Critical Evaluation of Current Concepts and Moving to New Horizons in the Management of IBD
Critical Evaluation of Current Concepts and Moving to New Horizons in the Management of IBD
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Scientific Organization

Prof. G. Mantzaris, Athens
Prof. B.E. Sands, New York
Prof. A. Dignass, Frankfurt
Dr. S. Danese, Rozzano

Text
Christine Vetter
Specialist medical journalist
Cologne (Germany)

Cover
Confocal Microscopy of the Intestinal Epithelium by S. Schürmann, M. Waldner, M.F. Neurath and O. Friedrich, Erlangen (Germany)

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Critical Evaluation of Current Therapy Concepts and New Treatment Strategies

Introduction

In the past, significant progress has been made in unraveling the etiopathogenesis of inflammatory bowel diseases (IBD), which in turn has been marked by a change in diagnostic and therapeutic approaches of the diseases. It is therefore appropriate to evaluate existing therapeutic concepts with respect to modern evidence-based medicine. Similarly important are critical evaluations of new and emerging treatment regimens, assessment of their significance for certain treatment situations and their integration into existing treatment algorithms.

In this regard, the talks and discussions held at the Falk Symposium 196 in Frankfurt (Germany) have made a major contribution. Amongst the areas subjected to critical scrutiny were new information on the etiopathogenesis of the diseases and particularly the current and probable future role of ‘omics’ for IBD. Also, the best diagnostic and therapeutic approaches were examined from various angles and were the subject of heated debate.

The Falk Symposium 196 was extremely well attended, with 660 physicians and scientists from 51 nations – and the lively discussions of the scientific findings highlighted in the presentations were ample evidence of the consistently high interest in new information on the underlying causes of inflammatory bowel diseases and on evolving diagnostic and therapeutic strategies for these diseases.

Prof. Dr. Axel Dignass,
Frankfurt
New Therapeutic Strategies – Challenges in the Management of IBD

Fig. 1  Targeted therapy of the relevant mediator/trigger (A. Dignass, Frankfurt, Germany)
The recent introduction of new drugs has widened the treatment spectrum for IBD. Trends are increasingly moving towards a new approach for Crohn’s disease and ulcerative colitis known as personalized treatment. This must address new and still changing therapeutic goals because the focus for IBD is now not solely on improving laboratory values and symptoms.

What are the most important therapy goals?

- Rapid and effective treatment of inflammatory episodes
- Sustained remission
- Good quality of life and ability to work
- Therapy without side effects
- Prevention of complications
- Avoiding loss of intestinal functionality
- Surgery and avoidance of long-term therapy with concurrent side effects
- Prevention of growth failure

Instead, the goal now is sustained improvement in quality of life and a treatment which restores patients’ ability to participate without restrictions of work and social living (Fig. 2).

Things are moving in the field of IBD. Intensive research is aimed at shedding light on the causes of the diseases and their pathogenetic mechanisms, as well as at understanding the complex interaction between genetic and environmental factors, which ultimately determines the emergence of the diseases.

Fig. 2 The most important therapy goals (A. Dignass, Frankfurt, Germany)
Shift in therapeutic goals

This is accompanied at present by a shift in therapeutic goals. A few years ago, the primary aims were improved laboratory tests and alleviation of the symptoms of the diseases whereas these days, according to A. Dignass, Frankfurt (Germany), there is a greater emphasis on patient-focused goals: “We now prefer to treat the disease with a view to enabling patients to regain a normal quality of life and become socially active again without impairment of their functional activity and, as far as possible, without absence from school or work because of their disease.”

There is also a continued and very lively debate on whether complete healing of the bowel mucosa should be adopted as a valid therapeutic goal. This may well prevent later complications of the disease such as the emergence of stenosis, fistulas and also the manifestation of cancerous or dysplastic lesions in the gastrointestinal tract (Fig. 3).

Thanks to new therapeutic options, the initial attempts at personalized treatment are now capable of producing better results for the new therapy goals than in the past. A further feature is that medications already in established use for years are now being applied in a different sequential order and in new combined treatment strategies.

According to A. Dignass, the new therapeutic options also involve the combined administration of rectal and oral mesalazine, the combination of different immunosuppressants or biologics and the first personalized treatment strategies designed to suit individual patients through identifying their ideal drug concentrations and/or evaluating various risk factors (Fig. 4).

Treatment is increasing in complexity

One effect of the new therapeutic options and concepts is that treatment concepts are becoming increasingly complex and place greater demands on the treating physician.

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Mucosal healing – a worthwhile therapy goal?

- Fewer hospitalizations
- Fewer operations
- Fewer disease-associated absences from work or school
- Post-operative strategy change – endoscopy 3 – 9 months subsequent to surgery
- Specific change to prophylaxis regime

Fig. 3 Mucosal healing – a worthwhile therapy goal? (A. Dignass, Frankfurt, Germany)
This is where evidence-based therapy guidelines can help, such as those developed by national and international bodies like the German Society for Digestive and Metabolic Diseases (DGVS) and the European Crohn’s and Colitis Organization (ECCO). Such guidelines can help to ensure that most patients receive the best possible treatment.

Mainly for the benefit of patients with a severe disease course, A. Dignass also called for care by an interdisciplinary team consisting of gastroenterologists, surgeons, nutrition experts, psychologists and where necessary pediatricians and IBD nurses. This is because, from the clinical standpoint, early interdisciplinary interaction is vital for continued overall improvement of the treatment of IBD patients.

New therapeutic strategies – Do we need them?

- Large spectrum of therapeutic options
- And yet not all IBD patients achieve an ideal treatment outcome
- New therapeutic strategies lead to improved treatment
  - personalized treatment
  - new medications or improved galenic formulation of established drugs
  - combination of various drugs
  - new therapy goals, e.g. mucosal healing

Fig. 4  New therapy strategies – Do we need them? (A. Dignass, Frankfurt, Germany)
Crohn’s disease and ulcerative colitis are 2 phenotypes of inflammatory bowel diseases (IBD). They are characterized by chronic inflammation of parts of the gastrointestinal tract. Both conditions have similar pathophysiological backgrounds and clinical pictures, albeit of different intensities. According to V. De Preter, Leuven (Belgium), in both diseases the pathogenesis is determined by the interaction of genetic predisposition and environmental factors and triggered by immune responses (Fig. 5).

