response of ulcerative colitis. The oxymatrine and mesalazine combined use have a better effect on blocking the TLR9 and NF-κB pathway to alleviate the inflammatory reaction in UC than oxymatrine or mesalazine use alone.
Safety profile of thiopurines in Crohn’s disease in a Southeastern China cohort: Analysis of 893 patient-years follow-up

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Introduction: Thiopurines have been associated with both clinical improvement and mucosal healing in treating Crohn’s disease (CD). Unfortunately, the high rate of adverse events (AEs) leading to drug withdrawal, represents a major limitation in the use of these drugs. We aimed to evaluate the safety of thiopurines in patients with CD. To identify predictive factors associated with the development of thiopurine-induced AEs and withdrawal.

Methods: This longitudinal cohort study examined patients from a university-based IBD referral center. Cox regression analysis was performed to identify potential predictive factors of AEs.

Results: 267 CD patients on thiopurines were included. A total of 143 AEs occurred at a median of 7.4 months (interquartile range, 3.7–15.3 months) after starting treatment. The cumulative incidence of adverse events was 26%, with an annual risk of 4.3% per patient-year of treatment. The most frequent was leucopenia (41/267, 15.36%), followed by infections (29/267, 10.86%). Independent factors predictive of leucopenia were a lower baseline hemoglobin (hazard ratio [HR] = 0.34; 95% confidence interval [CI] 0.18–0.67) and the concomitant use of 5-aminosalicylic acid (HR = 3.05; 95% CI 1.44–8.76). Of the 28.44% (76/267) CD patients discontinued therapy, 14.61% due to AEs. A lower body mass index (HR = 1.59; 95% CI 1.04–2.46), the present of extraintestinal manifestation (HR = 1.85; 95% CI 1.18–2.88) and the incidence of leucopenia (HR = 1.76; 95% CI 1.05–2.97) independently predicted thiopurine withdrawal. 37.5% of these patients started thiopurines again and 52.3% of them had same AEs again.

Discussion/Conclusion: About a quarter of patients on thiopurine therapy had AEs during follow-up and 1 of 7 patients had to discontinue thiopurines due to AEs. Several predictive factors for main AEs and treatment withdrawal have been identified.
Optimization of the preparation of the stump of the rectum to reconstructive surgery after total colectomy for ulcerative colitis

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The purpose of this study was to examine the state of microbiocenosis colon in patients with ulcerative colitis, as well as the impact of therapy aimed at correcting the intestinal microflora using probiotics on the disease, the incidence of relapse and resistance of clinical remission of ulcerative colitis.

Materials and methods: The study included 115 patients with inflammatory bowel disease (IBD), admitted to the Research Center of Coloproctology. All patients underwent total colectomy with a stump of the rectum and the imposition of ileostomy. Patients were divided into 2 groups: a study group comprised 62 patients who received postoperative basic (sulfosalazin, Salofalk®, corticosteroids) and bracing therapy and probiotics (lactobacterin, bifidumbacterin, colibacterin and bifikol), the control group consisted of 53 patients who received only basic and restorative therapy.

Results and Discussion: In the study group of 62 patients good results were achieved in 40 (64.5 ± 6.0%), satisfactory – in 22 (35.4 ± 6.0) patients. Different picture was observed in the control group: good results were observed in 21 (39.6 ± 6.7%), satisfactory – 29 (54.7 ± 6.8%), poor – in 3 (5.6%) patients. Good results in both groups in all cases accompanied by normalization of the structure of the mucosa (according to endoscopy, cytology and histology), improvement of general condition, reduction of emissions from the stump of the rectum. After recovery operations postoperative period was uneventful, with no complications.

Thus, long-term use of probiotics in patients with IBD in the pre- and postoperative periods led to a significant improvement in clinical and laboratory parameters, which is apparently due to their anti-inflammatory and adaptive properties and role of dysbiosis in immunopathological processes. Recommended the inclusion of long-term courses of probiotics in the complex therapy of IBD, as well as to prepare the stump of the rectum to the recovery operations.
**Inflammatory bowel disease and fatigue**

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**Introduction:** Inflammatory bowel disease (IBD) patients with quiescent disease frequently complain of fatigue. This usually interferes with their quality of life and work. We aimed to evaluate the reasons of fatigue in IBD patients in remission with biochemical and hematological test results.

**Methods:** This is a retrospective study investigating the biochemical and hematological test results which might be related to fatigue in remission patients consulting our IBD outpatient clinic from 01/2013–01/2015.

**Results:** 35% of the IBD patients in remission suffered from fatigue. Of those, 32% had anemia mostly due to iron deficiency and 46% had non-anemic iron deficiency. 5% had hypothyroidism, 13% had low vitamin B12 levels, 12% had electrolyte imbalance mostly due to dehydration, 4% had high liver function tests mostly due to drug induced liver disease and one of them was diagnosed as autoimmune hepatitis. Some of the findings overlapped in some of the patients. 54% of the patients did not have any laboratory finding which would explain fatigue. This could be because we have not looked for cortisol and testosterone levels and because some of these patients might have psychosomatic issues causing fatigue.

**Discussion/Conclusion:** Fatigue is an important feature in IBD in remission, adversely affecting the quality of life and should be investigated very well to upgrade our patients’ quality of life. Non-anemic iron deficiency seems to be the mostly seen factor related to fatigue in quiescent IBD.
Doctor-patient communication in inflammatory bowel disease

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Introduction: Psychosocial support in management of inflammatory bowel disease patients is as important as medical treatment. Assuring with the possibility of directly contacting the physician or someone who can contact the physician for 24 hours comforts the patients and helps in coping with the disease.

Methods: In March 2013 we have formed a website in the name of our clinic, the URL address of which is www.ibhileyasam.com (stands for “life with IBD”). Detailed knowledge regarding the disease, special topics like diet, adolescence, and pregnancy in IBD, videos are available on the site. During outpatients visits IBD patients were given telephone numbers of their physician and the address of the website. Patients were told that they may call anytime they need to in order to ask questions about their disease, especially the questions they forget or are ashamed to ask during the visit. Patient get their own login password for the site, questions and answers are accessible only to that patient.

Results: First month only 5 patients asked questions via internet or telephone. Three months later the number of patients increased to 15 and the average goes on 15 patients per month. The most frequently asked three questions were: 1. Will you be there in the outpatients clinic tomorrow when I come to visit you? 2. Can you remind me the dosages of my medications? 3. What shall I do, I have… (new unexpected events like fever, rash etc.)?
In follow-up visits patients were checked whether they keep the address and phone number and were asked how they felt about it. Most patients stated that they felt safer and more relaxed to know that they can use in case needed.

Discussion/Conclusion: The website was designed with the model of other intentional sites. On the contrary of our expectations not many patients visited and used the site actively. This may have some reasons: still there is a population in our country that cannot read or write. Computer may not be available in every house, and not everyone is an internet user. Some patients lost the given address and phone number, some did not feel any necessity.
This study helped in establishing a positive patient-doctor communication and providing a better understanding that the medical staff is there for the patients not only for diagnosis and treatment but also supporting in their daily life and in coping with the disease. The next step may be meetings with patients and relatives where they can meet other patients, be informed about their disease and education programme how to use the website.
Long-term outcome of low-dose azathioprine in ulcerative colitis

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Introduction: Whether low dose azathioprine (AZA) is effective in ulcerative colitis (UC) remains unclear.

Methods: Among 1226 UC patients from the Hong Kong IBD Registry, steroid-dependent patients on AZA for ≥ 4 months and achieved steroid-free remission for ≥ 3 months were included. Relapse was defined as Mayo symptomatic subscore > 0. Relapse rates and time to relapse were compared between patients on standard dose (≥ 2 mg/kg/day) and low dose (< 2 mg/kg/day) AZA. Kaplan-Meier analysis and Cox regression were used to assess relapse free survival and related factors for relapse.

Results: Of 161 steroid-dependent UC patients on AZA, 128 (53% male, mean age 55.3 ± 14.1 years, median UC duration 13 years, median follow-up on AZA 45 months) were included. Median AZA dose was 1.28 (interquartile range [IQR] 0.92–1.72) mg/kg/day. 17% of patients maintained on standard dose AZA. Relapse rates were similar between patients on standard dose and low dose AZA (28.8%, 47.2%, 54.8% vs. 28.2%, 44.7%, 53.8% in 12, 24, 36 months, respectively, p = 0.87). Median time to relapse was 17 (IQR 6–31) and 21 (IQR 9–44) months in patients on standard and low dose AZA, respectively (p = 0.21). In Cox regression, AZA dose was not an independent factor for relapse. Relapse rate at 12 months was higher in patients who discontinued AZA (52.6% vs. 29.4% of patients continuing AZA, p = 0.045). Time to relapse was also significantly shorter in patients who discontinued AZA (3 [IQR 1–8] months vs. 7 [IQR 5–9] months in patients continuing AZA, p = 0.038).

Discussion/Conclusion: Low dose AZA is effective for maintaining remission in Chinese UC patients.
Acute uniocular frosted retinal periphlebitis in ulcerative colitis patient under leukocytapheresis

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Introduction: Leukocytapheresis (LCAP) is considered as an effective and safe therapy for UC. Acute frosted retinal periphlebitis (FRP) occurs in young healthy individuals who typically had acute bilateral/unilateral visual loss, associated with anterior and posterior segment inflammation. To our knowledge acute FRP hasn't been described in association with either UC and/or LCAP.

Methods: A 23 yrs UC man, cytomegalovirus-free, received LCAP after admission and symptoms were relieved, but presented with blurred vision in right eye 6 hours later after LCAP and his visual acuity decreased abruptly (1.5–0.1 right) in subsequent days. Succedent funduscopic examination of right eye disclosed extensive white sheathing of the retinal veins, massive intraretinal hemorrhages, venous congestion, tortuosity, optic disc edema and hyperemia. LCAP was discontinued and 60 mg prednisolone/day was prescribed immediately with improvement in right visual acuity to 0.6 one month later. Second funduscopic examination showed marked improvement.

Results: Retinal periphlebitis is one of possible IBD ophthalmologic complications. Some FRP were reported in CD but none in UC before. No consistent etiological agent has been identified for FRP. Common hypothesis: hypersensitivity reaction to various infective agents may initiate FRP via a possible common pathway: immune complex deposition. FRP had been described in individuals with CMV/EB retinitis and AIDS. Propose etiologies included direct infection of blood vessels, immune complex deposition leading to vasculitis and local tissue inflammation. He was unilateral visual loss and condition improved rapidly after commencing high dose i.v. corticosteroids. His response argued an immunemediated reaction as the cause possibly was a sequela of subclinical EBV infection. Leukocyte count was decreased during LCAP. It could be imagined transient but significant elimination of peripheral leukocytes during LCAP might induce opportunistic EBV relapse which induced unilateral visual loss.

Discussion/Conclusion: This case presented an unusual correlation among acute FRP, UC and LCAP. EBV and immunemediated reaction might take part in the process of vision loss of FRP in UC treated by LCAP. Corticosteroid benefited both FRP and UC. Whether LCAP is associated with FRP is still unclear.
Effect and security of adjuvant therapy for ulcerative colitis with probiotic agents

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Objective: To observe the therapeutic effect and safety of probiotic agents on active ulcerative colitis and to investigate its effects on the cytokines in mucosa.

Methods: Eighty-six patients with active moderate UC were randomly assigned to the treatment group (46 patients) and the control group (40 patients). Besides the basic treatment of oral taking mesalazine, they were treated by retention enema with hydrocortisone sodium succinate plus Gentamicin and Smectite Powder. In addition, the patients in the treatment group were treated by orally took probiotic agents, 1.5 g each time, three times a day. The efficacy of treatment such as the clinical symptom score, colon mucosa inflammation and the expressions of IL-10, IL-6 and IL-18 in mucosa of patients with immunohistochemistry 6 months after treatment were evaluated.

Results: The clinical symptom, colon mucosa inflammation had no difference between groups before treatment. Six months after treatment. The clinical symptoms and colon mucosa inflammation were better significantly than before (P < 0.05), especially in experiment group (P < 0.05). The disease active index was lowered after treatment in both groups (P < 0.05), decrease of DAI in the treatment group were superior to those in the control group (P < 0.05). The expressions of IL-10 in mucosa was significantly increased, especially in experiment group (P < 0.05). The expressions of IL-6 in mucosa was significantly descended (P < 0.05), but the difference of IL-18 had no statistical significance.

Conclusion: The probiotic agents shows an effect obviously and with no adverse reaction. Its curative effect on ulcerative colitis is related to affecting IL-10, IL-6 and IL-18 in mucosa of patients.

Keywords: probiotic agents, ulcerative colitis, cell factors
Clinical significances of mean platelet volume and D-dipolymer in patients with inflammatory bowel disease

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Objective: To investigate the relationship of serum mean platelet volume (MPV) and D-dipolymer level in determination of disease activity of the patients with inflammatory bowel disease (IBD).

