CDDW DIGEST

Proceedings from the 2012 Canadian Digestive Diseases Week and the Annual CASL Winter Meeting

Nutrition & Probiotics

WELCOME LETTER

Dear Colleagues,

We are pleased to introduce the inaugural issue of ***CDDW Digest***, the proceedings publication from the 2012 CDDW/CASL Winter Meeting. Our hope is to provide clinically relevant coverage of key sessions in liver disease, as well as nutrition and probiotics.

In this section, we invite you to read some of the latest advances and clinical findings in the areas of nutrition and probiotics. Highlighted is the role of the gut microbiome in human health and disease, with a particular emphasis on the therapeutic use of probiotics.

We hope you enjoy this report and find it an informative resource.

Dr. Dan Sadowski
Co-Chair, CDDW 2012

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ROLE OF THE GUT MICROBIOME IN HUMAN HEALTH AND DISEASE

During the 2012 Canadian Digestive Diseases Week (CDDW) the role of the gut microbiome in human health and disease was discussed. The microbial community residing in the intestinal tract is a delicate balance of beneficial and potentially harmful microbial species (Figure 1). There is increasing recognition that dysbiosis, or alterations of this gut microbiome, may be implicated in bowel disease, obesity, and some behavioural abnormalities.

Dr. Alain Stinzi (University of Ottawa) discussed the role of the gut microbiota in inflammatory bowel disease (IBD), acknowledging the reduced microbial diversity observed in patients with IBD compared to healthy mice. Evidence from mouse models of colitis suggests that alterations of the gut microbiome are not a consequence of inflammation, but in fact contribute to the development of colitis. Additionally, the development of colitis was found to be dependent upon the host genotype. Interestingly, the subset of commensal bacteria, which was implicated in colitis development in the mouse, is also present in healthy individuals, highlighting the importance of investigating the role of microbes that are conserved between healthy and disease states, and not just those that are differentially abundant.

PROBIOTICS FOR THE MANAGEMENT OF IBD

The topic of restoring the balance of the gut microbiome is gaining considerable attention as a therapeutic approach for IBD, particularly through the use of probiotics. Probiotics, as defined by the World Health Organization (WHO), are live microorganisms, which when administered in adequate amounts, confer a health benefit to the host. At the 2012 CDDW, the current evidence regarding the efficacy of probiotics as a therapeutic option for IBD was discussed during a small, interactive group session led by **Dr. Elena Verdú** (McMaster University) and **Dr. Philip Sherman** (University of Toronto).

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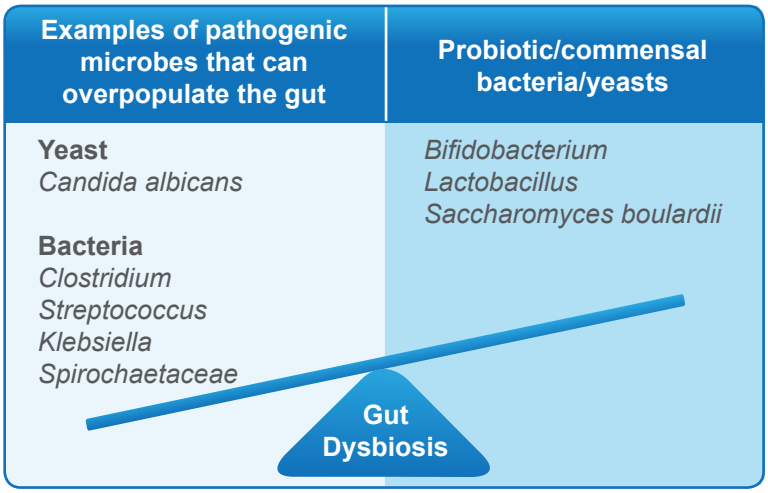
Figure 1: Gut dysbiosis. The microbial community residing within the gut is a delicate balance of beneficial and potentially harmful bacteria. Depicted are examples of pathogenic and commensal bacteria or yeast that reside within the gut, that could contribute to gut dysbiosis.