The role played by intestinal flora has so far been largely underestimated. According to V. De Preter, dysbiosis of the gut microbiota, for example, may have pathophysiological significance in both the manifestation and chronicity of inflammatory processes.

Alterations in the composition of gut microbiota will inevitably change metabolic activities in the microbiome, which may lead to the development of IBD. Analyzing this metabolome may therefore increase our understanding of the disease pathogenesis, as V. de Preter explained. The scientist emphasized the general significance of ‘omics’ technology, i.e. analysis of the genome, the transcriptome and also the proteome as an aid to a better understanding of the pathophysiology of chronic diseases. The metabolome is a good example of this because disturbance of the microbial colonization of the gut and the associated changes in the metabolic activity of intestinal flora combined with the genetic susceptibility of the particular patient probably activate the mucosal immune system. This can in turn trigger the induction and chronification of intestinal inflammation. „It is unclear whether the disturbance is a causal factor or whether it is more of a secondary feature,” emphasized V. de Preter.

However, it does seem at least possible to use a ‘metabolic profile’ of the microbiome to distinguish between healthy trial subjects and patients with IBD. There are also indications that this would make it possible to distinguish between the various IBD phenotypes. However, it remains unclear how specifically to interpret the data obtained in this way and also the therapeutic consequences are still a matter for discussion. „We are obviously searching for a needle in a haystack at present,” commented A. Dignass, Frankfurt (Germany), on the current state of research activities.

Fig. 5 The pathogenesis of Crohn’s disease and ulcerative colitis is determined by genetic predisposition, environmental factors and immune responses (V. De Preter, Leuven (Belgium))
**Translation – The link between genetics and the environment**

As explained by **A. Kaser**, Cambridge (Great Britain), the translation of genetic information may well also play a significant role in this, so the translation process could have crucial significance for the interaction of genetic and environmental factors.

„Translation can at least explain the sporadic disease pathogenesis,” said the clinician. This is a complex research area with underlying processes which are difficult to investigate because more than 160 gene loci are currently known to be associated with IBD.

Also, potential gene-gene interactions need to be addressed and there may be differences between Crohn’s disease and ulcerative colitis. Likewise, environmental influences may impact on cellular processes and modulate translation.

According to **A. Franke**, Kiel (Germany), this is also suggested by the marked association of IBD with autoimmune diseases such as psoriasis or ankylosing spondylitis. In this connection, genome-wide association studies (GWA) have demonstrated a close association with MHC (major histocompatibility complex) and the involvement of HLA antigens.

**Microbiome – the ecosystem in the gut**

**P. Seksik**, Paris (France), also claims that the microbiome can have an effect on pathogenesis. There is in effect what amounts to an independent ecosystem in the gut which can exert a considerable influence on its functions. After all, the human gut contains $10^{13} - 10^{14}$ bacteria plus further microorganisms, viruses and fungi, which means it has up to 10x more cells than the human body!

The intestinal flora lives in a state of symbiosis with the human host and under normal conditions seems to stabilize immunological responses. Hence, the microbiome can be seen as a type of ‘concealed organ’. There is so far only a sketchy understanding of its role and the possible consequences of dysbiosis, suggested P. Seksik.

„It is like a ‘black box’ in the gut.” Better research into human intestinal flora and into interactions between the bacteria and the human host organism could shed significant light on the pathogenesis of diseases and of IBD in particular.
Considerable progress has been made in diagnostic procedures which enable IBD to be identified and monitored as the disease progresses. Ultrasonography, a procedure gaining in significance for IBD, was given as an example of this by T. Kucharzik, Lüneburg (Germany): “However, the potentials and benefits of ultrasound examination are still often underestimated for these diseases” stated the clinician.

The non-invasive procedure is as important a diagnostic tool as magnet resonance imaging (MRI) for examining the small and large intestines of IBD patients. It now plays a significant role as a diagnostic tool for IBD in many countries. Sonography is a good means of examining the intestinal wall. The procedure delivers information on wall thickness, on the general echotexture and on structural rigidity and gives indications of prestenotic dilatation (Fig. 6).

Furthermore, vascularization and gut motility can be noted, intestinal activity can be monitored and complications of the disease such as fistula, abscesses and ileus or subileus can be detected.

CEUS – contrast-enhanced ultrasound

“Sonography is a diagnostic procedure which is easy to reproduce, can be carried out quickly and is cost-effective,” thought T. Kucharzik. “We use it in initial diagnostics as well as in the treatment and follow-up of Crohn’s disease and ulcerative colitis.” Apart from follow-up examinations, he also recommended long-term therapy monitoring and diagnostics of possible relapse. CEUS (contrast enhanced ultrasound) is a promising new procedure for the diagnosis of IBD, which makes it easier than conventional examination to detect inflammation in the gut in instances of IBD. The procedure allows abscesses in particular to be easily examined.
MRI remains the standard

However, MRI scanning continues to have a key significance, especially for IBD. H. Herfahrt, Chapel Hill (USA), stated that the procedure can be used to identify extended inflammations, structures and abscesses. A further benefit of MRI is that, unlike with computed tomography, there is no radiation exposure. According to H. Herfahrt, the procedure ought therefore to remain standard for the diagnostic identification of IBD.

It could become even more significant because MRI technology has also enhanced, which further improves the diagnostic options for IBD. Examples are MR enterography with DWI (diffusion weighted imaging) sequencing and magnetization transfer MRI (MT-MRI), a method which is currently recognized as enabling better detection of fibrotic changes.

Molecular endoscopy – a promising procedure

M.F. Neurath, Erlangen (Germany), presented molecular endoscopy as a further promising diagnostic advance. This involves microscopic tissue analysis and characterization of molecular mechanisms, for example TNF-receptor interactions and reactions during endoscopic examination. Molecular endoscopy not only allows morphology, and thus structural changes in vivo, to be visualized: “We can also examine molecular and biochemical changes on a cellular level,” says M.F. Neurath. “This opens up a whole new dimension for our diagnostic options.”