Methods: The contents of serum MPV and D-dipolymer of 27 UC sufferers at active stage, 25 at remission stage and 8 Crohn’s disease sufferers at active stage, 9 at remission stage and 53 normal controls were conducted by full-automatic blood cell analyzer, washing solution and ELISA respectively.

Results: Mean platelet volume (MPV) was significantly low in patients with active UC and Crohn’s disease compared with patients with remissive UC and healthy controls (P < 0.01). D-dipolymer of the UC and Crohn’s disease patients at active stage were remarkably higher than those of the other two groups (P < 0.01). The content of MPV of the UC patients at remission stage was lower than that of the controls (P < 0.05).

Conclusion: Mean platelet volume (MPV) level of inflammatory bowel disease (IBD) at active stage was lower, but D-dipolymer was higher. The levels of MPV, D-dipolymer can serve as useful indices in the estimation of the activity and seriousness of UC.
Correlation of neutrophil gelatinase B-associated lipocalin and matrix metalloproteinase-9 complex (NGAL-MMP-9) with common indices of intestinal inflammation in children with inflammatory bowel disease (IBD)

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Introduction: Matrix metalloproteinase-9 (MMP-9) is upregulated in many inflammatory conditions, including IBD. Therefore, the complex MMP-9/NGAL have been considered as serum biomarker for IBD.

Aim: To evaluate serum NGAL-MMP-9 complex concentrations as a marker of inflammation in children with Crohn’s disease (CD) and ulcerative colitis (UC) and to compare them with the common indices of intestinal inflammation.

Methods: Blood samples were obtained from children with Crohn's disease (n = 42), and ulcerative colitis (n = 43) for the diagnostic examinations. Concentration of NGAL-MMP-9 was determined with ELISA kit (R&D Systems, USA). Biochemical and hematological parameters were determined with standard laboratory techniques.

Results: Serum NGAL-MMP-9 complex concentrations were highly elevated in patient with IBD (104 ± 66.7, range: 8.99–476 ng/ml, n = 85) in comparison to apparently healthy volunteers examined by manufacturer (40.3, range: 8.7–164 ng/ml, n = 35). There was significant correlation between NGAL-MMP-9 complex and platelets (CD r = 0.56; UC r = 0.47), leukocytes (CD r = 0.63; UC r = 0.59) and C-reactive protein in children with UC (r = 0.67) but not with CD (r = 0.23). However, there was no significant correlation of the NGAL-MMP-9 complex with the erythrocyte sedimentation rate, hemoglobin nor hematocrit.

Discussion/Conclusion: NGAL-MMP-9 involvement in the intestinal inflammatory processes is likely, but its role in many settings, also in IBD, has yet to be determined. Strong correlation with biochemical and hematological parameters indicates the possibility of its use in the clinical IBD evaluation.
Infliximab plus azathioprine and monotherapy for inflammatory bowel disease: A meta-analysis

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Introduction: To compare the efficacy and safety of the infliximab and azathioprine combination therapy and monotherapy in moderate to severe inflammatory bowel disease, and to guide the choice of inflammatory bowel disease drug programs.

Methods: A comprehensive literature search was performed in Medline, Embase, Pubmed, Ovid, Google, Wanfang Database, Vip Database, China National Knowledge Infrastructure Database (CNKI) and The Chinese Biomedical Literature Database of randomized controlled clinical trials about infliximab and azathioprine curing inflammatory bowel disease. Data of included studies was extracted and their quality was evaluated to meta-analysis.

Results: Based on inclusion criteria, 6 prospective randomized controlled clinical studies were included in this study. There were significant improve of clinical remission rate in combination group when compared with infliximab or azathioprine monotherapy, as well as in endoscopic detection. However, there were no significant statistical differences on the term of overall adverse reaction between the two groups.

Discussion/Conclusion: For the first-line treatment of invalid in moderate to severe inflammatory bowel disease, Combination of infliximab and azathioprine is superior to monotherapy. Combination therapy for clinical remission and endoscopic mucosal healing efficacy are obvious, and the overall there was no significant difference in adverse event with monotherapy.
Retrospective analysis of clinical characteristics of patients with ulcerative colitis

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Introduction: To analyze retrospectively the clinical characteristics, therapy and follow-up of the patients with ulcerative colitis (UC) of the hospital for guiding treatment.

Methods: Collect the information of 77 inpatients with UC at the Second Affiliated Hospital of Chongqing Medical University between 2009 and 2014, and follow-up part of the patients.

Results: The ratio of male to female is 1:1.48. The peak age of the patients is 60–69 years old and 70–79 years old. 69.9% of the patients who are in the activity stage are moderate severity. E2 and E3 are the common lesions range. The main clinical manifestations are abdominal pain, diarrhea, mucopurulent bloody stool and bloody stool. The enteroscopy mostly shows that intestinal mucosa hyperemia, edema, erosion, and small ulcers are the common features of UC. The common biopsy results are chronic inflammation and/or erosion. The average value of serum ALB decreases while the severity of UC patients increases. Drug therapy is the main treatment of UC. The maintenance therapy is aminosalicylic acid.

Discussion/Conclusion: The effective ratio of treatment is 89.0% (55/73) and we should enhance the follow-up of UC patients.
Evaluation of the clinical efficacy of ShuangHuangLian, Yunnan Baiyao, bifid triple viable capsule combined with mesalazine in the treatment of ulcerative colitis

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Introduction: To evaluate the clinical efficacy of ShuangHuangLian, Yunnan Baiyao, bifid triple viable capsule combined with mesalazine in the treatment of ulcerative colitis, and provide a reference for a reasonable choice of drugs.

Methods: Totally 64 patients with ulcerative colitis patients in Cangzhou People’s Hospital were divided into two groups by random digital table classification. The control group was given mesalazine and bifid triple viable capsule per oral, while the observation group was given ShuangHuangLian (once every morning) and Yunnan Baiyao (once every evening) in 37–40°C for retention-enena on the basis of the observation group. The clinical effect was compared.

Results: In observation group, 20 cases were remarkably effective, 8 cases were effective, 4 cases were ineffective and the effective rate was 88%. While 15 cases were remarkably effective, 5 cases were effective, 12 cases were ineffective and the effective rate was 63% in the control group. There was statistically significant difference in therapeutic effect between two groups (P < 0.05).

Discussion/Conclusion: ShuangHuangLian, Yunnan Baiyao, bifid triple viable capsule combined with mesalazine is benefit for treating ulcerative colitis, and thus can inhibit the inflammation and significantly improve the curative effect.
Second harmonic imaging of collagen in intestinal tissue for discriminating intestinal tuberculosis from Crohn’s disease

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Introduction: Proper differential diagnosis between Crohn’s disease (CD) and intestinal tuberculosis (ITB) remained a challenging problem. This study was to observe collagen fibers characteristics of CD and ITB using Masson’s dyeing and second harmonic and two-photon excited fluorescence (SHG/TPEF) imaging.

Methods: The characteristics of collagen fibers in intestinal specimens from patients with CD, ITB and healthy controls were compared using Masson’s dyeing and SHG/TPEF imaging.

Results: The results of Masson’s dyeing showed that the content of collagen fiber and fiber deposit area were both higher in CD and ITB than healthy controls (P < 0.05), among which ITB was highest (P < 0.05). On the other hand, the content of collagen fiber and fiber deposit area were significantly higher in lesions with granuloma than those without granuloma (P < 0.05). The SHG/TPEF images demonstrated that collagen fibers deposited in different patterns between CD and ITB. The collagen fibers in CD distributed irregularly like clumps and curling, while those in ITB ranged around the caseating granuloma. Collagen fibers could be found scattering around the glands in endoscopic biopsy specimens. The fibrosis percentage of ITB group was also significantly higher than CD group, both in endoscopic (1.19 ± 0.07 vs 0.95 ± 0.04) and surgical specimens (11.53 ± 0.40 vs 9.74 ± 0.24).

Discussion/Conclusion: It is valuable to evaluate fibrosis characteristics of CD and ITB using Masson’s dyeing and SHG/TPEF imaging. SHG/TPEF imaging could be a new way to distinguish between CD and ITB.
Analysis to the effects of infliximab in the treatment of inflammatory bowel disease in the Yunnan province

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Introduction: A retrospective analysis from 2014 April to 2014 November in the First Affiliated Hospital of Kunming Medical University, at least two times of injection of infliximab in 8 patients with IBD (UC 1 cases, CD 7 cases) of the file data, analysis of the clinical efficacy and safety of infliximab in IBD.

Methods: A retrospective analysis of 8 cases of IBD patients with infliximab therapy. In 0, 2, 6 weeks were given 5 mg/kg intravenous infliximab induction therapy, then every 8 weeks for 5 mg/kg dose intravenous maintenance treatment. According to the assessment of the course CDAI score, biochemical index and adverse reaction.

Results: All patients achieved clinical remission, before treatment and the first use of infliximab induced after 2 weeks of treatment, CDAI score, ESR, CRP levels were significantly decreased compared with those before treatment, the difference was statistically significant (P < 0.05). 1 patient with leukopenia and 1 case of respiratory tract infection group, returned to normal after symptomatic treatment.

Discussion/Conclusion: IFX has a better therapeutic effect on IBD patients, but its long-term efficacy and safety need further observation.
Risk factors for bowel resection in Hong Kong patients with inflammatory bowel disease

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Introduction: Patients with inflammatory bowel disease (IBD) are primarily managed with medical treatment. However, for patients with severe disease, many required bowel resection eventually. This study aims to evaluate the risk factors associated with bowel resection among patients with IBD.

Methods: This study was a retrospective cohort study. Prevalent cases were identified from hospital record in Prince of Wales Hospital. Data were collected by reviewing medical notes. Risk factors for bowel resection were evaluated with log-rank test and multivariable Cox-regression.

Results: Four hundred ninety IBD cases (229 Crohn’s disease [CD], 261 ulcerative colitis [UC], median age 44, disease duration 8 years) were identified. In multivariate model, stricturing (Hazard ratio, 5.46; 95% CI, 2.23–13.39; P = 0.001) and penetrating disease behavior (HR, 6.03; 95% CI, 2.66–13.64; P < 0.001) were significant risk factors for surgical resection in CD. Early use of immunosuppressant with 12 months of diagnosis and before bowel resection was also a protective factor (HR, 0.27; 95% CI, 0.12–0.61; p = 0.002). In UC, extent of disease was a significant factor associated with surgical resection (p = 0.012) in univariate analysis but not in multivariate analysis. Early use of immunosuppressant was a significant risk factor in both univariate (p < 0.001) and multivariate analysis (HR, 8.33; 95% CI, 1.86–37.21; p = 0.006).

Discussion/Conclusion: In CD colonic diseases were associated with decreased risk while stricturing and penetrating behavior were associated with increased risk of surgical resection. In UC, extent of disease was associated with risk of surgical resection. Interestingly, early use of immunosuppressant showed protective effect in CD, but was a significant risk factor for surgical resection in UC.
Relationship between ulcerative colitis and lung injuries

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Introduction: To explore the relationship between ulcerative colitis (UC) and lung injuries by assessing their clinical manifestations and characteristics.

Methods: From July 2009 and April 2012, UC patients presenting to Longhua Hospital who met the established inclusion and exclusion criteria were enrolled in this retrospective study. According to the scores of disease activity index, the patients were divided into the mild, moderate, and severe groups. Meanwhile, pulmonary symptoms were recorded, and chest X-ray image and pulmonary function were analyzed.

Results: A total of 91 UC patients were enrolled. 68 (74.7%) had at least 1 pulmonary symptom, such as cough (38.5%), shortness of breath (27.5%), and expectoration (17.6%). 77 (84.6%) had at least 1 ventilation abnormality. Vital capacity value was significantly lower in the severe group than that in the mild group (91.82 ± 10.38 vs. 98.92 ± 12.12, P < 0.05).

Discussion/Conclusion: Lung injury is a common extraintestinal complication of UC. According to the theory in Traditional Chinese Medicine that the lung and large intestine are related, both the lungs and large intestine should be treated simultaneously. Treating lesions in the large intestine might be more important than treating ones in the lungs.
Management of enterocutaneous fistulas in Crohn’s disease: Retrospective data from the Romanian Health Insurance Company

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Introduction: Enterocutaneous fistula (ECF) represent a connection between gastrointestinal tract and the skin. Due to the transmural character of the inflammation seen in Crohn’s disease (CD), patients may develop this type of complication. Given the rarity of these patients and the scarce literature data regarding the appropriate management of ECF, surgical approach has been advocated. After the introduction of anti-tumor necrosis alpha (anti-TNF-α) agents which have shown efficacy in the treatment of perianal fistulas, surgical treatment of ECF may be challenged.

Methods: We conducted a retrospective analysis of the registries from the National Insurance Company between 2009 and 2013 regarding the patients with CD under treatment with anti-TNF-α agents. We selected the patients with ECF and analyzed the phenotype of the disease, location of the fistula, fistula tract (simple vs. complex), fistula output (high vs. low), received treatment and outcome. Patients with internal fistulas and perianal fistulas were excluded.