Probiotics have been shown to increase microbial diversity in the gut, and early trials have reported beneficial effects in patients with IBD. However, many unanswered questions remain regarding their usage. During this session there was a general consensus around the lack of guidance over which probiotic strain should be used in an IBD setting. This is an important question to address as the effects of probiotics are likely to vary between strains. Sherman believes the future of probiotics in IBD lies in identifying probiotic strains that have the capability to drive the production of Treg cells – cells which have been shown to block IBD in a mouse model.

Other important, unanswered questions were identified during this session, including; What is an appropriate probiotic dose?; How frequently should a probiotic be administered?; and Should probiotic therapy be administered with a single strain or combination of strains? Sherman commented that most gastroenterologists tend to favour the use of combinations; however this is not necessarily echoed in other specialties. Verdú cautioned that until more is known about the relationship between multiple probiotic strains, it is possible that the beneficial effect imparted by one strain may be masked by others, when multiple strains are administered simultaneously.

More data is required to clarify whether probiotics would be more effective for the purpose of maintaining remission as an adjunct to current IBD therapy or as a sole treatment option. Probiotics have been found to enhance success and reduce adverse effects when used adjunctively to therapy for upper intestinal tract diseases. Sherman believes this will echo for diseases of the lower intestinal tract and will be the way of the future for IBD management.

In Canada and the United States, probiotics are now classified as a drug product and are subject to thorough screening and evaluation. As an unintended consequence of this classification, Sherman commented that the science surrounding probiotics will benefit, since well-designed, randomized, controlled trials are required to assess the effectiveness of probiotics for clinical IBD management. It was highlighted that future research in this field will benefit from investigations into the composition of the microbiome over the time course of IBD progression. Additionally, probiotic-derived products (potentially responsible for the beneficial effects) are gaining interest as a future therapeutic avenue, as they have the potential to overcome safety concerns associated with administering probiotics in immunocompromised patients.

PROBIOTICS FOR THE MANAGEMENT OF IBS

The use of probiotics for irritable bowel syndrome (IBS) was addressed in a small, interactive, case-based group session led by **Dr. Stephen Collins** (McMaster University) and **Dr. Jan Irvine** (University of Toronto). Patients with IBS were noted to have a reduction of *Lactobacillus* or *Bifidobacterium* species in their gut microbiota. During this session it was discussed that the role of the microbiome in disease is still an evolving concept; the dysbiosis associated with IBS is still undefined, and as such, it was stressed that probiotics should not be viewed as a method to correct a problem, but instead as an effective management strategy. It was discussed that treatment strategies for IBS may depend on symptom severity, with probiotics considered in patients with mild IBS symptoms. Probiotics have the potential to influence gut functions that are relevant to IBS. Irvine reviewed the findings of a systematic review and four meta-analyses, which suggest that probiotics result in a 30% reduction in risk of IBS symptoms, with a number needed-to-treat (NNT) falling between 4 and 9.

The effects of probiotics are strain- and dose-specific. Currently two probiotics strains are approved in Canada for the treatment of IBS; *Lactobacillus plantarum 299v* and *Bifidobacterium longum* subsp. *infantis* 35624 (the latter being introduced in Q3 2012). Irvine reviewed the data available for both strains; however she commented that more information is required on adverse effects and safety (particularly in pregnant women, children and the elderly). Currently, probiotics are not recommended in immunocompromised patients, those taking immunosuppressants, or those who are experiencing 'red flag' symptoms such as nausea, fever, vomiting, bloody diarrhea or severe abdominal pain.

ROLE OF PROBIOTICS IN BEHAVIOUR

Depression and anxiety are common comorbidities in patients with chronic gastrointestinal disorders. There is increasing evidence suggesting that this is due to an interaction between the microbiota, the gut and the brain. At the 2012 CDDW the evidence supporting this relationship, along with the effects

of probiotics on behaviour was reviewed. **Dr. Premsyl Bercik** (McMaster University) discussed the results of several animal studies suggesting that the intestinal microbiota have a profound effect on behaviour and the brain biochemistry of the host, which is thought to be mediated through multiple pathways including immune, neural, and metabolic mechanisms. Probiotics, such as *Bifidobacterium longum* and *Lactobacillus rhamnosus*, have been shown to normalize or reduce anxiety-like behaviour in both disease and healthy mouse models. This effect has been shown to be mediated by signals from the vagus nerve. Bercik commented that human data in this area is limited, and more high-quality clinical trials in this area could provide insight into how to better manage patients with chronic gut diseases.