In future, it may be possible to use molecular endoscopy to predict whether patients will respond to administration of an anti-TNF-alpha antibody, for example by giving the patient an antibody during the examination and monitoring how the cells in the inflamed region react to the drug. In the view of M.F. Neurath, if apoptosis occurs immediately, the patient is likely to respond to subsequent anti-TNF treatment. If such a response is not observed, however, anti-TNF treatment is unlikely to be effective.

Observing mucosal healing in vivo?

This approach involves immunoendoscopy, a method currently the focus of intensive development work. The aim is even better resolution to allow differentiation between cell populations such as epithelial cells or immune cells. Making even cytokins, cytokin receptors and adhesion molecules visible seems to be a reasonable proposition, said M.F. Neurath. If this was successful it would open up completely new opportunities for IBD diagnostics and therapy monitoring including even the ability to observe mucosal healing.

IBD patients may benefit considerably if new imaging techniques become an integral part of clinical routine. In the opinion of G. Rogler, Zürich (Switzerland), what needs to be settled now is how the new options can become part of clinical routine and the timing and type of the ideal procedure to be applied. It is doubtless true that initially the new diagnostic options will be restricted to specialist centers. Even so, they open up further options for better identification of the clinical picture of specific IBD cases and so will help pave the way towards personalized therapy for Crohn’s disease and ulcerative colitis.
In addition to advances in diagnostics, intensive efforts are being made to develop therapeutic options for IBD. Patients with complicated disease courses are often difficult to treat using conventional procedures, so this is why efforts are also being directed at developing and establishing completely new treatment strategies, such as the transplantation of hematopoietic or mesenchymal stem cells or ex vivo expansion of regulatory T-cells, explains Prof. M. Allez, Paris (France).

Clinical trialing of stem cell transplantation in Crohn’s disease

While stem cell transplantation is already an established treatment method for oncological diseases, it could also be significant for treating IBD. Autologous stem cell transplantation for Crohn’s disease patients, for example, is a realistic option as part of the ASTIC trial (Autologous Stem cell Transplantation International Crohn’s Disease Trial).

Medication versus surgery

Even if these new options become established for drug treatment in the future, surgery will remain just as important for the treatment of IBD. Although medication is usually the preferred treatment method for patients with uncomplicated disease course, patients that develop complications, such as abscesses or perforations, have no other choice in the future than to undergo surgery, says Prof. A. D’Hoore, Leuven (Belgium).

What to do in the event of dysplasias?

A. Sturm, Berlin, cautioned that patients with IBD are also more at risk of developing dysplasias and carcinomas (Fig. 7). Particularly patients with ulcerative colitis, who have an increased risk of adenocarcinoma of the large bowel, should be monitored regularly for dysplastic lesions. These will be heterogeneous changes, with flat dysplasias in particular posing a significant risk of progression. This applies in particular to high-grade dysplasias. In almost 50% of cases, they lead to the development of adenocarcinoma so that if findings indicate this, proctocolectomy should be considered. However, if low-grade dysplasia is diagnosed, it is
generally sufficient to conduct a complete polypectomy with appropriate bioptic examination of the surrounding area.

According to A. Windsor, London (Great Britain), proctocolectomy should also be considered for atypical dysplasia-associated lesion (DALM), because DALM constitutes a heterogeneous group of lesions carrying varying degrees of carcinoma risk. “We can resect this carcinoma risk,” emphasized the clinician.

In this connection, it is worth considering that it is not only the disease itself but also the immunosuppressive treatment that promotes carcinogenesis. In the view of J.F. Colombel, New York (USA), the problem is absolutely relevant because opinions are increasingly being voiced in favor of applying therapies with immunosuppressive effect at already quite early stages of the disease.

Furthermore, with regard to such treatment options, J.-F. Rahier, Yvoir (Belgium), called for awareness of the risk of infection associated with immunosuppression including even the potential development of opportunistic infections: “The challenge for IBD management does not only consist in treating the disease but also in being aware of, recognizing and treating any such complications.” Infections generally develop in patients through the interaction of various different risk factors.

This is why it is important to inquire about prior serious infections before treatment starts and to rule out active or latent tuberculosis. It is also important to advise patients sufficiently on vaccinations and on precautions against infection when traveling, for example. Patients must be aware of the high risk of infection when they take immunomodulators.

Fig. 7 Dysplasia in ulcerative colitis (A. Sturm, Berlin, Germany)
Immunosuppression in IBD: Azathioprine reassessed

L. Beaugerie, Paris (France), believed that the safety of immunosuppressive treatment strategies is of paramount importance in the therapy management of IBD patients. This applies not only when prescribing biologics, but also when treating with thiopurines, which may increase the risk of infection and developing portal hypertension. Also, the risk of skin cancer is increased in patients receiving such therapy. “Patients must be made thoroughly aware of this and advised to protect themselves against the sun” explained the gastroenterologist.

Azathioprine – an established place in the treatment algorithm

In the view of P. Irving, London (Great Britain), this is all the more true since thiopurines, because of their delayed onset of effect, are usually administered on a long-term basis as maintenance therapy rather than for remission induction. Substances such as azathioprine have an established place in the IBD treatment algorithm, as demonstrated by the simple fact that the risk of relapse increases significantly if the treatment is discontinued. The active ingredient is effective in the maintenance of medically or surgically induced remission, particularly in patients with Crohn’s disease, and can be prescribed either as a monotherapy or in combination with other drugs. In addition, it can play an important role in inducing mucosal healing and reducing the necessity for surgical procedures.

However, an accurate indication of treatment is vital, says Prof. E.F. Stange of Robert-Bosch-Krankenhaus, Stuttgart (Germany). Both mercaptopurine and azathioprine are the “backbone” of maintenance treatment for Crohn’s disease and, albeit to a lesser extent, for ulcerative colitis. There is a clear indication for them in patients with steroid dependency. Another recent indication for thiopurine is to support the therapeutic effect of biologics and prevent the formation of antibodies.