Results: We found 268 patients with CD on biologic agents. Of these, 15 patients (5.59%) had in evolution at least one ECF. All patients had a stricturing pattern of the disease (B2 in Montreal classification). Fistula location was in the small bowel in 6/15 patients, at the ileocecal anastomosis in 7/15 patients and only 2/15 patients had their fistula located in the colon. Fistulas were complex defined as multiple tracts in 9/15 patients and simple in 6/15 patients. Only 5/15 patients were treated with anti-TNF-α agents, 4 with infliximab and 1 with adalimumab. All patients on biologics closed their fistulas.

Discussion/Conclusion: ECF represent rare complications of CD. AntiTNF-α agents may be a useful tool in the treatment of these complications. More data are needed regarding predictors of response in order to target the treatment.
TWEAK: A potential marker for Crohn’s disease related intestinal fibrosis

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Introduction: Intestinal fibrosis is a common complication of Crohn’s disease (CD), and is characterized by abnormal deposition of extracellular matrix (ECM) proteins. Tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK), a multifunctional cytokine that regulates cellular proliferation, apoptosis, et al. Recent studies have showed that TWEAK may be involved in the development of tissue fibrosis, such as kidney fibrosis, pulmonary fibrosis. However, whether TWEAK plays a role in CD related intestinal fibrosis remains poorly understood. The aim of this study is to investigate the expression of TWEAK and its receptor, fibroblast growth factor-inducible 14 (Fn14) in CD patients, to elucidate whether the expression of TWEAK can be used as an indicator for intestinal fibrosis.

Methods: The clinical types of CD were based on the Montreal Classification. Blood samples from 67 CD patients and 33 healthy controls were collected in this study. The level of TWEAK in the serum was measured by ELISA. At the same time, intestinal samples from 29 CD patients who received enterectomy and 15 normal people were included. The expression of TWEAK and Fn14 in intestinal biopsies was analyzed by immunohistochemistry.

Results: The expression of TWEAK in the serum was significantly increased in CD patients (P < 0.01). And its expression was positively related to intestinal stenosis (r = 0.29, P = 0.017), intestinal obstruction (r = 0.453, P < 0.01), and enterectomy (r = 0.295, P = 0.015). There was no relationship between the expression of TWEAK and CDAI (r = 0.059, P = 0.633). Meanwhile, the level of TWEAK and Fn14 in the intestinal samples from CD patients was highly elevated (P < 0.05). Additional, the cells which expressed Fn14 were also α-SMA positive.

Discussion/Conclusion: The expression of TWEAK was highly elevated in CD-related fibrosis, which may suggest that TWEAK may be a potential marker for CD-related fibrosis.
Ileocecal disease: Possible diagnosis other than inflammatory bowel disease

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Introduction: Chronic diarrhea, abdominal pain, fever and extraintestinal findings like arthritis, increased inflammatory markers in blood tests, ulcer seen with ileocolonoscopy and other lesions detected inflammatory bowel disease (IBD) is the first diagnosis to be considered but before starting treatment it is crucial to rule out infectious causes.

Methods: Here we present two cases that were first diagnosed as Crohn’s diseases (CD), but the diagnosis changed before starting immunosuppressive treatment because infectious etiology was detected.

Results:
Case 1: A 29-year-old female had abdominal pain, weight loss and chronic diarrhea for the last 6 months. She applied to a different medical center where wide spread linear ulcers were found in terminal ileum and antibiotherapy was started. First a slight response was seen, but soon her symptoms recurred, her general well-being deteriorated after methylprednisolone was started and she was administered to our clinic. Although biopsies taken from terminal ileum supported CD, terminal ileum resection was planned for both confirmation of diagnosis and for treatment. Histopathologic examination of the resected material did not reveal any prominent fistula formation, thickening of the muscularis mucosa or increase in periintestinal fat tissue but granulomas and mesenteric lymphadenitis was seen. Postoperatively the patient recovered. Intestinal tuberculosis was ruled out with tissue PCR. Although no serology was available with all the findings the patient was accepted to have Yersinia infection.

Case 2: A 26-year-old male patient had abdominal pain and chronic diarrhea that started 7 months ago. Ileocolonoscopy showed only a 7 mm ulcer at the ileocecal valve and biopsy was consistent with CD: Tissue PCR was negative for tuberculosis. Methylprednisolone was induced but was discontinued after there was bacterial growth at the Löwenstein media.

Discussion/Conclusion: Before starting immunosuppressive treatment for IBD, other causes should be ruled out especially when there is clinical doubt.
Screening and follow-up of colorectal cancer in ulcerative colitis patients

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Introduction: IBD is associated with increased risk for colorectal cancer, and the risk is related to the duration and extent of the disease. Surveillance is recommended to decrease mortality.

Methods: Patients with ulcerative colitis who were screened for colorectal cancer between 2008 and 2015 were analyzed retrospectively. Patients with extensive colitis for at least 8 years and patients with no history of previous colorectal cancer and/or dysplasia were included into the study. Demographic features, colonoscopic and pathological findings were recorded. Getting out of the screening programme and colectomy due to colorectal cancer and/or dysplasia were endpoints for the study.

Results: Results are summarized in table 1 and 2.

Table 1

<table>
<thead>
<tr>
<th>Demographic features</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>210</td>
</tr>
<tr>
<td>Total follow-up</td>
<td>2452 patient years</td>
</tr>
<tr>
<td>Number of colonoscopies</td>
<td>1470</td>
</tr>
<tr>
<td>Mean follow-up interval</td>
<td>1.3 years</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>End points</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients still on follow-up</td>
<td>151 (72%)</td>
</tr>
<tr>
<td>Number of colectomies</td>
<td>10 (5%)</td>
</tr>
<tr>
<td>Patients lost to follow-up because last control exceeds one year</td>
<td>49 (23%)</td>
</tr>
</tbody>
</table>

Malignancy or dysplasia was multifocal in 70% of patients who underwent colectomy due to colorectal cancer and/or dysplasia. Number of colectomies did not change over time.

Discussion/Conclusion: The incidence of developing malignancy and/or dysplasia on the basis of ulcerative colitis in our country is less than the incidence reported in literature from western countries. The incidence of cancer did not change of over time, and when found was multifocal.
TL1A drives the activation of NF-kappaB/IL-6/STAT3 signaling pathway in experimental colitis-associated cancer

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Introduction: Colorectal carcinogenesis is correlated with colitis, namely, colitis-associated cancer (CAC). However, the exact mechanism is unclear. Tumor necrosis factor ligand-related molecule1A (TL1A) takes part in development of many kinds of cancer through inducing endothelial cell apoptosis, increasing oxidative stress reaction, activating multiple cell signaling pathways including NF-kappaB and Stat3. The aim is to investigate the influence and mechanism of TL1A in the process of colitis to CAC.

Methods: T-cell-expressing TL1A transgenic (Tg) mice were used to establish the CAC model with dextran sulfate sodium (DSS) and azoxymethane (AOM). The WT and Tg mice were randomly divided as followed: Control/WT group; AOM/WT group; DSS/WT group; AOM+DSS/WT; Control/Tg group; AOM/Tg group; DSS/Tg group and AOM+DSS/Tg group. Severity of colitis was evaluated by body weight (BW), disease activity index (DAI), colon histology and pathology score. Tumor is evaluated by size, number, rate of mice burdened tumor and colon histology and pathology score. Expressions of PCNA, NF-kappaB, Stat3 and IL-6 were detected by immunohistochemistry assay and western blot.

Results: DAI score, colon morphology score, histopathology score, and MPO activity were markedly higher in the AOM + DSS/Tg group than AOM + DSS/WT group and DSS/Tg group (P < 0.05). Compared to the AOM + DSS/WT group, the size and number of tumor were more increased in the AOM + DSS/Tg group (P < 0.05). Similarly, the rate of tumorigenesis, the pathology score and the degree of dysplasia were also obviously higher in the AOM + DSS/Tg group. The protein expressions of PCNA, NF-kappaB, Stat3 and IL-6 in AOM + DSS/Tg group were obviously higher than those in the AOM+DSS/WT group.

Discussion/Conclusion: TL1A may play a positive role in colitis-associated carcinogenesis through activating the NF-kappaB/IL-6/Stat3 signaling pathway.
Detection and significance of hydrogen-methane breath test among Crohn’s disease patients with remission

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Introduction: To analyze the occurrence and related factors of small intestine bacterial overgrowth (SIBO) among Crohn’s disease (CD) patients with remission.

Methods: To conduct hydrogen-methane breath test with substrate of lactulose among 25 CD patients with remission (CDAI < 150) and 20 healthy people (control group). Then, based on testing result, CD patients with remission are further divided into SIBO positive and negative. Eventually, to compare differences about symptom score (abdominal pain and abdominal distension), stool character, serum inflammatory markers (TNF-α, IFN-γ, IL-6, IL-10) and oxidative stress related markers (GSH, LPO) among each group and conduct statistical analysis.

Results: 1) The occurrence of SIBO (44%) among CD is significantly higher than that in control (5%) group (P < 0.01). 2) Abdominal distension score among SIBO positive is higher than that in SIBO negative (P < 0.05). There are no significant differences about abdominal pain score, stool frequency and character between two groups (P > 0.05), but significantly higher than that in the control group (P < 0.01). Ages, course, location, behavior and CDAI scores are not discovered to relate to SIBO. 3) GSH in SIBO positive is lower than that in SIBO negative (23.65 ± 16.60 μmol/L vs 41.86 ± 19.33 μmol/L, P < 0.05). However, there are no significant differences about TNF-α, IFN-γ, IL-6, IL-10 and LPO between the two groups (P > 0.05).

Discussion/Conclusion: Compared with healthy people, the occurrence of SIBO is more common among CD patients, which may be one of reasons about the aggravation of digestive-related symptoms, especially abdominal distension. Intestinal microenvironment change and oxygen free radical removal take part in the occurrence and development of SIBO. If patients are SIBO positive, antibiotics and probiotics can be adopted. Because of the limited cases, more studies should be taken to identify the theory.
Refractory distal ulcerative colitis: Clinical manifestations and treatment

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Introduction: To investigate the clinical features and treatment of distal ulcerative colitis (DUC) and to analyze probable reasons and optimal therapeutic regimens for refractory DUC.

Methods: Clinical data for 145 DUC patients who were treated at the Affiliated Yijishan Hospital of Wannan Medical College from January 2005 to December 2011 were retrospectively analyzed. Based on the response to traditional treatments, the patients were divided into either an effective group or a refractory group. The two groups were compared in clinical and laboratory examination results to analyze probable reasons and optimal therapeutic regimens for refractory DUC.

Results: Of 145 DUC patients, 117 were eligible for evaluation, and 26 of 117 patients were confirmed to have refractory DUC. The percentages of patients with abdominal distention and abdominal pain or elevated white blood cell count differed significantly between the refractory group and effective group (42.3% vs 22.0%, P = 0.038; 30.8% vs 12.1%, P = 0.035), while no significant differences were found in bloody stools, diarrhea, extraintestinal manifestations, C-reactive protein, blood sedimentation between the two groups (all P > 0.05). Of all 117 cases, 43 were found to have rectitis (including 10 refractory cases), and 74 were found to have sigmoiditis (including 16 refractory cases). No significant difference was found between the two groups in the location of the lesions (P > 0.05). Of 26 refractory cases, only 1 was treated by surgery, and the others were treated by intravenous hormone therapy, addition of new dosage form of 5-ASA, or proper laxatives to gain relief.

Discussion/Conclusion: Diarrhea and bloody stools are the most common clinical symptoms of DUC. Significantly elevated leukocyte count can be expected to be an important factor for evaluating treatment outcome of DUC. Refractory DUC can be treated by intensification therapy, addition of new dosage form of 5-ASA, proper laxatives, or surgery to gain relief.
**Serum and mucosal IgG4 is closely associated with a small subset of patients with inflammatory bowel disease**

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**Introduction:** Immunoglobulin G4-related disease (IgG4-RD) is a rare autoimmune disease. Some studies have reported that IgG4+ plasma cells infiltration could be seen in UC and CD, but there was no increase in serum IgG4 in patients. This study was undertaken to explore the status of serum IgG4 and mucosal IgG4+ plasma cells in IBD patients.

**Methods:** In total, twenty three pairs of well-matched CD and UC were included at West China Hospital. Serum IgG4 level was assessed firstly. IHC staining with anti-IgG4 antibody was performed on intestinal biopsies for patients with high serum IgG4.

**Results:** Serum IgG4 was 0.70 ± 0.23 g/L (M±SE) in CD and 0.61 ± 0.14 g/L (M±SE) in UC. At group level, serum IgG4 was not associated with disease activity in both UC and CD (p > 0.05). There was no significant difference in serum level of IgG4 between UC and CD (p > 0.05). Among these IBD patients, four cases did demonstrate an increased level of IgG4 which was 5.25 g/L, 2.05 g/L in CD, 3.1 g/L and 1.6 g/L in UC, respectively. Among the four patients, only one has got PSC. Furthermore, IgG4 IHC staining reported that their intestinal biopsies demonstrated high IgG4+ plasma cell infiltration. Even there were more than 50 IgG4+ plasma cells/HPF. After the treatment with glucocorticoids, the activity of disease decreased. The level of serum IgG4 significantly decreased in these 4 patients. A second round of IgG4 IHC staining also showed that IgG4+ plasma cells count per HPF fundamentally decreased.