ECOSYSTEM THERAPEUTICS FOR THE TREATMENT OF *C. DIFFICILE*: REPOOPULATING THE GUT WITH SYNTHETIC STOOL

The incidence and severity of *Clostridium difficile* infections is increasing, in part due to the emergence of a hypervirulant strain. The limited arsenal of effective therapeutic options and the frequency of recurrent *C. diffilicle* infections make treatment quite challenging. Patients with *C. difficile* infections typically have a lower microbial diversity. As such, fecal transplants (microbial ecosystem therapeutics), which are thought to displace a damaged microbial ecosystem with a healthy one, have been shown to be a highly successful, albeit primitive, treatment option for patients suffering from severe, recurrent *C. difficile* infections. In fact, fecal transplants remain the single most effective therapy for recurrent *C. difficile* infections, with reported efficacy rates greater than 85%.

By culturing and identifying fecal bacteria species, **Dr. Emma Allen-Vercoe** (University of Guelph) in collaboration with **Dr. Elaine Petrof** (Queens University), has engineered a synthetic stool mixture (referred to as the rePOOPulate mixture) containing 33 bacterial strains, for treating recurrent *C. difficile* infections. At the 2012 CDDW they discussed the advantages of synthetic stool; namely, it provides a reproducible, controlled composition, absent of viruses, which is more stable and less unpleasant than stool. Additionally, they presented data showing the synthetic stool mixture is able to colonize and persist in the host, likely due to the fact that these bacteria are able to grow as a community. They commented that this could explain why probiotics are unable to colonize.

The synthetic stool mixture has been used in two patients suffering from recurrent *C. difficile* infections; in both cases reinfection was prevented. Allen-Vercoe said that in the future they will be looking to engineer synthetic stool mixtures derived for each of the three fecal microbial enterotypes identified by Arumugam and colleagues (2011). This could improve success by providing more personalized therapy, which is tailored to the patient's lifestyle.

CELIAC DISEASE

Dr. Connie Switzer (University of Alberta) and **Dr. Mohsin Rashid** (Dalhousie University) addressed relevant issues in the area of celiac disease during an interactive, case-based breakfast session. Rashid discussed a new perspective on celiac disease, which considers this to be a multisystem disorder involving a number of non-gastrointestinal symptoms (Table 1). He noted that many patients are asymptomatic and will go undiagnosed, stressing the importance of screening. Rashid commented that detection could be increased by 40-fold if celiac disease was to be investigated in patients with gastrointestinal symptoms, family history, chronic fatigue, thyroid disease and anemia.

Table 1: Celiac disease symptoms – a multi-system disorder

GI Symptoms	Non-GI Symptoms
Abdominal pain	Hematologic
Diarrhea	Neurologic
Weight loss	Hepatic
Poor appetite	Gynecologic
Nausea and vomiting	Musculoskeletal
Constipation	Oral and dental
Protuberant abdomen	Dermatologic

A response to a gluten-free diet is considered a defining criterion for celiac disease and this is often assessed using a biopsy of the duodenal cap. Switzer commented that in the past, she has typically performed this 1 year after diagnosis and subsequent treatment initiation. However, there is no Canadian consensus as to when this should be done. However, she discussed that recent evidence suggests mucosal healing takes much longer, i.e. 66% of patients had mucosal healing after 5 years. Symptoms in these individuals improved on a gluten-free diet, suggesting that there are most likely other factors beyond mucosal healing that influence how a patient responds.

Additionally, Switzer also discussed new labelling laws which will take effect in Canada in of August 2012. These will require all food and beverages (except for beer) to contain an allergy label highlighting food allergens and gluten sources. These labels should assist patients in adhering to a gluten-free diet.