Because of the increased side effect risk, azathioprine should not be administered to patients with low enzymatic activity of thiopurine methyltransferase (TPMT) (Fig. 8). E. F. Stange cited methotrexate, though rarely used for IBD, and cyclosporine and tacrolimus as alternative therapies in individual patients.
The subject of the Special Lecture, given by D.K. Podolsky, Dallas (USA), was 'The future of academic gastroenterology'. Here the claim was made that clinical efficacy and the risk of side effects of a medication had long since ceased to be the sole criteria underpinning therapy decisions. Increasingly, the costs and cost efficiency of a medication are playing a major role. This affects gastroenterology just as much as other medical specialties.

According to D.K. Podolsky, more specialization can be observed in centers, with the academic centers providing key initiatives for patient care and disease management. He also cited genome profiling and the integration of the internet and e-health in the field of disease and therapy monitoring as vital trends in medicine (and therefore also in gastroenterology), which he expects to become even more important in the future.

Apart from that, proactive preventive efforts will in future need to play a much greater role in disease management. He expects the entire healthcare system to be dominated by prevention. This will necessitate more interdisciplinary action and greater patient involvement as well as new technological possibilities like networking and setting up video conferences, in patients’ sick bays, for example.

Excellent posters

3 poster prizes were awarded at the Falk Symposium 196 in Frankfurt, Germany:

The first prize was awarded to K. Papamichail, Leuven (Belgium), for his work on the significance of early trough concentration of infliximab in further ulcerative colitis treatment plans.

The second prize went to Dr. M. Cintolo, Messina (Italy) for his analysis of risk factors for treatment-associated side effects and infections in older IBD patients.

The third prize went to T. Karrasch, Giessen (Germany), for his research on the role of adipokine expression in visceral adipose tissue using an IBD mouse model.

From left to right: Dr. R. Greinwald, Falk Foundation e.V., prize winner, Prof. A. Dignass, Frankfurt, Germany
New treatment strategies are paving the way to targeted, personalized IBD treatment. However, interesting developments should not obscure the fact that the majority of IBD patients can be adequately treated with conventional treatment regimens, emphasized Professor Dr. Axel Dignass, Frankfurt (Germany). At the Falk Symposium 196, he explained what we need to take on board as regards treatment and what advances we can expect.

Editor: Professor Dignass, has progress been made in the diagnosis and treatment of inflammatory bowel diseases?

Professor Dignass: In recent years, we have in fact made significant progress in the treatment of Crohn’s disease and ulcerative colitis. There are now medications with targeted mechanisms of action which we are continuously learning to understand better – anti-TNF therapies, for instance. Also, the first anti-adhesion molecule for the treatment of inflammatory bowel diseases has just been approved in Europe and the US about a year ago. This has considerably expanded the options for IBD management compared with what used to be available.

Editor: Do all IBD patients benefit from this progress?

Professor Dignass: It does not make sense for all patients to be treated with these new medications. On the contrary – the majority of IBD patients can be treated adequately with conventional drugs, ones with which we already have decades of experience. For example, 60% of ulcerative colitis patients respond well to once-daily dosing of mesalazine. Acute flare-ups can normally be controlled through the short-term administration of corticoids. However, of course, there are patients, in whom we cannot keep the disease activity under control with these established drugs. These are candidates for the new therapy options. With Crohn’s disease, about 25% of patients need no treatment or only mesalazine to manage
the disease, about 40% – 50% need a short-term course of systemically acting steroids and only about 40% – 50% need to be treated with other therapeutic agents such as azathioprine and/or anti-TNF antibodies or anti-adhesion molecules. Ultimately, there are only 15% to 25% of patients at most with inflammatory bowel diseases who do not respond well to these strategies and for whom there is an urgent need for other new therapy options.

Editor:
Will developments continue to make further progress?

Professor Dignass:
Yes, we can expect that because pharmaceutical manufacturers have further innovations in their pipelines. However, it is too soon to say which ones will enter the market, and when. Work is in progress, not only on the development of new drugs, but also on improving the galenic formulation of conventional substances. However, it remains to be seen what the innovations can actually achieve in clinical routine, because controlled studies do not always necessarily reflect routine therapeutic experience. To what extent a new medication is actually an improvement for patients often cannot be appreciated until it is used in normal practice.

Editor:
Which avenues of research are most expected to deliver progress?

Professor Dignass:
Many aspects of IBD are being researched. We are particularly hopeful that research into the role of the microbiome will advance understanding of the disease and aid the development of new treatment regimens. We know that gut bacteria have their own metabolism and we are well on the way to understanding this feature, known as the metabolome, and to making good therapeutic use of the interactions. Furthermore, it has recently been discovered that a barrier defect is involved in the pathogenesis of ulcerative colitis. The initial findings of clinical studies on phosphatidylcholine indicate that this substance can remedy the barrier defect. We are also working intensively to find out which mechanisms trigger the disease process in which patients, which will allow us to establish targeted therapy.

Editor:
Does this mean that personalized treatment is the aim here?

Professor Dignass:
We are already striving to provide personalized treatment in every case by trying to establish the optimal therapy for each patient. We could increase our future success if we deepened our understanding of how the microbiome changes in each patient and analyzed the expression profiles of cytokines more thoroughly, allowing us to see which cytokine is deregulated in each case. For example, there are ways of testing whether and where increased amounts of TNF-alpha are produced in tissue. It is also possible to test locally whether a particular patient responds or not to anti-TNF drugs. This makes it possible in an individual case – and probably within the foreseeable future – to assess before treatment starts whether or not treatment with TNF antibodies would be useful. This knowledge represents an important step towards targeted, personalized IBD treatment.

Editor:
Are there currently ways of optimizing IBD treatment?

Professor Dignass:
It is important that we use current treatment options optimally, i.e. as instructed in the guidelines. In many cases, however, treatment is still not administered according to these guidelines, which means that the recommended algorithm is not always followed and the optimal drug dosage is not always selected. All too often, patients are still not prescribed the active pharmaceutical ingredient most suitable to them. This is why we are urging all patients with Crohn’s disease or ulcerative colitis that cannot be completely controlled with conventional treatment to visit a specialist center.