**Discussion/Conclusion:** In general, IgG4 was closely associated with a small subset of IBD patients regardless of extra-intestinal manifestations such as PSC etc. Given that IgG4 was secreted by plasma cells, B cell lineage may play a key role in the pathogenesis of this subset of IBD. Further research was warranted to elucidate this issue.
Essential function of TL1A on Th9 cells activation and IL-9 expression in chronic experimental colitis in mice

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Introduction: Intestine mucosal dysimmunity is the key pathogenesis of ulcerative colitis. CD4+ T cells are the important effector cells in immune system. Th9 cells, which have been well studied in many autoimmune diseases, are the new subpopulation of CD4+ T cells. The tumor necrosis factor-like ligand 1 aberrance (TL1A) was also found to be a susceptibility gene for IBD and played a pro-inflammatory role in human intestinal inflammation. TL1A induce intestine mucosal dysimmunity by stimulating Th1, Th2 and Th17 cells to contribute to tissue inflammation. However, the effect of TL1A on Th9 cells activation remains unclear.

Methods: Transgenic (Tg) mouse with TL1A expressed in T cells was used in the study. Severity of colitis was evaluated by body weight (BW) changes, disease activity index (DAI), colon morphology, colon length, myeloperoxidase (MPO) activity. Hematoxylin and eosin (HE) staining was used to evaluate the histopathology changes. The lamina propria mononuclear cells (LPMC) were isolated and counted, and the percentage of Th9 cells (CD4+IL9+T) account for CD4+ T cells was measured by flow cytometry. IL-9 was detected by RT-qPCR, immunohistochemistry, ELISA and western blot.

Results: DSS treatment increased DAI score, colon length, colon morphology score, histopathology score, and MPO activity, and worsened histologic inflammation. The index above in DSS/Tg group were even worse than DSS/WT group. The total LPMC harvested from DSS/Tg group were significantly higher than Control/Tg group (P < 0.05) and DSS/WT group (P < 0.05). The percentage of Th9 in the DSS/Tg group was significantly higher than that in the Control/Tg group (P < 0.05) and DSS/WT group (P < 0.05), respectively. IL-9 in the serum, tissues and culture medium of LPMC were significantly increased in the DSS/Tg group than that in the Control/Tg group (P < 0.05) and DSS/WT group (P < 0.05), respectively.

Discussion/Conclusion: TL1A could aggravate the intestinal mucosa inflammation, probably through activating Th9 cells and promoting IL-9 expression.
Capsule endoscopy retention in inflammatory bowel disease: An elderly patient with atypical symptom and discussion of retrieval methods

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Introduction: Inflammatory bowel disease (IBD) is characterized by chronic inflammation in the gastrointestinal tract. Capsule endoscopy is widely used to investigate small intestine, and capsule retention is the most serious complication. There is little consensus as to endoscopic or surgical management employed.

Methods: A 72-year-old Chinese man initially diagnosed as chronic enteritis and UC (colon type) five years ago with abdominal hidden pain in local clinic. He has no change in bowel habit, weight or rectal bleeding. Every examination the colon was histopathologically normal, with slight erosion, erythematous and edema; biopsy showed only mild inflammation and revealed neither granuloma nor crypt abscess. Capsule endoscopy was performed for anemia. Capsule retention occurred at a jejunum stricture and he was subsequently diagnosed with Crohn’s disease in our hospital by CT enterography and jejunum lesion biopsy.

Results: Successful capsule retrieval was used basket extraction by double-balloon enteroscopy.

Discussion/Conclusion: Inflammatory bowel disease among the elderly could show atypical symptoms and hardly differentiate UC from CD. It is important to screen for intestinal strictures in an atypical presentation of IBD. Endoscopic methods is more benefit for patient with capsule retention.
Endoscopic ultrasound differentiate Crohn’s disease from ulcerative colitis

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Introduction: Sometimes it is difficult to differentiate Crohn’s disease from ulcerative colitis based on clinical presentation, colonoscopy and histology. Endoscopic ultrasound may be an alternative way by supplying a precise and reproducible morphological assessment of the intestinal tract and the surrounding tissues.

Methods: The patients with CD or UC underwent EUS in the sigmoid colon and mucosal, submucosal, total wall thickness (TWT) were assessed by EUS.

Results: Total wall thickness was $4.86 \pm 1.02$ mm in $n = 32$ with active IBD. In patients with active UC the mucosa thickness was significant increased while submucosa was nearly normal (mucosa UC = $3.26 \pm 0.43$ mm, mucosa CD = $1.78 \pm 0.64$ mm ($P < 0.001$); In active CD the submucosal layer was significant thicken while nearly normal mucosa (submucosa UC = $3.57 \pm 0.71$ mm, submucosa CD = $1.12 \pm 0.76$ mm ($P < 0.001$).

Discussion/Conclusion: Increased total wall thickness has a high positive predictive value for active IBD. EUS can differentiate active CD from UC by evaluating the layers of gastrointestinal tract.
Prognostic nutritional index predicts short-term post-operative outcomes after surgery for Crohn’s disease

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Conflicts of Interest and Source of Funding: None

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Background: Surgery is required in majority of patients with Crohn’s disease (CD) during their lifetime. We examined the ability of prognostic nutritional index (PNI) to predict short-term outcomes in patients with CD.

Methods: 73 patients who underwent bowel resection for CD were prospectively enrolled in the study. Patients were divided in two groups: PNI < 40 and PNI ≥ 40. Clinical and laboratory parameters were compared between the two groups.

Results: Post-operative overall and infectious complications occurred in 15 (50.0%) and 14 (46.7%) patients in group with PNI < 40 versus 10 (23.3%) and 7 (16.3%) in group with PNI ≥ 40 respectively (p < 0.05). In univariable logistic regression analysis, BMI < 18.5, penetrating behavior, open surgery, and PNI < 40 were associated with an increased risk of overall complications and infectious complications. In multivariate analysis, only PNI < 40 was an independent prognostic factor for infectious complications: odds ratio (OR): 3.846, 95% confidence interval (1.145–12.821).

Conclusions: Pre-operative PNI is a useful predictor of post-operative infectious complications in patients with CD.

Keywords: Crohn’s disease, prognostic nutritional index, surgery, complication
Risk of tuberculosis with infliximab therapy: A meta-analysis of randomized clinical trials

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Qiang Wang and Zhenzhen Wen have contributed equally to this work

Background: Infliximab is a promising drug with good outcomes for the diseases such as inflammatory bowel disease (IBD), rheumatoid arthritis (RA) and spondyloarthropathy (SpA). Nonetheless, treatment with this drug might increase the risk of tuberculosis infection. This study is aimed to investigate infliximab-related tuberculosis infection.

Methods: Literature searches in PUBMED, MEDLINE and EMBASE databases were performed. Randomized controlled trials with over 95% of the patients older than 18 years were included. Meta-analysis was performed to investigate the tuberculosis infection perils after infliximab infusion.

Results: The search strategy identified 6,892 articles, 23 of which were eligible, reporting 24 separate RCTs. In total, there were 21 (0.51%) tuberculosis infection among 4111 patients allocated to infliximab therapy, compared with 0 (0%) among 2229 assigned to placebo. The pooled OR of developing tuberculosis infection was significantly higher with infliximab therapy than with placebo (2.86; 95% CI 1.09–7.52). The OR of tuberculosis infection was 3.93 (95% CI 0.91–16.91) in RA, 2.46 (95% CI 0.38–15.92) in SpA and 1.66 (95% CI 0.26–10.57) in IBD. The rates of tuberculosis infection with infliximab therapy are, 0.70%, 0.22%, and 0.52%, respectively, in RA, SpA and IBD.

Conclusions: Contrasted with placebo, infliximab therapy obviously doubled the tuberculosis incidence rate in RA, SpA and IBD. More complete large data are advisable to avoid biased results. The risk of developing tuberculosis underlines the importance of prevention and management tuberculosis infection with infliximab therapy.

Keywords: tuberculosis, infliximab, inflammatory bowel disease, rheumatoid arthritis, spondyloarthropathy, meta-analysis
The roles of tight junction proteins in IBD

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Introduction: Inflammatory bowel disease is a recurrent chronic inflammatory disease. Defective intestinal epithelial tight junction (TJ) barrier has been shown to be a pathogenic factor in the development of intestinal inflammation. While tight junctions require the coordinated activity of several different proteins. Whether changes in tight junction proteins expression are a cause or a consequence of IBD is not clear.

Methods: This study based on IBD animal model of rats and patients with IBD biopsy samples detection claudin-1, -2, -3, -4 and ZO-1 protein expression by using immuno-histochemical, western blot and real time PCR analysis. The levels of TNF-α, IFN-γ and IL-4, 5, 10, 12 in the in colon tissue samples and serum were measured using an ELISA. The frequently used rat model of TNBS and OXZ colitis was used to model inflammation, injury and repair.

Results: Our data further show that claudin-1, -4 and ZO-1 were downregulated and redistributed off the tight junction, whereas the pore-forming tight junctions protein claudin 2 was strongly upregulated, which constitute the molecular basis of tight junction changes in active IBD.

Discussion/Conclusion: Upregulation of pore-forming claudin 2 and downregulation and redistribution of sealing claudins-1, -3, -4 lead to altered tight junction structure and pronounced barrier dysfunction already in active IBD.
The effect and mechanism of Wnt/β-catenin signaling path on the TL1a regulation of colitis associated cancer

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Introduction: Colitis associated colorectal cancer (CAC) refers that the intestinal tract goes through continuous hyperplasia based on the repeated inflammation stimulation. TNF-like ligand 1 aberrance (TL1A) is able to up-regulate the expression of tumor necrosis factors-α (TNF-α) and interleukin-17(IL-17). TNF-α and IL-17 are involved in progression of tumors. The aim is to investigate the role of TL1A in the development of CAC and its mechanism.

Methods: T-cell-expressing TL1A transgenic (Tg) mice were used to establish the CAC model with dextran sulfate sodium (DSS) and azoxymethane (AOM). The Tg mice and C57BL/6 WT mice were randomly divided into 8 groups below: Control/WT; AOM/WT; DSS/WT; AOM+DSS/WT; Control/Tg; AOM/Tg; DSS/Tg and AOM+DSS/Tg group. Severity of colitis was evaluated by disease activity index (DAI), gross score, histopathological score as well as the levels of TNF-α and IL-17A. The assessment of tumorigenesis included the calculation of the number, diameter, formation rate of tumor and histopathological score, on the other hand PCNA protein in colon were checked by immunohistochemistry and western blot. GSK-3β, β-catenin and cyclinD1 protein expressions were detected by immunohistochemical staining and Western blot.

Results: DSS administration increased DAI score, gross score, histopathological score as well as the levels of TNF-α and IL-17A. It is noteworthy that they were significantly higher in AOM+DSS/Tg group compared with AOM+DSS/WT group. Meanwhile the mice in AOM+DSS/Tg group are hypersusceptible to AOM/DSS-induced CAC accompanied by more number of tumor bodies, larger diameter, higher tumor formation rate, hyperplasia score and expression of PCNA. In line with this, the protein expression of GSK-3β was significantly reduced while β-catenin and cyclinD1 were significantly increased in AOM+DSS/Tg group as compared to the WT mice.

Discussion/Conclusion: TL1A may advance the course of CAC, which might be related to the activation of Wnt/β-catenin signaling pathway.
Expression of heat shock factor 2 and proinflammatory cytokines in ulcerative colitis

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Introduction: Ulcerative colitis (UC) is a kind of non-specific chronic inflammatory disease, which affects the intestinal tract. Its pathogenesis is still not clear. UC can be found in any age, but most of the patients are young and middle-aged. The disease seriously impacts patients’ health and social productivity. By now, the diagnosis is still based on clinical manifestation, endoscopy features and biopsy. Although there are some indicators like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactoferrin, calprotectin can reflect the inflammation activity levels, all of them are non-specific and cannot accurately predict mucosal healing. So, screening markers with better specificity and accuracy is inevitable. Our group screened differential genes and proteins expressed in UC patients using gene microarray, two-dimensional gel electrophoresis and mass spectrum methods and found HSF2 expression was up-regulated in both gene and protein level. The outcome of immunohistochemistry showed that HSF2 mRNA expression in UC mucosa was correlated with disease severity. These suggested that HSF2 might be a new marker which can be used to evaluate inflammation activity levels in UC. Thus, further study on HSF2 and proinflammatory cytokines expression correlation with disease activity index is important to explore its role in UC diagnosis and treatment.

Objective: To explore UC patients’ transcription and translation levels of HSF2 and proinflammatory cytokines (TNF-α, IL-1β, IL-8) in colonic mucosa and serum.