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Liver Disease

Canadian Digestive Diseases Week

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In this section, we invite you to read the latest advances and clinical findings in liver disease. Of special interest is a review of the new Canadian guidelines for viral Hepatitis C and key findings in the management of autoimmune liver diseases and hepatocellular carcinoma.

We hope you enjoy this report and find it an informative resource.

Dr. Kevork Peltekian
Co-Chair, CDDW 2012

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HEPATITIS C

At the 2012 Canadian Digestive Disease Week (CDDW), treatment approaches and considerations regarding the management of hepatitis C virus (HCV) were addressed, with a focus on the new protease inhibitors, boceprevir and telaprevir. Of interest, the new Canadian practice guidelines were presented, along with results from the supporting clinical trials.

CASL Practice Guidelines – Viral Hepatitis: New Canadian Recommendations
New Canadian guidelines for the management of HCV, which resulted from the Canadian Association for the Study of Liver (CASL) Consensus Conference on Viral Hepatitis held in November 2011, were presented for the first time at the 2012 CDDW. **Dr. Rob Meyers** (University of Calgary) and **Dr. Jordan Feld** (University of Toronto) presented the guidelines, followed by discussion led by **Dr. Jean-Michel Pawlotsky** (Université Paris-Est) on guideline challenges, issues and considerations. Currently there is no international consensus regarding the management of HCV, due in part to the fact that available data on direct-acting protease inhibitors, boceprevir and telaprevir, are industry-generated. As such, there is a need for industry-independent studies. Following is a summary of the key points raised during this session.

Patient Selection: It was suggested that in Canada, all patients with chronic HCV should be considered, and those with evidence of liver fibrosis should be strongly considered, as candidates for antiviral therapy (AVT). Pawlotsky stressed the importance of individualizing treatment based on the likelihood that patients in different stages of disease will be cured. He called into question who should be making the decisions regarding which patients to treat, and proposed that considering our current economic situation, the decision-makers should be the government or the payers providing support.

Assessing Liver Severity: CASL members are of the opinion that treatment decisions should be made on an individualized basis, taking into account factors other than the stage of fibrosis. Additionally, liver biopsy may not be necessary in all patients and there are alternative methods shown to be effective in identifying moderate fibrosis. During a CASL Paper Session, **Dr. Giada Sebastiani** (McGill University Health Centre)

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cautioned that the accuracy of assessing liver fibrosis and cirrhosis using non-invasive biomarkers (such as Aspartate aminotransferase (AST)-to-Platelet Ratio Index (APRI) or Fibrotest-Fibrosure) may be affected by the etiology of liver disease and the stage of fibrosis, and these factors should be considered when evaluating fibrosis level.

Interleukin-28B Genotyping: The Canadian and American guidelines differ in their recommendations for the use of interleukin-28B *(IL28B)* genotyping as a pre-treatment predictor. The American Association for the Study of Liver Disease (AASLD) considers *IL28B* genotyping to be a robust pre-treatment predictor, while the Canadian guidelines suggest it should not to be used to determine treatment decisions. Pawlotsky considers *IL28B* to be a "dead marker," believing that it is not a useful predictor with triple combination therapy. Additionally, Meyers stressed that a non-favourable genotype should not preclude treatment.

Treatment Algorithms: The Canadian treatment recommendations for boceprevir and telaprevir in treatment-naïve and treatment-experienced patients were summarized by Meyers and Feld, respectively. Simplified algorithms are outlined in Table 1. In the boceprevir treatment group, response-guided therapy (RGT) is an option for treatment-naïve and non-cirrhotic patients; while in the telaprevir treatment group, RGT is considered for treatment-naïve or non-cirrhotic relapsers. Those patients who meet the RGT criteria are eligible to follow the treatment algorithms for early responders. It was noted that there are differences between the Canadian, American and European recommendations, however it is important to recognize that although the guidelines provide direction, treatment should be individualized to ensure each patient receives the best possible care.