Professor Dignass,
thank you very much for the interview.
Treatment of IBD – are established methods still good enough?

On the one hand, therapy for inflammatory bowel diseases must ensure that the newly developed treatment advances benefit patients requiring therapy escalation. On the other hand, however, patients with a good response to the conventional regimens should not be over-treated to avoid an unnecessarily high risk of side effects. Hence the central topic of a press conference held during the Falk Symposium 196 in Frankfurt (Germany) was the question of which patient would benefit from which therapy.
There is wide variety of drugs for the treatment of inflammatory bowel diseases. Treatment options range from established substances like mesalazine and steroids to azathioprine, anti-TNF-inhibitors and – more recently – anti-adhesion molecules.

Substances like mesalazine and steroids are also available in a variety of galenic formulations, which provides additional opportunities for individualizing treatment (Fig. 9).

“The point is to administer the right medication to the right patient at the right time and in the right dosage,” emphasized A. Dignass.

Medication-based IBD therapy must also be integrated into the overall treatment concept, which should also include nutrition and supportive therapies.

When evaluating the various treatment options it is essential to be aware of whether the medication acts topically or systemically.

Whenever possible, topical efficacy – i.e. at the site of the inflammation – should be the preferred option as it keeps the risk of systemic side effects particularly low.

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**Fig. 9** Medication and surgery therapy options for IBD (A. Dignass, Frankfurt, Germany)

**Conventional therapy of IBD**

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<th>5-ASA derivatives</th>
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<td>others</td>
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**Supportive therapy**

- Loperamide
- Cholestyramine
- Spasmolytics
- Pain medication
- Vitamins

**Nutrition therapy**

- parenteral
- enteral

**Immunomodulators and Biologics**

- Azathioprine/6-MP
- MTX
- Infliximab/Adalimumab/Certolizumab
- Vedolizumab
- Cyclosporine/Tacrolimus

**Antibiotics/Probiotics**

- Ciprofloxacin
- Metronidazole
- ECN/VSL
- others

**Treatment goals**

<table>
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<th>Symptoms</th>
<th>Quality of life</th>
<th>Prognosis</th>
<th>Cure</th>
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**Surgery**

Strictures, neoplasia, refractory disease, therapy-associated side effects

**Fig. 10** IBD and new therapy strategies – Is the established option still good enough? (W. Kruis, Cologne, Germany)
Topical or systemic efficacy?

Topical efficacy can also be produced by medications that are administered orally or rectally, as these terms merely describe the route of administration. Other routes of administration are intravenous, intramuscular or subcutaneous (Fig. 11).

However, the route of administration does not necessarily have an impact on whether a substance acts systemically or locally. For example, drugs such as mesalazine and budesonide are administered both orally and rectally, but always take clinical effect locally, i.e. topically. They take effect directly on the inflamed mucosa and then are largely metabolized in the gut and/or liver before they enter the systemic circulation.

This is not the case for azathioprine, prednisolone and biopharmaceuticals, which tend to work systemically. In A. Dignass’ opinion, the release profiles of active ingredients like mesalazine, which primarily depends on the galenic formulation, make them suitable for use as a targeted therapy. Mesalazine granules containing a galenic formulation that combines an Eudragit shell with a matrix core (such as Salofalk® Granules) are significantly more effective in inducing remission in patients with ulcerative colitis than Eudragit-L-coated mesalazine without a matrix core (such as Salofalk® Tablets), which produces a stronger effect in the terminal ileum.

For the majority of patients conventional regimes are sufficient

Mesalazine is a good example of the fact that many patients can be treated with modern strategies such as targeted, personalized therapy for Crohn’s disease and ulcerative colitis using conventional therapeutics. For example, as reported by W. Kruis, Cologne (Germany), good disease management can be achieved for the majority of patients using long-established therapy options.

For ulcerative colitis, mesalazine is indisputably the first-line treatment. Steroids are administered when mesalazine does not induce remission on its own.

The importance of mesalazine in the treatment of patients with Crohn’s disease, which is generally primarily treated with steroids, is continually under discussion. However, this does not mean that mesalazine is not of therapeutic importance. On the contrary – “A glance at prescription statistics shows that this drug stands in second place,” emphasized W. Kruis (Fig. 12). This reflects the great importance of this established substance for the daily clinical treatment of patients with Crohn’s disease.

Study outcomes confirm a number-needed-to-treat (NNT) of only 6 for the administration of mesalazine in a dosage regime of more than 1.5 g/day for Crohn’s disease. “That’s something our colleagues in cardiology can only dream of achieving with conventional treatment methods used in that area,” says Prof. Kruis.

Significance of biologics is overestimated

The usual treatment for remission maintenance in chronic active disease progress is the immunosuppressive agent azathioprine. Current data demonstrate that azathioprine can improve prognosis.

“In the long term, patients treated this way less commonly develop fistulas and stenosis and also colon carcinoma,” emphasized W. Kruis. According to W. Kruis, the significance of biologics is overestimated with regard to IBD.

These were only indicated, he claimed, if a satisfactory therapy outcome could not be achieved with conventional strategies. “Scant attention is paid to the fact that, regrettably, after monotherapy with anti-TNF antibodies, the optimal therapy outcome is not achieved for around 70% of patients with a serious disease history over a year.”

It is such findings that underscore the need for further advances in the treatment of IBD, stated A. Dignass. By way of example, he cited combining rectal and oral therapies and combining various immunosuppressants or also immunosuppressants plus biologics.
Phosphatidylcholine in clinical studies

The therapeutic options for Crohn’s disease and ulcerative colitis can be expected to expand still further in the future.

For example, phosphatidylcholine, a drug currently undergoing clinical development, should improve the mucosal barrier in ulcerative colitis (Fig. 13). This is because the recorded evidence shows that there is less of this substance in the intestinal mucus of patients with ulcerative colitis.

One therapeutic goal consists in balancing out the lack of phosphatidylcholine in the colon of patients in order to stabilize the mucosal barrier. This concept works, as is shown by the initial success of the substance currently being trialed in the phase III-study PROTECT. Provisional findings indicate that remarkable therapy outcomes can be achieved, particularly with ulcerative colitis.