Methods: Colonic mucosa and blood specimens were obtained from patients with UC who were admitted in The 1st Affiliated Hospital of Kunming Medical University from February 2013 to February 2014. Patients with abdominal pain or discomfort and eventually diagnosed of IBS according to Rome III criteria without finding any lesions under colonoscopy were taken as controls. UC disease activity evaluation was performed using UC-DAI. The mRNA expression levels of HSF2, TNF-α, IL-1β and IL-8 in mucosa were detected by real-time fluorescence quantitative PCR. Serum concentrations of HSF2, TNF-α, IL-1β and IL-8 were detected using ELISA method. Statistics analysis was performed using SPSS 17.0 to explore the expression correlations between HSF2 and disease activity, TNF-α, IL-1β and IL-8 in UC.

Results: 20 UC and 5 control mucosa specimens were collected. 60 UC and 20 control blood specimens were obtained. (1) UC patients from mild to severe group had a higher mRNA expression of HSF2 (mild: 1.30 ± 0.11 vs 1.00 ± 0.00, P < 0.05; moderate: 1.50 ± 0.14 vs 1.00 ± 0.00, P < 0.01; severe: 2.02 ± 0.19 vs 1.00 ± 0.00, P < 0.01), TNF-α (mild: 6.28 ± 1.79 vs 1.00 ± 0.00, P < 0.05; moderate: 10.21 ± 1.68 vs 1.00, P < 0.01; severe: 19.23 ± 4.38 vs 1.00 ± 0.00, P < 0.01), IL-1β (mild: 49.12 ± 17.28 vs 1.00 ± 0.00, P < 0.05; moderate: 99.12 ± 17.28 vs 1.00 ± 0.00, P < 0.01; severe: 22.77 pg/mL ± 7.19 pg/mL vs 4.93 pg/mL ± 2.92 pg/mL, P < 0.01) and IL-8 (mild: 27.49 ± 4.55 vs 1.00 ± 0.00, P < 0.05; moderate: 54.73 ± 12.00 vs 1.00 ± 0.00, P < 0.01; severe: 60.19 pg/mL ± 9.71 pg/mL vs 8.25 pg/mL ± 2.23 pg/mL, P < 0.01) than controls. And HSF2 had a positive transcriptive expression correlation with these
proinflammatory cytokines ($r = 0.89, 0.89, 0.80, P < 0.0001$). (2) The serum concentrations of HSF2 (mild: 0.91 ng/mL ± 0.33 ng/mL vs 0.42 ng/mL ± 0.29 ng/mL, $P < 0.05$; moderate: 1.26 ng/mL ± 0.28 ng/mL vs 0.42 ng/mL ± 0.29 ng/mL, $P < 0.01$; severe: 2.15 ng/mL ± 0.42 ng/mL vs 0.42 ng/mL ± 0.29 ng/mL, $P < 0.01$), TNF-α (mild: 17.29 pg/mL ± 1.71 pg/mL vs 13.45 pg/mL ± 3.63 pg/mL, $P < 0.05$; moderate: 17.42 pg/mL ± 1.85 pg/mL vs 13.45 pg/mL ± 3.63 pg/mL, $P < 0.01$; severe: 21.16 pg/mL ± 2.15 pg/mL vs 13.45 pg/mL ± 3.63 pg/mL, $P < 0.01$), IL-1β (mild: 11.86 pg/mL ± 5.18 pg/mL vs 4.93 pg/mL ± 2.92 pg/mL, $P < 0.05$; moderate: 15.05 pg/mL ± 7.19 pg/mL vs 4.93 pg/mL ± 2.92 pg/mL, $P < 0.01$; severe: 22.77 pg/mL ± 7.19 pg/mL vs 4.93 pg/mL ± 2.92 pg/mL, $P < 0.01$) and IL-8 (mild: 9.49 pg/mL ± 4.38 pg/mL vs 8.25 pg/mL ± 2.23 pg/mL, $P < 0.01$; moderate: 32.18 pg/mL ± 6.81 pg/mL vs 8.25 pg/mL ± 2.23 pg/mL, $P < 0.01$; severe: 60.19 pg/mL ± 9.71 pg/mL vs 8.25 pg/mL ± 2.23 pg/mL, $P < 0.01$) in UC patients were higher than those in controls, and HSF2 concentration is also positively correlated with these proinflammatory cytokines ($r = 0.77, 0.73, 0.85, P < 0.0001$).

**Discussion/Conclusion:** The colonic mRNA expression levels and serum concentrations of HSF2, TNF-α, IL-1β and IL-8 were increased in UC. And the expression level of HSF2 was positively correlated with TNF-α, IL-1β and IL-8, which suggested HSF2 might be a new marker for evaluating inflammation activity level in UC.
Effects of anti-tumor necrosis factor-α on the intestinal permeability of dextran sulfate sodium-induced colitis in mice

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Introduction: To investigate the effect of anti-tumor necrosis factor (TNF)-α on the intestinal mucosal permeability in dextran sulfate sodium (DSS)-induced colitis and to determine its associated mechanism.

Methods: Experimental colitis was induced in C57BL/6J mice by administration of 5% DSS. Anti-TNF-α was injected intraperitoneally at doses of 5 mg/kg twice a week (d1 and d4). The disease activity index (DAI) scores were evaluated and colon tissue was collected for the assessment of histological changes. The myeloperoxidase (MPO) activity, TNF-α and interferon-γ (IFN-γ)-levels in the colon were determined. The small intestinal mucosa was ultrastructurally examined with transmission electron microscopy, epithelial myosin light chain kinase (MLCK) protein expression and enzymatic activity were determined, and intestinal permeability was assayed using FITC-dextran(FD-4) and Evans blue(EB).

Results: Anti-TNF-α was found effective in reducing the DAI score and histological index (HI) score, and decreasing MPO activity, TNF-α and IFN-γ levels. The amount of FD-4 in blood and EB permeating into the intestine were decreased by anti-TNF-α in colitis mice. The small intestinal epithelial MLCK protein expression and enzymatic activity were downregulated by anti-TNF-α.

Discussion/Conclusion: Anti-TNF-α showed a significant anti-colitis effect in colitis mice. The mechanism is partly associated with inhibiting the epithelial MLCK protein expression and enzymatic activity, which resulting in ameliorated intestinal mucosal permeability.
Ulcerative colitis and proctitis – The clinical efficacy of traditional Chinese medicine suppository treatment

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In 2014, we examined the clinical efficacy of the treatment of ulcerative colitis and proctitis. This study observed a total of 90 cases at the Affiliated Hospital of Shandong University of Traditional Chinese Medicine, where the patients were receiving ano-rectal treatment.

Ulcerative colitis was diagnosed using Western diagnostic criteria. Patients with the disease located in the rectum were randomly divided into a treatment group (60 cases) and a control group (30 cases) and were observed. Selected cases of mild to moderate ulcerative proctitis were studied. Before treatment, the patients were grouped according to their gender, age, disease duration, disease, lesions, endoscopic grading, TCM syndrome, symptoms and signs of comparison, the statistical analysis (all \( p > 0.05 \)) being comparable between the two groups.

Treatment groups: colitis bolt (TCM suppository) [prescription]; thirty-seven astragalus 600 g, 200 g, 80 g; frankincense ampelopsis gallnut 200 g, 600 g, 200 g white (a total of 1000). The prescription was provided by Jinan Public Health Pharmaceutical Technology Development Co., Ltd., which has many years of clinical experience, to a pharmacy in accordance with the national Chinese registration requirements and the relevant guidelines and pharmacological safety studies. The results prove that the product is safe and effective, and the quality can be controlled. [Indications] Qi stasis, bleeding and diarrhea. In patients with chronic ulcerative proctitis, Zheng Jian abdominal pain, diarrhea, mucus or pus, physical fatigue, pale or purple tongue, thin pulse string or astringent. Dosage of anal suppository: 1–2 times once a day. [Specification] Each capsule weighted 2.0 g.

Control group: mesalamine suppository, produced by Heilongjiang Tianhong Pharmaceutical Co., Ltd., batch number: 20140201.

Dosage: 1 to 2 times a day for adults, or as prescribed by a doctor.
Specification: 1 g.

Courses: The first course of treatment was followed for a month, after which the efficacy was evaluated by means of a comparative analysis between the two groups. The patients were then selected and a second course was given from the treatment group. To determine the efficacy, 30 patients continued to be given two courses of suppository.

Test results: Comprehensive clinical comparison of the efficacy of the first course of treatment: 20% efficiency in the treatment group, (72% efficiency, 8% inefficiency, total efficiency of 92%, no adverse reactions found); 17% efficiency in the control group (60% efficiency, 23% inefficiency, total efficiency of 77%), with a significant difference between the two groups (\( p < 0.05 \)). After three courses of treatment, the comprehensive clinical efficacy was evaluated: The efficiency of the treatment group was 70% (27% efficiency, 3% inefficiency, total efficiency of 97%, no adverse reactions found).
**Analysis:** Since ulcerative proctitis is a chronic disease requiring long-term medication, anal suppositories need to have a more direct effect on lesions, eliminating the need for patients to take oral medication to ease symptoms in their stomachs. This suppository is easy to carry, has a wide range of development prospects and is clearly an effective treatment. It is therefore greatly beneficial to patients.
The pectic polysaccharides extracted from Rauwolfia verticillata (Lour.) Baill. var. hainanensis Tsiang suppressing inflammation by regulation of NF-κB pathway and interleukin-17 in mice with dextran sulphonate sodium-induced ulcerative colitis

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Introduction: To investigate the effects of pectic polysaccharides extracted from Rauwolfia verticillata (Lour.) Baill. var. hainanensis Tsiang on an experimental murine colitis model.

Methods: Experimental colitis was induced by dextran sulfate sodium (DSS), and mice were divided into 4 groups: control, DSS alone, DSS plus SASP, DSS plus pectic polysaccharides. The disease activity index (DAI) and histological score were observed. The tumor necrosis factor (TNF)-α and interleukin (IL)-17 levels were measured by enzyme-linked immunosorbent assay. IκB and NF-κB p65 expression were assessed by western blot analysis. Myeloperoxidase (MPO) activity was determined by using MPO assay kit.

Results: Administration of pectic polysaccharides significantly reduced the severity of DSS-induced colitis as assessed by DAI and histological score, and resulted in down regulation of MPO activity and NF-κB p65 expression and subsequent degradation of IκB protein, strikingly reduced the production of TNF-α and IL-17.

Discussion/Conclusion: Pectic polysaccharides extracted from Rauwolfia verticillata (Lour.) Baill. var. hainanensis Tsiang exerts beneficial effects in experimental colitis and may therefore provide a useful therapeutic approach for the treatment of UC.
The association of XRCC1 and OGG1 single nucleotide polymorphisms with ulcerative colitis and colorectal cancer

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Introduction: Ulcerative colitis (UC) is associated with colorectal cancer (CRC). XRCC1 and OGG1 have been reported to be associated with CRC susceptibility in different population. Our aim is to study the association of XRCC1 and OGG1 single nucleotide polymorphisms (rs25487, rs1799782 and rs105213) with UC and CRC.

Methods: Peripheral blood samples were obtained from patients with UC, CRC and healthy controls during 2012–2014 in Peking University 3rd Hospital. Genomic DNA was extracted. According to NCBI sequence information, using primer3 online primer design software to amplify and sequence primers. After PCR amplification and purification, we detected XRCC1 and OGG1 single nucleotide polymorphisms (rs25487, rs1799782 and rs105213) by classical sequencing technology.

Results: 121 cases were enrolled, with 39 UC, 40 CRC and 40 healthy controls. Genotype frequencies of rs25487 AA, AG and GG in UC group were 7.7%, 25.6%, 66.7%; in CRC were 5.0%, 27.5%, 67.5%; and in control were 2.5%, 42.5%, 55.0% respectively. There was no significant difference between any two groups or among these 3 groups (P > 0.05). Also, the genotype frequencies of rs105213 CC, CG and GG in UC, CRC and control group were 7.7%, 56.4%, 35.9%; 20.0%, 55.0%, 25.0%; 15.0%, 57.5%, 27.5% respectively. The genotype frequencies of rs1799782 GG, GA and AA in UC, CRC and control group were 38.5%, 56.4%, 5.1%; 37.5%, 52.5%, 10.0%; 45.0%, 47.5%, 7.5% respectively. There was no significant difference between any two groups or among these 3 groups for above SNP (P > 0.05).

Discussion/Conclusion: There was no significant difference of XRCC1 and OGG1 single nucleotide polymorphisms (rs25487, rs1799782 and rs105213) between UC, CRC and healthy controls.
Systematic meta-analyses and field synopsis of genetic association studies in pediatric inflammatory bowel disease

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Introduction: Pediatric inflammatory bowel diseases (IBD), diagnosed during childhood, accounted for about 25% of all IBD cases. Early age of onset may be a variable that is likely to have a greater genetic predisposition to IBD or that is determined by exclusive loci to pediatric IBD. We aim to provide a comprehensive field synopsis of the current understanding of all genetic associations for pediatric IBD by evaluating results from previous studies.