Boceprevir	Early Responders	Late Responders
Naïve (RGT)	**28 weeks** (PR4 + BPR24)	**48 weeks** (PR4 + BPR24 + PR20)
Non-cirrhotic (RGT)	**36 weeks** (PR4 + BPR32)	**48 weeks** (PR4 + BPR32 + PR12)
Cirrhotic or null responder	**48 weeks** (PR4 + BPR44)	
Telaprevir	**Early Responders**	**Late Responders**
Naïve (RGT)	**24 weeks** (TPR12 + PR12)	**48 weeks** (TPR12 + PR36)
Non-cirrhotic relapser (RGT)	**24 weeks** (TPR12 + PR12)	**48 weeks** (TPR12 + PR36)
Cirrhotic or partial/null responder	**48 weeks** (TPR12 + PR36)	

RGT: response guided therapy;
B: boceprevir; P: peginterferon; R: ribavirin; T: telaprevir.

Of note, response during a lead-in phase (4–week treatment with peginterferon [PegIFN]) and ribavirin [RBV]) has been shown to be a good predictor of treatment response, although it is only recommended for the boceprevir treatment regimen. Pawlotsky suggested streamlining the use of a lead-in phase based on whether an individual is treatment-naïve or treatment-experienced; a lead-in phase would only be required in treatment-experienced patients. The response of a treatment-experienced patient during this phase could be used to subsequently decide whether a protease inhibitor should be introduced.

Virological Monitoring: The virological monitoring time points used to assess boceprevir and telaprevir management strategies are currently based upon those for PegIFN monitoring. Since the pharmacokinetics of these treatments differ, the current time points may not represent the most appropriate checkpoints for the newer agents. Pawlotsky commented that more information should be gathered on the use of earlier time points (before week 4), which may help to better assess patients who fall slightly above the futility rules. To this end, he also suggests being flexible with respect to futility rules, monitoring patients for an additional week if necessary with the hopes of achieving a sustained virological response (SVR) in a larger number of patients.

Side Effects: Feld discussed side effects for both telaprevir and boceprevir, cautioning the audience to expect anemia, monitor patients frequently and respond aggressively, including reducing the RBV dose by 50%, if required. Skin disorders, such as rash, are also common side effects of telaprevir that tend to disappear once treatment is completely stopped. Pawlotsky recommended collaboration with a dermatologist to help decide if treatment should be stopped.

Results from an interim analysis examining treatment in cirrhotic patients, suggest the side effect profile of each agent is worse than originally documented in their pivotal trials. The take-home message was that real-life situations will be different from clinical trial observations and results. The panelists advised the audience that until they have gained experience in treating patients with boceprevir and telaprevir, they should be comfortable managing simpler cases (treatment-naïve patients with no complications), before attempting more complex cases.

Resistance: To minimize resistance, it is imperative to adhere to futility rules, ensure patients are compliant and maximize the interferon response. Direct-acting antiviral agents cannot be given as monotherapy and must be administered in combination with PegIFN and RBV at all times. Additionally, there appears to be no interclass cross resistance with direct-acting antivirals, meaning the future may bring new therapeutic options for patients who are resistant to the currently available agents.

Management of Hepatitis C Viral Infections

The new direct-acting antiviral agents, when added to PegIFN/RBV regimens, offer improved management of chronic HCV

infections over dual PegIFN/RBV therapy. During the Viral Hepatitis Paper Sessions 1 and 2, the results from telaprevir clinical trials were discussed. This serine protease inhibitor has been shown to be superior to dual therapy in treatment-naïve patients – regardless of liver fibrosis stage (F0-F2/F3-F4) – and treatment experienced patients including prior-relapsers, partial-responders and null-responders. Prior-relapsers respond very well to RGT with SVR rates comparable to, or even higher than, those observed for treatment-naïve patients. Additionally, telaprevir in combination with PegIFN/RBV in HCV/HIV co-infected patients was found to be comparable across all antiretroviral therapy (ART) regimens, with a safety and tolerability profile comparable to that observed in monoinfected patients.