Despite the development of further novel therapy options such as, for example, anti-adhesion strategies, A. Dignass still believes that treatment concepts for IBD are becoming significantly more complex.

Less phosphatidylcholine (PC) is present in the intestinal mucus of patients with ulcerative colitis. Substituting the lack of PC in the colon boosts the PC concentration and stabilizes the mucosal barrier.
Factors influencing pharmacokinetics and biologics

Genetics and body weight, comorbidities, the degree of severity of the disease and its type are amongst the most important influencing factors. It may be assumed that clearance in IBD is 40% – 50% higher than with other conditions such as rheumatoid arthritis, for example.

According to F. Baert, Roeselare (Belgium), the development of antibodies against the biologic, which may restrict its clinical efficacy or even compromise it completely, is a key factor. Whether or not antibodies against the monoclonal antibody are produced, depends partly on when and how the medication is prescribed.

Strategies against antibody production

The risk is particularly high if comparatively low concentrations of biologics are administered early on in the disease course. It seems to be more effective if the initial dose of the drug is high since the chances of inducing long-term remission or even mucosal healing are better. According to W.J. Sandborn, La Jolla (USA), the opposite is the case with high antibody levels, which are associated with a lower response rate and a therapy response of shorter duration. Which is why every effort should be taken to counteract the formation of antibodies against infliximab and adalimumab.

This could be supported by a consistent maintenance therapy without ‘drug holidays’, concurrent treatment with immunosuppressants such as azathioprine, and premedication with steroids administered intravenously.

Biosimilars pushing into the market

This problem is likely to become even more relevant in future as biologics have been in use for 15 years now and patent protection for some drugs has already expired. The first biosimilars have already been licensed. “These preparations are neither better than, nor identical to, existing drugs,” reported F. Gomollón, Zaragoza (Spain).

Biosimilars are ‘copy-cat’ products produced by biological systems and possibly entailing a certain biological variability compared with the original preparation. This means that the preparations, unlike generics, are not identical to the original but only biologically similar. Their biosimilarity must be documented in one clinical study, though it can then be extrapolated to other indications.

The advantage of biosimilars lies essentially in the fact that the medication is generally significantly more affordable than the original preparation.
Session VI

New treatment strategies

According to P. Michetti, Lausanne (Switzerland), the problem of relapses in patients with Crohn’s disease following surgery has yet to be solved. “A large proportion of patients experiences relapses after surgery and, in many cases, this happens comparatively quickly.”

Postoperative prophylaxis in Crohn’s disease

Around 70% of Crohn’s patients will require an intestinal resection during the course of the disease, with one in two patients needing a second operation at some point. “Approx. 60% of patients redevelop Crohn’s disease within just a year of surgery,” remarks Prof. Michetti.

Is there also a ‘window of opportunity’ with Crohn’s disease?

In the view of L. Peyrin-Biroulet, Nancy (France), a treatment goal for Crohn’s disease could be mucosal healing. In this connection, he advocated the consistent use of biologics and anti-adhesion molecules such as vedolizumab and also natalixumab known from the treatment for multiple sclerosis.

This is because it can be assumed that just as with multiple sclerosis and rheumatoid arthritis there is also a ‘window of opportunity’ with Crohn’s disease with a particularly positive potential to influence the future course of the disease through consistent management.

‘Treat to Target’ also with IBDs

Unlike with many other diseases, the ‘treat to target’ treatment concept has so far not been created for IBD. There is still no firm description of clear treatment goals with precisely defined end points such as HbA1c for diabetes, the activity index for rheumatoid arthritis or the target blood pressure value for hypertension.

And yet according to S.B. Hanauer, Chicago (USA), there are definite points of comparison between these disorders. IBD and diabetes are alike in that they are both diseases with a chronically progressive course, with a high risk of later complications if consistent treatment is not applied right from the start.

So a ‘treat to target’ concept is important to institute good disease management at an early stage and so minimize the risk of complications.

Therefore, we should not shy away from early treatment with biologics, especially since the drugs can always be discontinued once the treatment goal has been achieved. However, emphasized E. Louis, Liège (France), if a repeat administration of a biologic is necessary later, its efficacy will be improved if the substance is combined with an immunosuppressant such as azathioprine.
**Session VII**

**Novel therapy options for inflammatory bowel diseases**

**Novel therapy options for IBD**

As a current therapy strategy for mild to moderate ulcerative colitis, B. Siegmund, Berlin (Germany), cited mesalazine for which oral and/or rectal administration should be considered depending on the disease site. If mesalazine as a monotherapy is not successful, then steroids are indicated.

**Phosphatidylcholine – hope for a new therapy option for ulcerative colitis**

If mesalazine is not tolerated, the alternative indication is administration of E. coli Nissle 1917. The Berlin-based clinician also pointed out that the treatment options for ulcerative colitis are likely to expand in the foreseeable future since a new therapy option in the form of phosphatidylcholine is at the clinical development stage. The initial findings look very promising (Fig. 14 and 15).

Gastroenterologists are also hopeful for further new therapy options currently the object of intensive development work. B.E. Sands, New York (USA), quoted the example of anti-interleukin antibodies such as the drug ustekinumab, which acts against IL-12 and is already applied for treating psoriasis.

Ustekinumab also seems to be effective against Crohn’s disease, as initial studies document. However, the risk/benefit profile of the drug still needs to be corroborated by further studies. In the view of B.G. Feagan, Ontario (Canada), this applies just as much to the anti-adhesion molecule, which is currently still at clinical development stage (Fig. 16).

In the view of P. Marteau, Paris (France), the therapeutic value of drugs directed at influencing intestinal flora has ultimately not been clarified. He quoted the example of probiotics, prebiotics and antibiotics such as rifaximin.

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**Anti-interleukin therapy – continued review of the risk/benefit profile**

**Fig. 14**

**Fig. 15**
Also, the therapeutic possibilities of a stool transplant, a procedure which repeatedly makes attention-grabbing headlines, have so far not been identified for IBD.