Methods: We searched Medline, Embase and Human Genome Epidemiology Network to identify papers that investigated associations between genetic variants and pediatric IBD. We reviewed 5498 titles, then collated and extracted data from 66 studies reporting 138 Single Nucleotide polymorphisms (SNPs) on 59 different genes. Meta-analyses were carried out for variants that had at least three independent data sources. Four genetic models were used to derive summary effect for 14 SNPs on 6 different genes of pediatric Crohn’s disease (CD) and for 7 SNPs on 4 different genes of pediatric ulcerative colitis (UC). For assessing the credibility of associations, we applied the Venice criteria and the Bayesian False Discovery Probability (BFDP) test.

Results: We considered 5 independent variants (rs2066844, rs2066847, rs11209026, rs2241880, 3020insC) at 3 loci (NOD2/CARD15, IL23R, ATG16L1) to have the most highly credible associations (lower heterogeneity, higher statistical power, BFDP < 0.2) with pediatric CD. We identified less-credible associations with 5 variants (rs2066845, rs7517847, rs1050152, rs12521868, rs2631376) for pediatric CD and 4 variants (rs2066847, rs11209026, rs1050152, rs2631367) for pediatric UC. The analyses of other 4 variants (rs11739135, rs1248696, rs2289311, rs2836878) of pediatric CD and 3 variants (rs2066844, rs2066845, rs1248696) of pediatric UC for which associations have been previously reported showed evidence of no associations.

Discussion/Conclusion: Our study highlights a number of SNP associations that could be incorporated into genetic risk prediction of pediatric IBD as further risk factors are identified and highlights loci at which further research effort should be targeted.
Low-dose infliximab for induction and maintenance therapy for Chinese patients with moderately to severely active ulcerative colitis

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Introduction: No significant statistical differences were observed between the clinical therapeutic efficacy of high-dose (10 mg/kg) and standard-dose (5 mg/kg) infliximab treatment of active ulcerative colitis. 4–5 mg/kg infliximab treatment also proved effective in treating moderate-to-severe ulcerative colitis. There is at present no relevant research on the effectiveness of infliximab doses lower than 4 mg/kg in ulcerative colitis patients.

The aim of this study is to evaluate the efficacy of low-dose infliximab (3.5 mg/kg) for induction and maintenance therapy for Chinese patients with ulcerative colitis.

Methods: A prospective, randomized, double-blind, placebo-controlled study was designed. A total of 123 patients (from 17 provinces of China) with moderate-to-severe active ulcerative colitis despite treatment with concurrent medications received placebo or low-dose infliximab (3.5 mg/kg) or standard-dose infliximab (5 mg/kg) intravenously at weeks 0, 2, and 6 and then every eight weeks through week 22. Patients were followed up for 30 weeks.

Results: 73% of patients who received low-dose infliximab (3.5 mg/kg) and 78% of those who received standard-dose infliximab (5 mg/kg) had a clinical response at week 8, as compared with 37% of those who received placebo (p < 0.01 for both comparisons with placebo). A response was defined as a decrease in the Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute rectal-bleeding subscore of 0 or 1.

More patients who received low-dose infliximab (3.5 mg/kg) or standard-dose infliximab (5 mg/kg) had a clinical response at week 30 (63% and 66%, respectively) than did those who received placebo (27%, p < 0.01 for both comparisons).

Discussion/Conclusion: Chinese patients with moderate-to-severe active ulcerative colitis treated with low-dose infliximab (3.5 mg/kg) or standard-dose infliximab (5 mg/kg) at weeks 0, 2, and 6 and every eight weeks thereafter were more likely to have a clinical response at weeks 8, 30, than were those receiving placebo.
The relationship between IL-6, RANKL/OPG and osteoporosis in ulcerative colitis

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Introduction: To observe the relationship between interleukin-6 (IL-6), RANKL, OPG and osteoporosis in patients with Ulcerative Colitis (UC).

Methods: Thirty patients with UC and twenty healthy subjects (the control group) from the health examination center from 2012 to 2013 were enrolled in the study. The serum levels of IL-6, OPG and RANKL were detected by ELISA. Bone mineral density (BMD) was measured at lumbar span (L1–L4) with dual energy X-ray absorptiometry.

Results: There were 13 subjects in UC patients suffering low bone mineral density. The average of BMD was 0.97 ± 0.18 g/m², which was lower than that in control group (1.11 ± 0.14 g/m², P = 0.007). The serum level of IL-6, RANKL and OPG in UC patients was higher than those in the control group (P < 0.001). The IL-6, RANKL levels in UC patients with normal BMD were significantly higher than those in the control group (P < 0.01). The levels of IL-6, RANKL and OPG in UC with osteopenia and osteoporosis were significantly higher when compared with those in the control group (P < 0.01). The levels of IL-6 were different among the three subgroups in which UC patients were with normal BMD, osteopenia, and osteoporosis (P < 0.01). The levels of OPG in subgroups with osteoporosis and osteopenia were higher than that in subgroup with normal BMD (P < 0.01). The difference of OPG was not significant between the subgroups with osteoporosis and osteopenia. BMD were negatively correlated with serum OPG levels and IL-6 levels (respectively \( r = -0.528 \), \( P < 0.05; \) \( r = -0.437 \), \( P < 0.05 \)).

Conclusion: IL-6, RANKL, OPG play important roles in the osteoporosis in patients with UC. Measuring the serum levels of IL-6, RANKL and OPG will benefit the prevention and diagnosis of the osteoporosis in patients with UC.
Variation analysis for DNA repair gene in a family with UC and CRC

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Introduction: Ulcerative colitis (UC) is associated with colorectal cancer (CRC). Genetic susceptibility may play a role in both UC and CRC. Our aim is to investigate the genetic difference and correlation in UC and CRC.

Methods: 2 UC and 1 CRC were diagnosed in three daughters from one family. We recruited the mother (91 years old, healthy) and her all four daughters including 1 CRC, 2 UC and 1 healthy. The father died of glioma 20 years ago. Peripheral blood was collected and genomic DNA was extracted. Whole exome sequencing was done by NGS. Variants were analyzed and annotated based on online database and also compared the data with “General Han population”.

Results: Here we focused on mutations in DNA repair gene. Total 740 variants in DNA repair gene were identified. 532 variants existed in CRC, in contrast to 2 UC (473, 482) and 2 healthy individuals (482, 479). According to 1000 Genomes Project, 16 nonsynonymous mutations in exon region from 13 genes (including ATR, BIVM-ERCC5/ERCC5, BRCA2, FAAP24, DCLRE1C, EME1, EME2, FANCG, LIG1, MSH2, POLD4, POLE2, RAD51D) were screened out for low frequency (MAF < 0.1). Comparing the five members, two heterozygous A865C, A2971G in BRCA2 were found only in CRC. A1886G in MSH2 existed only in the healthy individuals (the mother and one healthy daughter). G116C in POLD4 and C990G in POLE2 existed only in the mother. Neither special variants seen only in UC nor significant difference for other variants in DNA repair gene among five members in this family.

Discussion/Conclusion: In this family, A865C, A2971G in BRCA2 tend to be related to the genetic susceptibility of CRC. A1886G variant in MSH2 tend to play a protective role against both UC and CRC. There is no significant variants in DNA repair gene associated with UC in this family.
Defective repair gene in an ulcerative colitis associated colorectal cancer patient: Case report and landscape of genetic characterization

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Introduction: Ulcerative colitis (UC) is associated with colorectal cancer (CRC). Genetic alterations may play a role in UC-CRC. Our aim is to investigate the genetic characteristics in UC-CRC.

Methods: A 42-year-old male with UC and ankylosing spondylitis (AS) was found colonic adenocarcinoma. Peripheral blood, inflammatory and cancer tissue from colon were collected through operation. Genomic DNA was extracted. Whole genome (WGS) and exome (WES) sequencing were done using NGS. Variants were analyzed and annotated based on online database and compared with “General Han population”.

Results: 3,195,782 variants in blood (germ-line), 45,133 in inflammatory and 62,361 in cancer tissue (somatic) were identified respectively. Based on disease database, 40 germ-line variants were found associated with IBD, CRC or cancer including 16 variants in DNA repair gene (MSH2, MSH6, FEN1, TP53, TP63, BRCA2, APC, NQO1, MUC1, RAD23B), 8 variants in UC susceptibility gene (IL17REL, IL23R, ATG16L1, CARD9, TNSF15), 3 in AS susceptibility gene (SNAPC4, CARD9 and ERAP1), and the rest variants were cancer related genes (SMAD7, ZNF365, LAMA5, MDM4, FGFR2, COLCA2, CCHCR1, CCAT2, CASC16). The number of mutations in DNA replication and repair pathways was much higher than average level of “General Han population” especially rare variants were the highest compare to “General Han population”. Cancer-related genes (JAK2, KRAS, MSN and SMAD7) were found as somatic mutations in colonic mucosa. Mutations in genes of signalling molecules were involved in multiple inter-related pathways including PI3K/Akt, IL23/Th17, JAK-STAT, NF-κB, Wnt/β-catenin associated to innate immunity, autophagy, barrier function and carcinogenesis.

Discussion/Conclusion: In this case, many mutations susceptible to UC, AS and associated with CRC existed in germ-line, imply its genetic susceptibility to UC-CRC. Some functional mutations are related to immunity across of UC and cancer. Defection of DNA repair relative genes might contribute to the pathogenesis of his UC-CRC.
Synchronous onset of CMV colitis and ulcerative colitis in an immunocompetent patient: A case report

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Background: Cytomegalovirus (CMV) infection has been confirmed being associated with ulcerative colitis (UC). The prevalence of CMV infection in UC patients is ranging from 10% to 16%. It is particularly high in the patients with steroid-refractory UC and those treated with immunosuppressants. However, synchronous onset of CMV colitis and UC in an immunocompetent patient is rare. It was originally described in 1990 and since then sixteen cases have been reported as our knowledge. Here we present a case of CMV colitis and UC synchronously developed in an elderly immunocompetent woman.

Case presentation: A 61-year-old woman was admitted to our hospital with abdominal pain, fever and diarrhea for 10 days. She was quite healthy before, without history of diabetes and medication exposures. Laboratory data showed elevated erythrocyte sedimentation rate, high C-reactive protein, mild anemia and leukocytosis. She had liquid stools with blood and mucus more than 10 times per day. Colonoscopy demonstrated diffuse congestion and edema in the entire colonoscopy with multiple ulcers scattered in the transverse colon, descending colon and sigmoid colon. The biopsies suggested crypt abscess and crypt branch, and UC was diagnosed. Sulfasalazine resulted in improvement of her symptoms, except the temperature. Before steroids were given, immunohistochemistry (IHC) for CMV was ordered, and the results were positive. Intravenous ganciclovir was prescribed. Her symptoms gradually disappeared and repeated colonoscopy after three weeks showed the colon inflammation was significantly improved and the immunohistochemistry for CMV was negative.

Discussion/Conclusion: The CMV infection in our patient was missed in the beginning, and finally diagnosed through the tissue immunohistochemistry. Our case demonstrated that in patients with severe active UC, even with new onset of the disease, CMV infection needs to be ruled out before initiating an aggressive immunosuppressive therapy.
Clinical features of 62 cases of small bowel Crohn’s disease

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Objectives: To investigate the clinical features of small bowel Crohn’s disease (CD).

Methods: From January 2009 to September 2012, a total of 138 patients diagnosed as CD who underwent examinations of colonoscopy, digestive tract radiography, capsule endoscopy, double-balloon enteroscopy and computed tomography (CT) enterography were enrolled. According to the Montreal Classification criteria, the disease was typed by the age at diagnosis, location of the lesions and behavior of the disease. The clinical symptoms, laboratory examinations, diagnostic methods and recurrence condition were also evaluated. Through the comparison of the clinical features of ileocolonic and colonic CD, the clinical features of small bowel CD were analyzed. Measurement data were analyzed with t-test, analysis of variance or non-parametric test. Chi square test was performed for count data. Spearman’s correlation analysis was used for correlation analysis and multivariate Logistic regression analysis was used for risk factors screening.

Results: A total of 62 (44.9%) cases were simple small bowel CD. Fifty-three patients (85.5%) were male, and the mean age at diagnosis was 35.3 years old. The age of 67.7% (42/62) of small bowel CD patients were less than 40 years old when diagnosed. The ratio of stricture in small bowel CD group (35.5%, 22/62) was significantly higher than that of ileocolonic (18.8%, 6/32) and colonic CD group (13.9%, 5/36) (x² = 6.594, P = 0.037). Jejunal involvement was an independent risk factor for structure in CD (OR = 3.481, 95% CI: 1.250 to 9.693). The patients with obstructive symptoms as primary symptom in small bowel CD (38.7%, 24/62) were more than those with colonic CD (16.7%, 6/36) (x² = 5.210, P = 0.022). However, patients with diarrhea as primary symptom in small bowel CD (21.0%, 13/62) were less than those with ileocolonic (37.5%, 12/32) and colonic CD (44.4%, 16/36) (x² = 6.512, P = 0.039). Patients with two or more extraintestinal manifestations in small bowel CD (3.2%, 2/62) were also significantly less than those with ileocolonic (15.6%, 5/32) and colonic CD (19.4%, 7/36) (x² = 7.957, P = 0.019). The score of CD activity index was generally low, and with no statistical correlation to serum inflammation markers such as C reaction protein. The average time duration between induction of remission and clinical recurrence of small bowel CD ([23.64 ± 17.08] months) was shorter than that of ileocolonic type ([35.07 ± 29.84] months, t = -4.285, P = 0.002) and colonic CD ([32.35 ± 28.46] months, t = -3.700, P = 0.004). However, there was no significant difference in the rate of clinical recurrence between small bowel CD and ileocolonic, colonic CD.