Telaprevir treatment should be stopped in poor-responders with greater than 1000 IU/mL HCV RNA at week 4. Additionally, the week 12 futility rule of less than 2 $\log_{10}$ decrease of HCV RNA has been replaced in telaprevir clinical trials by the futility rule of more than 1000 IU/mL of HCV RNA. **Dr. Nathalie Adda** (Vertex Pharmaceuticals Incorporated) noted that she does not expect this to be revised in the product monograph.

Other direct-acting antiviral agents are being investigated for the management of HCV. One such agent, VX-222, a selective, non-competitive inhibitor of HCV NS5B polymerase, when used in combination with telaprevir/PegIFN/RBV, was found to have a high-rate of SVR after 12 weeks, with no viral breakthroughs reported at the interim of the study.

AUTOIMMUNE LIVER DISEASE

At the 2012 CDDW, the current and emerging therapeutic strategies for autoimmune liver disease were discussed. Following is a summary of the key findings for primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH).

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is a chronic disease of the liver characterized by inflammation and scarring of the bile duct. **Dr. Aldo Montano-Loza** (University of Alberta) reviewed diagnostics, disease variants and medical therapies associated with PSC. He commented that it is important to distinguish PSC from disease variants such as small-duct PSC, IgG4-associated cholangitis (IAC), or PSC with overlapping features of AIH, as the clinical course and treatment strategies related to each differ.

Primary sclerosing cholangitis is regarded as a difficult disease to treat, with no effective medical therapies available. Montano-Loza noted that in practice, he may consider the use of low- or moderate-dose ursodeoxycholic acid (UDCA). However, he acknowledged there is currently no evidence to support its use and that clinical data is required to evaluate UDCA at these doses. He cautioned the audience not to use UDCA at high-doses, as this is associated with poor outcomes including a 3-fold higher risk of death (perhaps due to an increase of lithocholic acid). New medications, such as 24-norursodeoxycholic acid, are emerging with promising results, although further evaluation in randomized-controlled trials is required. Currently, liver transplantation is the only effective therapy that is indicated for patients with advanced liver disease. When contemplating liver transplantation it is important to consider the disease stage (timing) and the probability of PSC recurrence.

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is an immune-related disease that leads to the destruction of the small bile ducts. Currently the main treatment for PBC is UDCA, which has been shown to improve outcomes and life expectancy. A modified bile acid, obeticholic acid, is under investigation and has shown promising results as an adjunct to UDCA.

Dr. Andrew Mason (University of Alberta) remarked that it is an exciting time in PBC management; as we gain a better understanding of the immune, genetic and environmental factors which influence PBC, new targets and potential treatments are emerging. He commented that immunosuppression has limited utility in the management of PBC and that genetic and environmental findings may prove to have a greater influence on novel management strategies.

Primary biliary cirrhosis is associated with interleukin-12 (IL-12) variants; currently the therapeutic potential of IL-12 antibodies is being investigated in a pilot study with PBC patients. Additionally, research efforts seek to identify additional genetic

elements that may be involved. This genome-wide analysis has identified a different gene expression pattern, particularly in metabolic-related genes, in PBC-derived cells when compared to cells derived from other liver samples (such as PSC).

Recently, human beta-retrovirus (HBRV) infections have been implicated as a possible etiology of PBC. Mason discussed the difficulties in proving an association between HBRV and PBC using traditional polymerase chain reaction (PCR) methods. During a CASL Paper Session, an alternative method for detecting HBRV infection by identifying viral integration sites was presented. HBRV integration sites were identified in 80% of patients with PBC, which was significantly more frequent than in other liver diseases. These findings suggest that ART may have utility in the management of PBC. Initial investigations of ART have shown promising results, reducing alkaline phosphatase levels to normal. A randomized-controlled, 6-month proof-of-principle trial is currently underway to investigate the use of lopinavir/ritonavir and emtricitabine/tenofovir in patients with PBC.