**Summary for clinical practice**

Despite all the potential new therapy options, it is always the complex pathogenesis of IBDs that needs addressing, cautioned G.J. Mantzaris, Athens (Greece), in his concluding summary of the Falk Symposium (*Fig. 17*). There is indeed cause for hope in many areas for new treatment options and hence expansion of the therapeutic repertoire, yet the innovations need to be scrupulously and critically evaluated. In addition, there is a need for accurate analysis of which patients can benefit from the new options.
In discussions on treatment for inflammatory bowel diseases, C. Fiocchi, Cleveland (USA), has repeatedly noted the key phrase ‘personalized therapy’. But there is no precise definition of this term.

If it is taken very narrowly, treatment should be geared to the genetic make-up of the patient, a requirement not yet established for IBDs. But that does not mean that treatment should not be tailored to the individual situation of the patient.

However, it would be helpful to have a better classification of patients according to therapy-relevant characteristics (Fig. 18). Here, epigenetic influences may certainly be significant because they can play a major role in determining how the disease progresses.

Also, the influencing factors do not have a constant weighting but may well change throughout a lifetime. C. Fiocchi highlighted this by taking the example of the microbiome. The composition of intestinal flora can vary according to the age of the individual (Fig. 19), a fact which may impact on disorders such as Crohn’s disease and ulcerative colitis and so may well have therapeutic implications as well.

Personalized therapy for IBDs in the narrow sense is currently still only a pipe dream. It would need specific knowledge of the genome, the exposome, the microbiome, the immunome and, of course, of the interactions between these ‘omes’ (Fig. 20).

This makes the nexus of interrelations unimaginably large. It has also not been possible so far to elicit the key mechanisms which trigger the intestinal inflammation in a particular case. But that would be an essential premise for any tailored, personalized treatment.

Fig. 18 Patient classification – Role of epigenetic influences (C. Fiocchi, Cleveland, USA)
Environment

Continuos dynamic changes of gut microbiome composition

Risk of IBD

Fig. 19  Age-dependent change in intestinal flora (A. Fiocchi, Cleveland, USA, mod. by S. Duncan & H. Flint. Maturita. 2013;75:44–50)

Fig. 20  Interactions between the ‘omes’ (A. Fiocchi, Dig Dis. 2014;32(Suppl1):96–102)

The IBD interactome:
a network of positive and negative ‘omes’ interactions

Chronology of the gut microbiota in the human lifeline

Continuos dynamic changes of gut microbiome composition

Environment

Risk of IBD

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Fig. 20  Interactions between the ‘omes’ (A. Fiocchi, Dig Dis. 2014;32(Suppl1):96–102)
Speakers, moderators and scientific organizers

Prof. Dr. Matthieu Allez  
Hôpital Saint-Louis  
Service de Gastroentérologie  
1 Ave. C. Vellefaux  
75010 Paris  
France  
matthieu.allez@gmail.com

Prof. Dr. Gert van Assche  
University Hospital Leuven  
Gastroentérologie  
Herestraat 49  
3000 Leuven  
Belgium  
gert.vanassche@uz.kuleuven.ac.be

Dr. Filip Baert  
Heilig Hart Ziekenhuis  
Gastroenterologie  
Wilgenstraat 2  
8800 Roeselare  
Belgium  
fbaert@hhr.be

Prof. Dr. Laurent Beaugerie  
Hôpital Saint Antoine  
Department of Gastroenterology  
184, Rue du Faubourg St.-Antoine  
75012 Paris  
France  
laurent.beaugerie@sat.aphp.fr

Jean-Frederic Colombel, M.D.  
Professor of Medicine  
Mount Sinai School of Medicine  
Gastroenterology & Hepatology  
One Gustave L. Levy Place  
New York NY 10029  
USA  
jean-frederic.colombel@mssm.edu

Dr. Silvio Danese  
Istituto Clinico Humanitas IRCCS  
IRCCS in Gastroenterology  
Via Manzoni, 56  
20089 Rozzano  
Italy  
sdanese@hotmail.com

Prof. Dr. André D’Hoore  
University Hospital Leuven  
Dept. Abdominal Surgery  
Herestraat 49  
3000 Leuven  
Belgium  
andre.dhoore@uz.kuleuven.ac.be

Prof. Dr. Axel Dignass  
Medizinische Klinik I  
Agaplesion Markus Krankenhaus  
Wilhelm-Epstein-Str. 4  
60431 Frankfurt  
Germany  
axel.dignass@fdk.info

Dr. Brian G. Feagan  
Robarts Clinical Trials Inc  
Robarts Research Institute  
University of Western Ontario  
100 Perth Drive, PO Box 5015  
London, Ontario N6A 5K8  
Canada  
brian.feagan@robartsinc.com

Claudio Fiocchi, M.D.  
Professor of Medicine  
The Cleveland Clinic Foundation  
Lerner Research Institute  
Pathobiology / NC 22  
9500 Euclid Avenue  
Cleveland OH 44195  
USA  
fiocchc@ccf.org

Prof. Dr. Andre Franke  
Klinische Molekularbiologie  
Christian-Albrechts-Universität  
Schittenhelmstrasse 12  
24105 Kiel  
Germany  
a.franke@mucosa.de

Dr. Fernando Gomollón  
Hospital Clínico Universitario  
Losano Blesa  
Avenida San Juan Bosco 15  
50009 Zaragoza  
Spain  
fgomollon@telefonica.net
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FALK FOUNDATION e.V.
Leinenweberstr. 5
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Germany
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Stephen B. Hanauer, M.D.
Professor of Medicine
Northwestern University
Gastroenterology Section
Digestive Health Center
676 North St. Clair Street
Chicago IL 60611
USA
shanauer@northwestern.edu

Prof. Dr. Franz Hartmann
AGAPLESION MVZ am
AGAPLESION Markus Krankenhaus
Wilhelm-Epstein-Straße 4
60431 Frankfurt
Germany
hartfra@me.com

Hans Herfarth, M.D.
Professor of Medicine
University of North Carolina
Gastroenterology & Hepatology
4151 Bioinformatics Bldg.
130 Mason Farm Road
Chapel Hill NC 27599-7080
USA
hherf@med.unc.edu