Conclusions: Patients with small bowel CD account for a large proportion in patients with CD, especially in males. Stricture is more common in jejunum CD. The time duration between induction of remission and clinical recurrence of small bowel CD is short.
Outcome of deep remission after short-term scheduled infliximab therapy in ileocolonic Crohn’s diseases

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Background and Aims: Deep remission means clinical remission with mucosal healing (MH). Infliximab is the most effective drug in Crohn’s disease (CD) for induction of deep remission. However, it is undetermined that how long infliximab therapy will achieve deep remission. In China, due to economic burden, most CD patients choose short-term (often 6 times) scheduled infliximab therapy. So far, It is unknown if this short-term duration of infliximab therapy can achieve deep remission. Our study was designed to investigate, how often did patients achieve deep remission after short-term (6 times) scheduled infliximab therapy in ileocolonic Crohn’s diseases.

Methods: The total of 40 ileocolonic Crohn’s disease (CD) patients who prospectively received scheduled infliximab for at least 6 times and underwent ileocolonoscopy before and after the 36 weeks of infliximab therapy were included between January 2013 and July 2014. All patients began to combine one immunomodulator at week 2. We collected endoscopic findings, patient characteristics, clinical symptoms, C-reactive protein (CRP) and hemoglobin (HB) levels and data on infliximab and combined antimetabolite therapy. Defining deep remission as clinical remission (Crohn’s Disease Activity Index, CDAI < 150 points) and endoscopic remission (the simple endoscopic score for Crohn’s disease, SES-CD 0–2).

Results: Of the 40 CD patients, 38 (95%) were in clinical remission and 25 (62.5%) in deep remission after a scheduled 36 weeks (6 times) of infliximab therapy. And at week 36, 35% (14/40) had partial mucosal healing, whereas 2.5% (1/40) had no improvement of mucosal inflammation. Median CDEIS score decreased from 14 to 0 at week 36.

Conclusion: This short-term duration (6 times) of scheduled infliximab therapy can achieve deep remission in the ileocolonic CD patients. Outcome of remission maintained by antimetabolite therapy after infliximab withdrawal need to be further investigated.

Keywords: Crohn’s disease, infliximab, deep remission, mucosal healing, IBD
Placental growth factor enhances angiogenesis in human intestinal microvascular endothelial cells via PI3K/Akt pathway: Potential implications of inflammatory bowel disease

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Introduction: Angiogenesis plays a major role in the pathogenesis of inflammatory bowel disease (IBD). Placental growth factor (PIGF), a member of vascular endothelial growth factor (VEGF) family, is dispensable for the development and health, thus it has been suggested that PIGF blockade might inhibit disease processes without affecting normal health. High concentration of PIGF have been detected in the serum of IBD patients. We examined whether PIGF signaling has a role in inflammatory bowel disease (IBD).

Methods: PIGF expressions were examined with ELISA and quantitative PCR in samples from patients with IBD. The capacity of PIGF to induce angiogenesis was tested in human intestinal endothelial cells (HIMECs) using cell-migration and matrigel tubule-formation assays. To explore the potential mechanisms of PIGF signaling, ERK1/2 and PI3K/Akt pathways were investigated by Western blotting.

Results: PIGF expression increased in serum and diseased intestinal mucosa from patients with IBD compared with those of controls. mRNA and protein expression of PIGF and its receptors VEGFR-1 and NRP-1 significantly increased in the HIMECs of IBD patients. Exogenous hPIGF-1 treatment induced the HIMECs migration and tube formation in a dose-dependent manner, which were remarkably suppressed by inhibition of PIGF, while increased PIGF-1 had little effect on HIMECs proliferation. We further found that hPIGF-1 elicited increased phosphorylation of Akt in HIMECs but had little effect on MAPK pathway. Moreover, PIGF-mediated migration and tube formation were inhibited by PI3K inhibitor (LY294002).

Discussion/Conclusion: Our results confirmed the angiogenic effects of PIGF on HIMEC in IBD. The potential mechanism includes activation of the PI3K/Akt signaling pathways. PIGF/PI3K/Akt signaling may serve as a potential target for therapy in IBD.
Risk of ulcerative colitis-associated colorectal cancer in Inner Mongolia of China: A single center study

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Introduction: The number of patients with ulcerative colitis (UC) in China has increased during the last decade. Patients with ulcerative colitis are at an increased risk for colon cancer. However, the risk of CRC in UC patients is still unknown in inner Mongolia of China. The aim of this study was to identify the risk and risk factors of UC-CRC in inner Mongolia of China.

Methods: A total of 590 patients with UC were retrospectively collected from Affiliated Hospital of Inner Mongolia Medical University, in which high-quality endoscopic and histological diagnoses were available from 2004 to 2014. The database of the UC and UC-associated CRC patients was evaluated.

Results: 6 patients were diagnosed with colorectal cancer, and the overall prevalence of CRC in patients with UC was 1.02%. The cumulative risk of developing CRC after a disease duration of 10 years was 1.23% (95% confidence interval [CI] 0.82–1.63%); 20 years, 4.01% (95% CI 1.89–6.37%). Longer course, extensive colitis, and dysplasia were identified as risk factors for developing CRC. 5-aminosalicylic acid (5-ASA) therapy was identified as a protective factor of UC-CRC.

Conclusion: In inner Mongolia of China the period prevalence of CRC was lower than that reported from Western countries, but higher than that reported by China. 5-ASA therapy is valuable for preventing UC-CRC.

Keywords: ulcerative colitis, colorectal cancer, 5-aminosalicylates
Fluorofenidone attenuates hepatic fibrosis by suppressing the proliferation and activation of hepatic stellate cells

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Introduction: Fluorofenidone (AKF-PD) is a novel pyridone agent. The purpose of this study is to investigate the inhibitory effects of AKF-PD on liver fibrosis in rats and the involved molecular mechanism related to hepatic stellate cells (HSCs).

Methods: Rats treated with dimethylnitrosamine or CCl₄ were randomly divided into normal, model, AKF-PD treatment, and pirfenidone (PFD) treatment groups. The isolated primary rat HSCs were treated with AKF-PD and PFD respectively. Cell proliferation and cell cycle distribution were analyzed by bromodeoxyuridine and flow cytometry, respectively. The expression of collagen I and alpha-smooth muscle actin (alpha-SMA) were determined by Western blot, immunohistochemical staining, and real-time RT-PCR. The expression of cyclin D₁, cyclin E, and p27kip¹ and phosphorylation of MEK, ERK, Akt, and 70-kDa ribosomal S6 kinase (p70S6K) were detected by Western blot.

Results: AKF-PD significantly inhibited PDGF-BB induced HSC proliferation and activation by attenuating the expression of collagen I and alpha-SMA, causing G0/G1 phase cell cycle arrest, reducing expression of cyclin D₁ and cyclin E, and promoting expression of p27kip¹. AKF-PD also downregulated PDGF-BB-induced MEK, ERK, Akt, and p70S6K phosphorylation in HSCs. In rat liver fibrosis, AKF-PD alleviated hepatic fibrosis by decreasing necroinflammatory score and semiquantitative score, and reducing expression of collagen I and alpha-SMA.

Discussion/Conclusion: AKF-PD attenuated the progression of hepatic fibrosis by suppressing HSCs proliferation and activation via the ERK/MAPK and PI3K/Akt signaling pathways. AKF-PD may be used as a potential novel therapeutic agent against liver fibrosis.
Double-balloon colonoscopy: Experience from a tertiary care center

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**Background:** The failure rate of caecal intubation with conventional colonoscopy is 5% to 10%. Double-balloon endoscopy is a new technique for antegrade or retrograde examination of the small intestine, with a flexible scope and a sliding overtube with a balloon at the distal end of both. The entire colon can be shortened and evaluated by the push-and-pull technique, which allows diagnostic and therapeutic interventions (e.g. biopsies).

**Objective:** To evaluate the utility of the double balloon enteroscope used for complete examination of the colon in patients with incomplete standard colonoscopy.

**Methods:** Retrospective single-center case series on the caecal intubation rate using standard double balloon enteroscope technique in patients with previous incomplete conventional colonoscopy.

**Main outcome measurements:** Completion rate of double-balloon colonoscopy, therapeutic success of standard procedures, and post-procedure complications.

**Results:** Thirty-six patients (20 women and 16 men; mean age, 60 years, mean age 20–89) had retrograde double-balloon endoscopy from December 2008 to December 2012 after a prior incomplete colonoscopy. Use of the standard double balloon enteroscope technique permitted complete colonoscopy to be achieved in 97% of the patients (35/36). Sixteen patients (44%) had significant pathology mostly (93%) beyond the extent of the prior incomplete colonoscopy. We performed endoscopic mucosal resection, Argon Plasma coagulation, polypectomy or biopsy. **The mean time to reach the caecum was 28 min (S.D. ± 20 min, range 6–90 min).** The sedation was mostly similar to conventional colonoscopy (Mean Midazolam dose 3.15 mg; range 0–8, Mean Fentanyl dose 73 mcg; range 0–150 mcg). No complications occurred.

**Conclusions:** Double-balloon colonoscopy has a high rate of effectiveness for completion of colon evaluation in patients with incomplete conventional colonoscopy. It allows diagnostic and therapeutic interventions well beyond the reach of conventional colonoscope and can be performed with the patient under conscious sedation with reasonable success.
Effect of YiQi JieDu HuaYu decoction on IL-23/IL-17 axis of TNBS-induced experimental colitis in rats

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Introduction: Inflammatory bowel disease (IBD) including Crohn’s disease and ulcerative colitis are a group of diseases characterized by chronic and relapsing gastrointestinal inflammation. The etiology of IBD remains uncertain, but accumulating evidence suggests that immunomodulatory disorder plays important roles in IBD pathogenesis. Interleukin (IL)-17, is a potent proinflammatory cytokine. IL-23 induces the differentiation of native CD4+ T cell into highly pathogenic helper T cells (Th17) that produce IL-17. Most researches suggests that IL-23/IL17 axis have a profound impact on the pathogenesis of IBD. Immune disorders have similar with spleen deficient in traditional Chinese medicine. According to spleen deficient for IBD, we put forward the YiQi JieDu HuaYu method (YQJD) in the treatment of IBD and observe the effect of YQJD on IL-23/IL17 axis of trinitrobenzenesuphonic acid (TNBS)-induced experimental colitis in rats.

Methods: Fifty male Sprague-Dawley rats were randomly divided into five groups: normal group, model group, salicylazosulfapyridine (SASP) group and low-and high-dose YQJD groups. The experimental colitis was induced by TNBS into all rats except those in normal group. The SASP group and YQJD groups received respective treatments for 4 weeks. The colon macroscopic damage index (CMDI) was determined by visual inspection, and the tissue damage index (TDI) was determined under a light microscope. The expressions of IL-17 and IL-23 in serum were determined by enzyme-linked immunosorbet assay.

Results: The scores of CMDI, TDI and the levels of serum IL-23 and IL-17 were significantly decreased in all treatment groups (P < 0.01), as compared with the model group. The high-dose YQJD group showed significantly more improvements in the above indices than the low-dose YQJD group and SASP group (P < 0.05 or P < 0.01).

Discussion/Conclusion: YQJD can effectively adjust IL-23/IL-17 axis of the TNBS-induced experimental colitis in rats. This could be one of the immune mechanism in the treatment of colitis.
Effect of YiQi JieDu HuaYu decotion on intestinal mucosal barrier of TNBS-induced experimental colitis in rats

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Introduction: Inflammatory bowel diseases (IBD), typified by Crohn's disease and ulcerative colitis, is a common disorder characterized by recurrent and serious inflammation of the gastrointestinal tract. Etiology and pathogenesis of IBD is still unclear, but accumulating evidence suggests that intestinal mucosal barrier plays a pivotal role in IBD pathogenesis. YiQi JieDu HuaYu (YQJD) is a traditional Chinese formula, which has been used for many years to clinically treat conditions associated with inflammatory bowel diseases. However, whether it can adjust intestinal mucosal barrier of IBD is unclear. In this study, we evaluated the effect of YQJD on intestinal mucosal barrier of trinitrobenzenesulphonic acid (TNBS) -induced experimental colitis in rats.

Methods: Fifty male Sprague-Dawley rats were randomly divided into five group: normal group, model group, salicylazosulfapyridine (SASP) group, and low-and high-dose YQJD groups. Colitis was induced by TNBS into all rats except those in normal group. The SASP group and YQJD groups received respective treatments for 4 weeks. The expressions of IL-6 and IL-10 in serum were determined by enzyme-linked immunosorbent assay. The expression of the colonic mucosa filamentous actin was determined by immunohistochemical method. Microstructures were detected by transmission electron microscope.