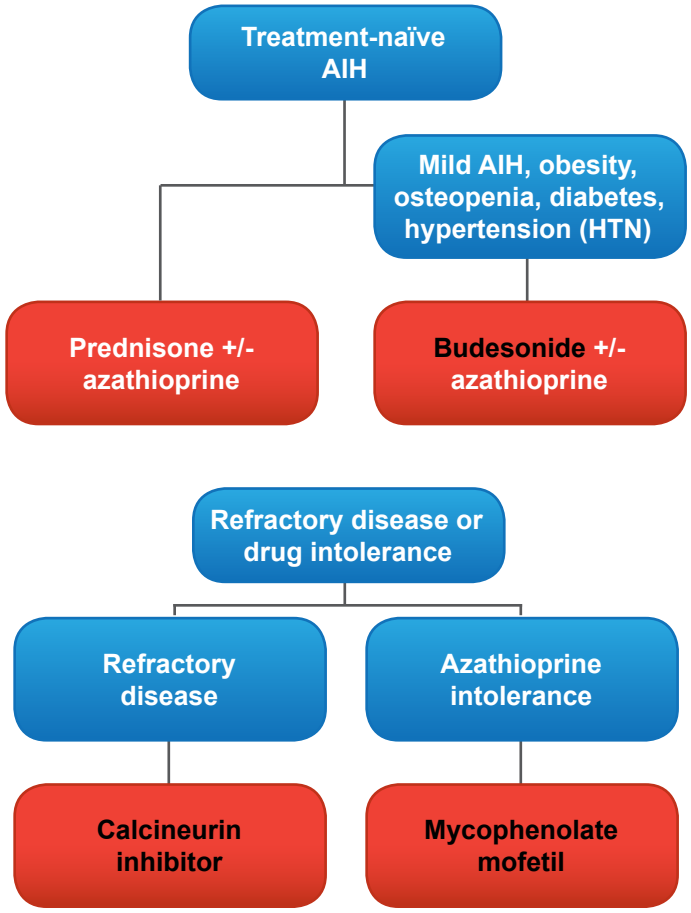
Management of Autoimmune Hepatitis

At the 2012 CDDW, **Dr. Albert Czaja** (Mayo Clinic) discussed new and emerging off-label drug regimens and feasible cellular interventions, which could replace traditional corticosteroid therapy in the management of AIH. Overall, he indicated a belief that medications offering both anti-inflammatory and anti-proliferative activity will be the most successful in AIH.

Czaja reviewed the current evidence supporting the off-label use of calcineurin inhibitors such as cyclosporine and tacrolimus, the purine antagonist mycophenolate mofetil, and the oral glucocorticoid formulation budesonide, followed by a discussion on the specific concerns associated with each agent. Treatment of patients with these agents requires an individualized, well-monitored approach. Czaja discussed a potential treatment algorithm for AIH incorporating the off-label use of these agents (Figure 1). The calcineurin inhibitors were regarded as a salvage therapy for cases of refractory liver disease. Their use has not caught on within the AIH community and Czaja expects that calcineurin inhibitors will likely disappear as a management option. Mycophenolate mofetil was also regarded as a salvage therapy effective in cases of azathioprine (AZT) intolerance. Budesonide in combination with AZT has emerged as a front-line option for non-cirrhotic, non-complicated, treatment-naïve patients.

Site-specific, molecular and cellular interventions, such as monoclonal antibodies to CD3 or CD20 (targeting T- and B-cells, respectively), recombinant molecules, and immune cell modulators are also regarded as feasible therapeutic options for AIH due to their observed successes in animal models and other immune-related diseases. These interventions require further study in AIH. During a CASL Paper Session, autoantigen intranasal desensitization was discussed as a potential therapeutic strategy for AIH, as it has been shown to prevent AIH and induce remission in a murine model. These findings are still in the early stages and require further investigation.

Figure 1: Treatment algorithms for AIH incorporating the emerging off-label therapies (shown in black), for treatment naïve patients, drug-intolerant patients, or those with refractory disease.