Dr. Peter Irving
Guy’s and St. Thomas’ Hospital
Department of Gastroenterology
First Floor College House
North Wing, St. Thomas’ Hospital
Westminster Bridge Road
London SE1 7EH
Great Britain
peter.irving@gstt.nhs.uk

Prof. Dr. Arthur Kaser
University of Cambridge
Addenbrooke’s Hospital
Division of Gastroenterology & Hepatology
Hills Road
Cambridge CB2 0QQ
Great Britain
ak729@cam.ac.uk

Prof. Dr. Wolfgang Kruis
Innere Medizin
Evang. Krankenhaus Kalk
Buchforstrstr. 2
51103 Köln
Germany
kruis@evkk.de

Prof. Dr. Torsten Kucharzik
Allgemeine Innere Medizin
Klinikum Lüneburg
Bögelstr. 1
21339 Lüneburg
Germany
torsten.kucharzik@klinikum-lueneburg.de

Prof. Dr. Peter L. Lakatos
Semmelweis University
Medical School
I Department of Medicine
Koranyi u. 2/a
1083 Budapest
Hungary
lakatos.peter_laszlo@med.semmelweis-univ.hu

Prof. Dr. Edouard Louis
C.H.U. Sart Tilman
Gastroentérologie
Domain du Sart Tilman
4000 Liège
Belgium
edouard.louis@ulg.ac.be

Prof. Dr. Fernando J. Magro Dias
Hospital de S. João
Servico de Gastroenterologia
Av. Prof. Hernani Monteiro
4200-319 Porto
Portugal
fm@med.up.pt

Prof. Dr. Gerassimos J. Mantzaris
Evangelismos Hospital
Dept. of Gastroenterology
45-47, Ypsilantou str., Kolonaki
106 76 Athen
Greece
gjmantzaris@gmail.com

Prof. Dr. Philippe Marteau
Lariboisière Hôpital
Service d’Hépato-Gastroenterologie
2, rue Ambroise Paré
75010 Paris
France
philippe.marteau@lrb.aphp.fr
Gut-Liver Interactions:
From IBD to NASH

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Congress Innsbruck
Rennweg 3
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Scientific Organization
A. Kaser, Cambridge (Great Britain)
M. P. Manns, Hannover (Germany)
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H. Tilg, Innsbruck (Austria)
M. Trauner, Vienna (Austria)
Prof. Dr. Pierre Michetti  
La Source-Beaulieu  
Gastroentérologie  
Avenue Jomini 8  
1004 Lausanne  
Switzerland  
pmichetti@gesb.ch

Diane R. Mould, Ph.D.  
Projections Research Inc.  
535 Springview Lane  
Phoenixville, PA 19460  
USA  
drmould@pri-home.net

Prof. Dr. Markus F. Neurath  
Medizinische Klinik 1  
Universitätsklinikum Erlangen-Nürnberg  
Ulmweg 18  
91054 Erlangen  
Germany  
markus.neurath@uk-erlangen.de

Prof. Dr. Laurent Peyrin-Biroulet  
Hôpitaux de Brabois  
C.H.U. de Nancy  
Dept. of Hepato-Gastroenterology  
Allee du Morvan  
54511 Vandoeuvre-Nancy  
France  
peyrinbiroulet@gmail.com
Prof. Dr. Dr. Gerhard Rogler  
Universitätsspital Zürich  
Klinik für Gastroenterologie & Hepatologie  
Rämistrasse 100  
8091 Zürich  
Switzerland  
gerhard.rogler@usz.ch

William J. Sandborn, M.D.  
Professor of Medicine  
UCSD School of Medicine  
Division of Gastroenterology  
Building UC 303, Room 220  
9500 Gilman Drive  
La Jolla CA 92093  
USA  
wsandborn@ucsd.edu

Bruce E. Sands, M.D.  
Professor of Medicine  
Mount Sinai School of Medicine  
Department of Gastroenterology  
One Gustave L. Levy Place  
New York NY 10029  
USA  
bruce.sands@mssm.edu

Prof. Dr. Jürgen Schölmerich  
Klinikum der Johann Wolfgang Goethe-Universität Frankfurt  
Theodor-Stern-Kai 7  
60596 Frankfurt  
Germany  
aed@kgu.de
Prof. Dr. Philippe Seksik
Gastroenterology and Nutrition Department
Hôpital Saint Antoine, AP-HP
Paris
France
philippe.seksi@sataphp.fr

Prof. Dr. Britta Siegmund
Gastroenterologie
Charité Universitätsmedizin
Campus Benjamin Franklin (CBF)
Hindenburgdamm 30
12203 Berlin
Germany
britta.siegmund@charite.de

Prof. Dr. Andreas Stallmach
Gastroenterologie/Hepatologie
Klinikum der
Friedrich-Schiller-Univ. Jena
Erlanger Allee 101
07747 Jena
Germany
andreas.stallmach@med.uni-jena.de

Prof. Dr. Eduard F. Stange
Innere Medizin I
Robert-Bosch-Krankenhaus
Auerbachstr. 110
70376 Stuttgart
Germany
eduard.stange@rbk.de

Prof. Dr. Dr. Jürgen M. Stein
MVZ Immunologie
Schifferstraße 59
60594 Frankfurt
Germany
j.stein@em.uni-frankfurt.de

Prof. Dr. Andreas Sturm
Innere Medizin/Gastroenterologie
DRK-Kliniken Westend
Spandauer Damm 130
14050 Berlin
Germany
a.sturm@drk-kliniken-berlin.de

Dr. Alastair Windsor
Department GI Surgery
University College Hospitals London
250 Euston Road
London NW1 2BU
Great Britain
alwindsor@aol.com
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FALK FOUNDATION e.V.
Leinenweberstr. 5
79108 Freiburg
Germany

Congress Department
Tel.: +49 (0)761/1514-125
Fax: +49 (0)761/1514-359
E-Mail: symposia@falk-foundation-symposia.org
www.falk-foundation-symposia.org