Results: The level of serum IL-6 was significantly decreased, the expressions of filamentous actin and serum IL-10 were significantly increased and the microstructures significantly ameliorated in all treatment groups (P < 0.01), as compared with the model group. The high-dose YQJD group showed significantly more improvements in the above indices than the low-dose YQJD group and SASP group (P < 0.05 or P < 0.01).

Discussion/Conclusion: YQJD can regulate the expression of cytokines, ameliorate the microstructures and increase the expression of filamentous actin of the TNBS-induced experimental colitis in rats, which maybe one of the mechanisms that YQJD can effectively modulate the intestinal mucosal barrier function.
The genetic study of ATG16L1 in IBD

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Introduction: Genetic studies identified a missense polymorphism (Thr300Ala) in the essential autophagy gene ATG16L1 to be associated with Crohn’s disease. Previous studies showed that ATG16L1 T300A variant leads to its enhanced cleavage and thus, reduced function of autophagy (loss-of-function). An intact ATG16L1 has been shown to play an essential role in Paneth cell function and intestinal homeostasis. However, the functional consequence of ATG16L1 in myeloid cell, in particular macrophages, has not been demonstrated.

Results: Here, we generated mice with ATG16L1 deficiency in myeloid and dendritic cells and showed worsened colonic inflammation in 2 acute and 2 chronic models of murine colitis with increased production of Il1b, Tnfa, and Il6. Mechanistic studies performed in primary murine macrophages and dendritic cells showed that ATG16L1 deficiency leads to increased reactive oxygen species production, reduced microbial killing, impaired processing of antigen for presentation, increased IgA coated microbes, and altered intracellular trafficking. Similar findings were shown in human primary macrophages from control and Crohn’s disease patients carrying the ATG16L1 T300A genetic variant.

Discussion/Conclusion: These results indicate impaired macrophage function with ATG16L1 deficiency that may contribute to the severity of Crohn’s disease.
The role of interleukin-33 in the pathogenesis of inflammatory bowel disease in the Han people of southern China

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Introduction: We investigated the expression of interleukin-33 in the intestinal mucosa of IBD patients and discussed whether the SNPs in interleukin-33 are associated with IBD.

Methods: Intestinal mucosa was obtained from 114 patients with Crohn’s disease (CD), 68 patients with ulcerative colitis (UC) and 88 healthy controls. The expression of interleukin-33 in the intestinal mucosa was evaluated by immunohistochemistry.

Eight tag SNPs were selected from the interleukin-33 gene using the HapMap database. These tag SNPs were genotyped in 250 CD patients, 115 UC patients and 622 healthy controls by MALDI-TOF MS assay.

Results: Interleukin-33 can be expressed in the intestinal mucosa of both IBD patients and healthy people. The number of interleukin-33 positive cells in the lamina propria of the CD group was greater than in the control (p = 0.006). Interleukin-33 expression has nothing to do with the clinical features of IBD. No differences in the frequency distributions of genotypes and alleles were observed between the patients with CD and UC and the controls (p > 0.05). The genotypes of rs10118795, rs7025417, rs10975519 and rs10975509 were associated with clinical phenotypes of CD, while the genotypes of rs10118795, rs10975509 and rs7025417 were associated with mucosal healing at week 30 during treatment with infliximab.

Discussion/Conclusion: The expression of interleukin-33 in the intestinal mucosa of CD patients was increased. Eight polymorphisms of interleukin-33 chosen by us do not increase the risk of CD and UC, but some of them have an effect on the clinical phenotypes of CD. However, three SNPs may be potential predictors of the effectiveness of treatment with infliximab. Interleukin-33 appeared to play a role in the pathogenesis of CD in the people of southern China.
Inflammatory bowel diseases (IBDs), such as Crohn’s disease and ulcerative colitis, are chronic relapsing disorders of the gastrointestinal tract, that are characterized pathologically by intestinal inflammation and epithelial injury. Cytokines have been directly implicated in the pathogenesis of IBD in recent genetic and immunological studies, especially the Th1/Th17 cytokines, and they seem to have a crucial role in controlling intestinal inflammation and the associated clinical symptoms of IBD. Interferon (IFN)-γ is a signature Th1 cytokine and has been shown to have a pro-inflammatory role in a number of autoimmune and inflammatory diseases including IBD. Galectin-9 (Gal-9) was first identified as a chemoattractant and activating factor for eosinophils. It is abundantly expressed in various tissues, especially the epithelium of the gastrointestinal tract, and in a variety of cells such as macrophages, eosinophils, mast cells, etc. Our previous studies have found that the expression level of Gal-9 on intestinal epithelial cells is lower in IBD, but the specific mechanism is still unclear. Here we focused on the paracellular permeability of T84 monolayer and Gal-9 express influenced by IFN-γ.
Qingchang Huashi recipe attenuate TNBS-induced colitis by mechanisms involving down-regulation of IL-6/STAT3 signaling via IL-6 trans-signaling

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Introduction: Activation of the IL-6/STAT3 via IL-6 trans-signaling plays an important role in the pathogenesis of inflammatory bowel disease. In the present study, we discuss the predominant role of IL-6/STAT3 via IL-6 trans-signaling and the therapeutic efficacy of Qingchang Huashi Recipe in IBD.

Methods: The colitis model of mice was induced using TNBS/ethanol. Soluble IL-6R was detected by ELISA in colon. The mRNA expression of IL-6, gp130, JAK2 and STAT3 were examined by real time PCR in the colon tissues of mice. The protein expression of IL-6, gp130, p-JAK2 and p-STAT3 were analyzed by Western Blot.

Results: Soluble IL-6R concentrations, IL-6 and gp130 expression, JAK2 and STAT3 phosphorylation increased significantly in the colon tissues of TNBS-treated mice (all P < 0.01). Treatment with Qingchang Huashi Recipe significantly reduced the sIL-6R level (P < 0.01) and induced down-regulation of IL-6, gp130, p-JAK2 and p-STAT3 in the colon tissues (all P < 0.01).

Discussion/Conclusion: Enhanced activation of IL-6/STAT3 via IL-6 trans-signaling-mediated immune and inflammatory responses may play an important role in the development and perpetuation of colitis. Qingchang Huashi Recipe could attenuate the experimental colitis by mechanisms involving down-regulation of IL-6/STAT3 signaling via IL-6 trans-signaling.
The rectal anal function of Chinese ulcerative colitis patients

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Introduction: Most patients of ulcerative colitis (UC) suffered from abdominal pain, diarrhea, bowel movement endless sense and defecation urgency. But the rectal anus function of UC is unclear. This study is to explore the rectal anal function of UC by HRM technology.

Methods: Twelve UC patients in activity period (n = 12, 6 male, 6 female, age 45.2 ± 17.5 yr) were enrolled and patients with IBS-D (n = 15) and healthy people (n = 15) were included as control. After the informed consent signed, all subjects received anorectal manometry and rectal visceral perception to balloon distention. The data of rectal anal pressure and perception were compared.

Results: The demographic data such as age, gender were all matched among groups (P > .05). There were significant difference between UC and other two groups in rectal anal function. The resting pressure of internal anal sphincter of UC (59.17 ± 24.35 mmHg) was higher than that of IBS-D (8.22 ± 2.19 mmHg) and healthy control (10.08 ± 1.11) (all P < .001), the maximal squeeze pressure was also higher in UC than in IBS-D and healthy control (100.00 ± 50.77 mmHg vs. 18.42 ± 2.35 P < .001; vs. 19.91 ± 3.16, P < .001). The rectum-anal inhibition reflex (RAIR) could be recognized in every subjects in IBS-D and healthy control, while only 2 patients in UC group could be recognized with RAIR, the difference was significant (P < .001). The thresholds of the first sensation volume and pain volume of rectum of UC (24.51 ± 15.26 mL, 54.42 ± 48.21 mL) were all lower than IBS-D (83.67 ± 10.60 mL, 138.27 ± 13.52 mL) and healthy control (48.6 ± 8.85 mL, 198.00 ± 22.74 mL) (all P < .001). In addition, there were also differences in the first sensation volume and pain volume of rectum between IBS-D and healthy control (all P < .001).

Discussion/Conclusion: There were great difference in the rectal annual function among UC and IBS-D and healthy control. Patients with UC were mostly manifested as more tensive inner anal sphincter and more sensitive anus and rectus. The RAIR was almost damaged in UC patients.
Effect of serum interleukin-10 (IL-10) and tumor necrosis factor (TNF-α) in ulcerative colitis with combination of mesalazine and kangfuxin

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Introduction: Ulcerative colitis (UC) is an inflammatory gastrointestinal disease of the colon; we examined the efficacy of combination of mesalazine and kangfuxin on serum TNF-α, IL-10 levels in patients with ulcerative colitis.

Methods: Sixty-four patients with active mild to moderate distal ulcerative colitis in accordance with inclusion criteria, were randomly divided into treatment group (n = 33, kangfuxin, 30 ml + 0.9% NaCl 150 ml enema, once a day; mesalazine, 60 g, enema, once a day) and control group (n = 31, mesalazine, 60 g, enema, once a day). They all underwent retaining enema for 8 weeks as a course. Serum TNF-α, IL-10 levels were tested by double antibody sandwich enzyme-linked immunosorbent assay between pre- and post-treatment.

Results: Between the two groups after treatment, on day 56, TNF-α level in two groups were significantly lower compared to before (P < 0.05), while IL-10 level expression in the combination therapy group were significantly higher compared to patients receiving mesalazine alone (P < 0.05). Moreover, in treatment group, the decreased degree of clinical symptom score was obviously higher than in control group (P < 0.05), the rate of adverse events in two groups was similar (15.7% vs 16.3%, P > 0.05).

Discussion/Conclusion: Combinatorial intervention with mesalazine and kangfuxin can more effectively reduce serum level of TNF-α and increase serum IL-10 level in patients with ulcerative colitis.
CCR5 expression in biopsic intestinal mucosa of inflammatory bowel disease and its correlation with degrees of inflammatory cells infiltration and expression of β-arrestin 2

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Objective: In this study, we analyzed the expression levels of CCR5 in the intestinal mucosa, and its correlation with leucocyte infiltration and expression of β-arrestin2. By this way, we aimed to elucidate the function of CCR5 and β-arrestin2 in IBD, thus to interpret partial regulatory mechanism of leucocyte infiltration in IBD.

Methods: Paraffin sections were derived from 53 patients with active IBD, 26 patients with alleviated IBD and 30 healthy people. Immunohistochemical Envision two-step method was used to test the expression levels of CCR5 and β-arrestin2 in the biopsic intestinal mucosa. HE and toluidine blue staining were used to detect the pathological cytological analysis and classification in lamina propria of colonic mucosa.

Results: The positive rate, strong positive rate and immunohistochemical score of CCR5 expression in active IBD group were significantly higher than that in normal control group and alleviate IBD group (P < 0.05). CCR5 expression had no obvious correlation with clinical severity, lesion distribution, and endoscopic classification of active IBD. The number of neutrophils, eosinophils and lymphocytes in active IBD group were significantly higher than that in normal control group and alleviated IBD group (P < 0.05). While the lymphocyte grade has a positive correlation with CCR5 expression (P = 0.042, r = 0.286). The number of mast cells in active IBD group, alleviated IBD group and normal control group had no obvious difference (P > 0.05). β-arrestin2 expression was significantly lower in active IBD group than that in alleviated IBD group and normal control group. β-arrestin2 expression had a negative correlation with CCR5 expression (P = 0.01, r = -0.247).

Conclusion: Our results suggest that CCR5 and β-arrestin2 could be one of the crucial factor for leucocyte infiltration in IBD.

Keywords: inflammatory bowel disease, CCR5, β-arrestin2, neutrophil, eosinophil, lymphocyte, mast cells, immunohistochemistry staining
Antagonistic active peptide of specific binding the first and the second extracellular membrane loops of rat CCR5 were panned and identified by technology of phage display peptide library

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Objective: To pan active peptides that specifically bind to rat CC chemokine receptor 5 (CCR5) and identify the binding efficiency by phage display.

Methods: The amino acid sequences of the first and second extracellular loop of rat CCR5 were searched in the protein database and chemically synthesized corresponding linear peptides were used as targets in biopanning. After three to four rounds of screening with Ph.D.-7 library, specific phages were collected and identified.

Results: The sequences of peptides displayed on the selected phages were GHWKVWL, HYIDFRW respectively, both of them exhibited positive in phage binding ELISA and the bound of phages and targets could be concentration-dependent and saturable.

Conclusion: Two antagonistic active peptides of CCR5 were obtained successfully, they may inhibited the physiological function of CCR5 by binding to the first and second extracellular loop and might be further used in the treatment of autoimmune diseases.

Keywords: CC chemokine receptor 5, antagonistic active peptide, phage display, rat
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IBD: East Meets West
September 11 – 12, 2015
InterContinental Shenzhen
Shenzhen, P. R. China

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