HEPATOCELLULAR CARCINOMA

Therapeutic Approaches for Hepatocellular Carcinoma

The therapeutic strategy for hepatocellular carcinoma (HCC) varies depending on whether the tumour is in an early, intermediate or advanced stage. Treatment options with curative potential are used in early stage tumours and include ablation, resection, or liver transplantation. Liver transplantation has the best 5-year disease-free survival rate; however, it is associated with the highest rate of morbidity and mortality. Proper patient selection is required and possible alternatives with lower mortality risk should be considered first. The criteria used for patient selection will vary depending on the center and typically follow the Milan or UCSF criteria. **Dr. Norman Kneteman** (University of Alberta) discussed his experience using total tumour volume (TTV) and alpha-fetoprotein (AFP) as criteria for liver transplant selection and predictors of success. He commented that this approach appears to improve the accuracy of classification and appears more effective than tumour size or the Milan/UCSF criteria.

At the intermediate tumour stage, transarterial chemoembolization (TACE) is considered. **Dr. Morris Sherman** (University of Toronto) stated that appropriate patients for TACE are those with a good performance status, a Child-Pugh score less than 7, and no venous invasion. This technique can also be considered as a method to maintain a patient's status while awaiting transplantation, or to bring a patient within liver transplantation criteria. Sherman equates TACE to "cooking with your mother's recipe:" there is no standardized method due to variations in the chemotherapeutic agents, embolizing agents, and the method of delivery.

Chemotherapy is an option for advanced stage HCC. However, at present, there is limited evidence supporting the use in HCC with the available agents. **Dr. Peter Metrakos** (McGill University) remarked that this is an area of active investigation and discussed upcoming trials for sorafenib, the first systemic therapy to demonstrate prolonged survival in patients with HCC, and for the emerging angiogenic and growth signalling targeted therapies. Of notable mention, early results look promising for the combination of sorafenib with yttrium-90 (Y-90). This combination is thought to enhance the effectiveness of radiation by increasing the oxygen level within the tumour. Metrakos commented that there is a long, yet interesting road ahead, with many molecules emerging.

LIVER DISEASE: ALTERNATIVE CONSIDERATIONS

The impact of alternative strategies, including lifestyle, nutritional and herbal therapies, for the management of liver disease was addressed at the 2012 CDDW.

Malnutrition in cirrhotic patients is associated with complications, including increased morbidity and mortality. As such, it is important to perform a nutritional assessment to identify and help correct malnutrition in these patients. **Dr. Puneeta Tandon** (University of Alberta) reviewed the available assessment tools and concluded that the subjective global assessment (SGA) test is the most effective standard available. Tandon commented that using muscle function to assess malnourishment may prove to be a more sensitive assessment; however more supportive data is required.

For liver diseases, such as non-alcoholic fatty liver disease (NAFLD), where no specific therapies are available, alternative approaches are needed. In the case of NAFLD, regular exercise and weight loss are the only interventions with proven benefits. According to **Dr. Saumya Jayakumar** (University of Virginia), treatment with pre/probiotics, vitamin E (either alone or in combination with vitamin C), or omega-3 supplements may also be beneficial, however more data is required to support current findings. **Dr. Melanie Beaton** (Western University) presented results from a prospective study showing that reducing serum ferritin levels through phlebotomy was a safe and well-tolerated approach to NAFLD, improving liver transaminases and NAFLD activity scores (NAS). However, no improvement in insulin resistance was observed; as such, the overall impact on disease remains unclear.

Herbal remedies are also commonly utilized. It is critical to identify all such complementary and alternative medicines being used by the patient, as they can impact treatment options, particularly invasive procedures. In liver disease, milk thistle is the only well-studied herbal therapy, and has been found to safely improve liver enzymes and the patient's energy level. However, it is unclear whether there is any impact of this therapy on disease. During discussions on herbal therapies for liver disease, **Dr. Kevork Peltekian** (Dalhousie University) captivated the audience with a talk on the beneficial impact of coffee, which has been reported to slow the progression of liver disease to cirrhosis.

In the context of liver disease, nutritional and alternative therapies have shown utility in improving liver enzymes, with some benefit on patients' quality of life, even if the impact on disease state is uncertain.